ChemPubSoc Europe

DOI: 10.1002/chem.201402254

CHEMISTRY
A European Journal
Full Paper

Natural Product Synthesis

Studies Toward the Total Synthesis of Pluraflavin A

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Abstract: A synthetic strategy towards the potent cytostatic agent pluraflavin A has been developed. Formation of the enantioenriched anthrapyran core bearing a halogen atom enabled the introduction of the α C-aryl glycoside by Stille cross-coupling and subsequent hydrogenation of the aryl glycal. Chemo- and stereoselective O-glycosylations of α oliose and β 3-*epi* vancosamine residues afforded a fully glycosylated aromatic core. Attempts to install the dimethylamino group of the C-disaccharide suggest that introduction of an azide group by displacement and subsequent reduction may pave the way to the total synthesis of pluraflavin A.

Introduction

The first member and namesake of a family of antibiotics known as the pluramycins was discovered in 1956 (**1**, Figure 1).[1] Since then, a large collection of pluramycins have been isolated and structurally characterized (Figure 1). Amongst the structural characteristics that are conserved in most members of this family, an anthrapyran core bearing C-glycosidic appendages is both a necessary component for its mechanism of biological activity and a synthetic roadblock to assembling these targets in the laboratory. Thus, despite the rapid discovery of many new entries in this natural product family, there are relatively few approaches to their synthesis.

Efforts toward the synthesis of anthrapyran antibiotics have culminated in the total synthesis of the aglycones of altromycin (**2**) and kidamycin,[2] the indomycinones,[3] espicufolin,[4] and related products.[5] Notably, the Martin group completed a synthesis of the glycosylated pluramycin, isokidamycin (**3**), which featured the application of a benzyne–furan cycloaddition to append the C-glycosidic residue.[6]

The pluramycins' cytotoxic activity became apparent when White and White identified both reversible interactions with and irreversible modification of DNA by rubiflavin and hedamycin.[7] Further research clarified this early work and assigned the strong reversible interaction as intercalative in nature and the irreversible modification a covalent attachment formed by reaction with the epoxide group of the side chain.[8] Elucidation of the pluramycins' mechanism of action was provided by Hurley's study of the covalent modification of DNA by altromycin B.[9] Ultimately, a consensus as to the general mode of action of these natural products has been put forward involving nucleophilic attack of N7 of guanine onto the C14/C15 oxirane ring, resulting in DNA damage and subsequent cell death.[10]

In 2001, Vértesy and co-workers reported the isolation of several new natural products from cultures of *Saccharothrix* sp. DSM 12931 (**4**–**6**, Figure 1).[11] Due to their structural similarities to the pluramycin family, the newly isolated products were named the pluraflavins. The pluraflavins' structures consist of an anthrapyran core with appendages at the C2, C5, and C10 positions. The C-linked disaccharide, conserved amongst the pluraflavins, is composed of α(1–4) oliose and α C-linked rhodosamine residues. Pluraflavins A and B possess a hydroxymethyl group at C5 bearing a β 3-*epi* vancosamine residue. While pluraflavin A bears a *trans* epoxide at C2, its congeners contain a diol of unknown relative and absolute stereochemistry. While the stereochemical relationships within the side chains of pluraflavin A were determined by 2D NMR spectroscopy, the absolute configurations of the widely separated sectors with respect to each other remain undetermined. Total synthesis of the putative structure and related structures bearing enantiomeric side chains will enable definitive structural elucidation; the current study employs D sugars.

In addition to antibiotic activity against gram-positive bacteria, the isolation team found that the epoxide-bearing isolate, pluraflavin A, demonstrated potent cytostatic activity against a number of human cancer cell lines. Given our group's long-standing interest in the application of total synthesis to cancer chemotherapy and the challenge posed by the architecture of pluraflavin A, we embarked on the synthesis of this intriguing molecule.

Inspection of the pluraflavins' structure suggested a few key problems that would have to be solved before a successful total synthesis could be carried out. In particular, the highly functionalized aromatic core, epoxide side chain, and position

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Supporting information, which contains experimental details and compound characterization, is available on the WWW under http://dx.doi.org/10.1002/chem.201402254.

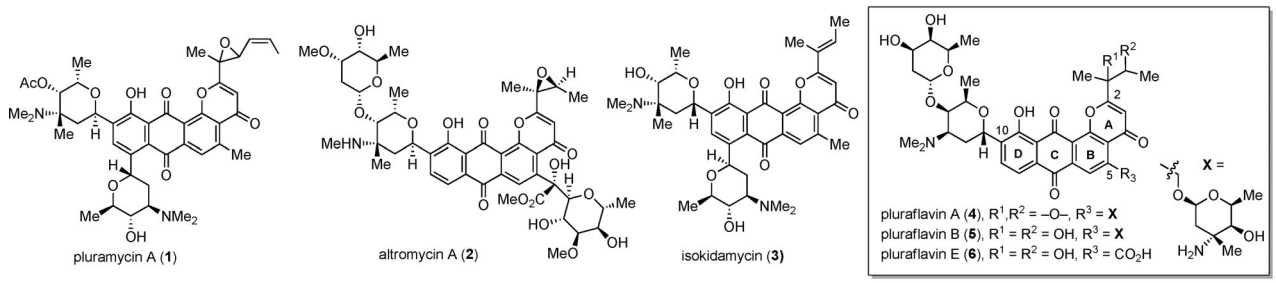
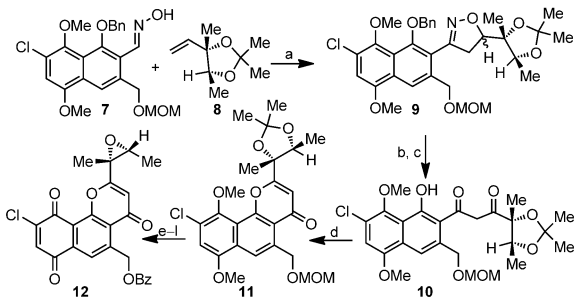


Figure 1. Structures of representative pluramycins.

and orientation of the C-glycosidic bond in pluraflavin A pose a formidable synthetic challenge. Our first subgoal was thus to accomplish the synthesis of a suitable "aglycone," which would serve as a platform for the installation of the glycosidic appendages. We were successful in accomplishing this goal and, in the process, developed an approach featuring a key [3+2] cycloaddition to form a functionalized isoxazoline, which could be conferred into the pyrone ring of the natural structure.[12] We describe herein an asymmetric synthesis of a late-stage intermediate en route to pluraflavin A.

Results and Discussion

In our global strategy, the aromatic core would be constructed in the BC→ABC→ABCD direction. However, in contrast to the prior syntheses of anthrapyran natural products, we decided to store what would eventually become the A ring in the form of an appropriately substituted isoxazoline intermediate. A subsequent ring-cleavage and oxidation reaction sequence would unveil the desired β-diketone, which would readily condense onto a phenol to form the pyrone ring of pluraflavin A. This approach had the added benefit that formation of the isoxazoline could function as the union of the aromatic core and the side chain that would eventually contain the epoxide.



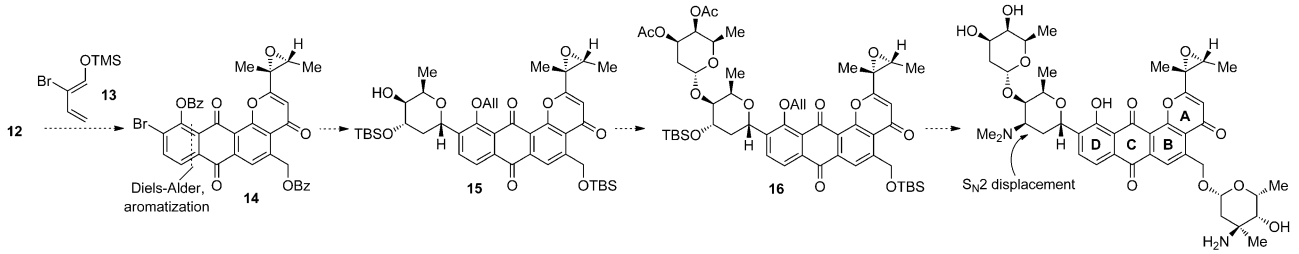
Scheme 1. Synthesis of Diels–Alder precursor **12**. Reaction conditions: a) **8** (2 equiv), chloramine-T, CH_2Cl_2/EtOH/H_2O, 50 °C, 81%; b) Raney-Ni, $B(OH)_3$, H_2 (1 atm), EtOH/H_2O, 68%; c) IBX, EtOAc, 65 °C, one starting material recycle, 82%; d) NaOAc, AcOH, 80 °C, 86%; e) HCl, THF/MeOH, 50 °C; f) 2,2-dimethoxypropane, *p*TsOH, acetone; g) AcOH/H_2O; h) BzCl, Et_3N, CH_2Cl_2, 0 °C, 86% (over four steps); i) HCl, THF/MeOH, 50 °C; j) MsCl, iPr_2NEt, CH_2Cl_2, 0 °C; k) K_2CO_3, MeOH/THF, 0 °C, 60% (over three steps); l) CAN, 0 °C. Bz = benzoyl, CAN = cerium ammonium nitrate, IBX = 2-iodoxybenzoic acid, MOM = methoxymethyl, Ms = methanesulfonyl, Ts = toluenesulfonyl.

The synthetic plan that previously succeeded in furnishing the racemic pluraflavin A aglycone[12] has presently been adapted to provide enantioenriched material (Scheme 1). Accordingly, the synthesis of [3+2] cycloaddition partner **8** was modified to produce enantioenriched material by application of the Sharpless asymmetric dihydroxylation.[13] Addition of enantioenriched **8** to the nitrile oxide derived from **7**, resulted in cycloaddition to form isoxazoline **9** as an inconsequential mixture of diastereomers. Cleavage of the N–O bond and hydrolysis of the resultant β-hydroxy imine proceeded in 68% yield with Raney nickel and boric acid.[14]

Initial attempts to oxidize the β-hydroxy ketone were unsuccessful. Treatment with pyridinium dichromate, pyridinium chlorochromate, or tetrapropylammonium perruthenate and 4-methylmorpholine-*N*-oxide all resulted in clean recovery of starting material. At first, iodoxybenzoic acid (IBX) in ethyl acetate appeared to be ineffective, but an increase in temperature improved the rate of reaction. The insolubility of IBX in ethyl acetate likely contributed to the lack of reaction at room temperature. An optimized procedure (IBX, 65 °C, one recycle of starting material.) furnished an 82% yield of the β-diketone product **10**. Cyclization of **10** in acetate buffer furnished the pyrone of **11** in 86% yield.

A high-yielding (56% over seven steps) sequence converted **11** to the epoxide-containing intermediate **12**. Treatment with hydrochloric acid removed the acetonide and methoxymethyl ether to afford a highly insoluble triol. The vicinal diol grouping was reprotected as the acetonide with inevitable formation of the mixed ketal on the southeast alcohol. The mixed ketal could be selectively hydrolyzed owing to its greater instability in acid. Protection of the resultant benzylic alcohol with benzoyl chloride and pyridine afforded the benzoate. Treatment of acetonide with HCl unveiled the *cis* diol, which was converted to the *trans* epoxide in 60% yield by monomesylation and intramolecular displacement with potassium carbonate. Finally, CAN oxidation afforded intermediate **12**.

Motivated by the success of this strategy, we devised a plan for the total synthesis of pluraflavin A (Scheme 2). We anticipated that the Diels–Alder cycloaddition could be used to form the C10 halogenated D ring. This modification of our original route to the pluraflavin aglycone, which took advantage of a known chlorojuglone synthesis to supply ample amounts of starting material,[15] would aid in the stereoselective installation of the C-glycoside. Subsequent O-glycosyla-



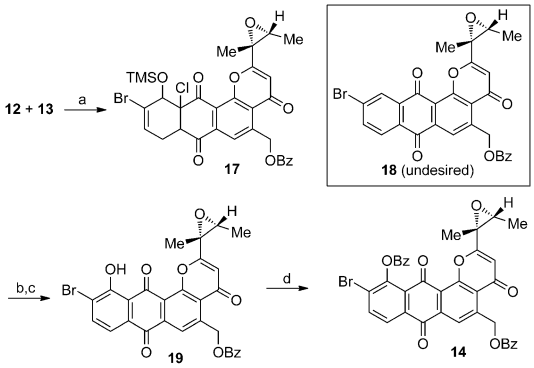
Scheme 2. Synthetic plan. TBS = *tert*-butyldimethylsilyl.

tions to append the oliose and 3-*epi* vancosamine residues would proceed with judicious choice of mild glycosylation conditions. Having accomplished introduction of the full complement of carbohydrate domains, a sequence to install the dimethylamino group onto the proximal C-glycosidic residue and globally deprotect the resultant product would produce pluraflavin A, itself.

With a viable approach to significant quantities of enantioenriched tetracyclic core, we focused on the task of synthesizing the halogenated pluraflavin A aglycone. It was concluded that a halogen atom would be a versatile precursor to investigate transition-metal-mediated transformations and could be readily accommodated on a 1,3-butadiene fragment.[16] Thus, the known[17] 2-bromo-1-trimethylsiloxy-1,3-butadiene (**13**) was synthesized by treatment of 2-bromo crotonaldehyde with a mixture of sublimed zinc chloride in triethylamine and trimethylsilyl chloride. It was predicted that the regiochemistry of Diels–Alder cycloaddition with chloroquinone **12** would be governed by the substitution patterns on both reaction partners. It has been shown that electron-releasing substituents on C1 of 1,3-butadiene exert a stronger influence over the regiochemistry in Diels–Alder cycloadditions than substituents on C2.[18] Moreover, the chloride substituent on the quinone dienophile has been shown to bias bond formation at the distal carbon atom.[19] The combination of these reactants was predicted to form a cycloadduct possessing the desired regiochemistry.

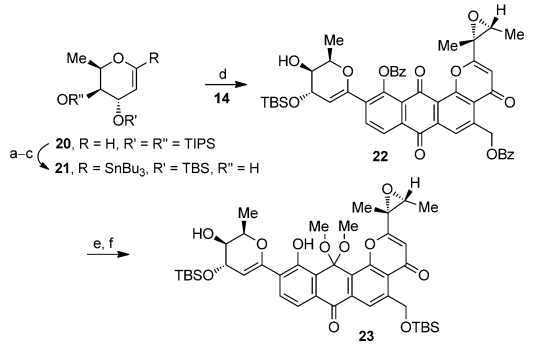
In line with our hypothesis, cycloaddition of **13** and chloroquinone **12** proceeded cleanly to form a single adduct (**17**). However, treatment of the cycloadduct with standard oxidation/aromatization conditions yielded the deoxygenated product **18**.[20] While the Jones reagent is widely employed for the desilylative oxidation of secondary alcohols, Diels–Alder adduct **17** was resistant to the reaction conditions. The subsequent aromatization of **17** to form the aromatic D ring required that the Jones oxidation be conducted in the presence of potassium fluoride.[21] We propose that fluoride ion most likely assists the desilylation of the trimethylsilyl ether to provide the alcohol in situ, which is converted to the unsaturated ketone by the agency of chromic acid. Treatment of the crude oxidation product with triethylamine provided the phenol **19** in 52% yield over three steps. Subsequent protection of the free phenol under standard conditions afforded the benzoylated aromatic core (**14**) in 87% yield (Scheme 3).

With the functionalized aromatic core in hand, our next objective was the synthesis of a carbohydrate precursor to the C-



Scheme 3. Completion of the bromo "aglycone." Reaction conditions: a) **13** (6 equiv), 100 °C, toluene; b) Jones reagent, KF, acetone, 0 °C, 2 days; c) Et_3N, 1 h, 52% (over three steps); d) benzoyl chloride, pyridine, CH_2Cl_2, 0 °C, 87%. TMS = trimethylsilyl.

linked disaccharide residue. Glycal **20** (Scheme 4) was prepared by adaptation of a known route (see the Supporting Information for more details).[22] The silylated 6-deoxy glycal **20** was metalated with Schlosser's base[23] and quenched with excess tributylstannyl chloride to yield the desired C1 stannylated product. The triisopropylsilyl groups were required for successful metalation; attempts with *tert*-butyldimethylsilyl groups resulted in recovery of starting material.[24] Removal of the TIPS groups with TBAF and selective monosilylation under standard conditions provided the C3 protected stannyl glycal **21**. Stille



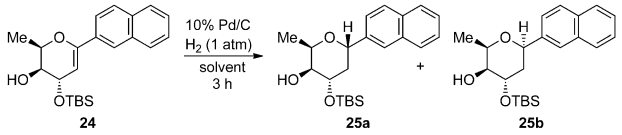
Scheme 4. Glycosyl donor synthesis and Stille coupling. Reaction conditions: a) *n*BuLi, KO*t*Bu, Bu_3SnCl, THF, −78–23 °C, 82%; b) TBAF, THF, 0–23 °C; c) TBSCl, imidazole, DMF, 49% (over two steps); d) **21** (2 equiv), [Pd(*t*$Bu_3P)_2$] (10 mol%), 80 °C, 80%; e) K_2CO_3, CH_2Cl_2/MeOH, 0–23 °C; f) TBSCl, imidazole, DMF, 73% (over two steps). TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

coupling of **14** with the monoprotected stannyl glycal **21** catalyzed by bis(tri-*tert*-butylphosphine) palladium[25] proceeded rapidly (30 min) and afforded **22** in 72% yield.[26]

Initial attempts to hydrogenate compound **22** resulted in hydrogenolysis of the southeast benzyl ester. Accordingly, the protecting group scheme was altered to avoid the formation of this product. Treatment of **22** with potassium carbonate in methanol and dichloromethane resulted in clean formation of the debenzoylated dimethyl ketal. Selective protection of the primary hydroxyl as its *tert*-butyldimethylsilyl derivative afforded an intermediate (**23**) better suited for the investigation of the glycal reduction step.

Given the thermodynamic preference for formation of the undesired β C-glycoside, due to the absence of stabilization afforded by the anomeric effect, we considered approaches for the directed functionalization of the glycal double bond. It was proposed that coordination of a suitable reagent with the free C4 hydroxyl would override the strong preference and afford the desired α glycoside. Initial studies were conducted on a simple model system, bearing an identical protecting group scheme and an unfunctionalized naphthalene ring.

Model glycal **24**, which possesses a free hydroxyl group at C4, presented an opportunity to conduct a hydroxyl-directed homogeneous hydrogenation.[27] However, treatment of **24** with $[Rh(PPh_3)_3Cl]$ or $[Ir(cod)PCy_3(pyr)]PF_6$ under high H_2 pressures resulted in recovery of starting material. It was discovered that heterogeneous conditions (Pd/C, H_2) were more effective at reducing the glycal double bond (Scheme 5). A relationship between solvent polarity and stereoselectivity was observed (Table 1). An equal amount of both stereoisomers **25a** and **25b** formed in methanol. In less polar media, hydrogenation from the same face as the free hydroxyl became increasingly favored to afford the desired α-glycoside **25a**. The best stereoselectivity (α/β 14:1) was obtained when conducting the reduction in hexanes. Hydrogenation of related substrates bearing a methoxymethyl ether instead of a free alcohol showed low stereoselectivity and no solvent dependence. These results strongly suggest a hydroxyl-directed process, which could be used to form the α C-aryl glycoside of pluraflavin A.

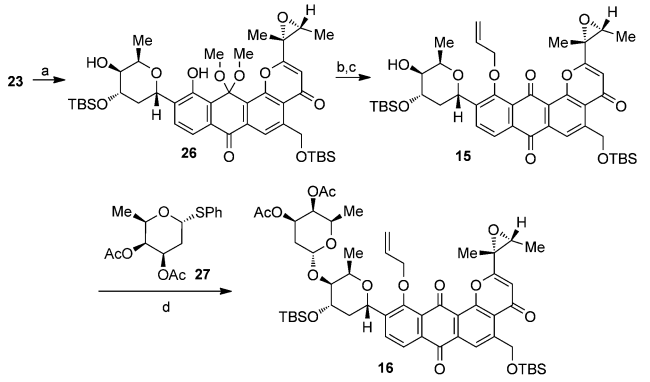


Scheme 5. Hydrogenation of a model C-aryl glycal (see Table 1 for more details).

Table 1. Solvent dependence of stereoselectivity.

Solvent	α/β ratio
methanol	1:1
ethyl acetate	5:1
benzene	11:1
hexanes	14:1

Encouraged by the results of the model study, we sought to transform glycal **23** into the desired α glycoside. Low solubility of **23** in hexanes precluded the use of this solvent, and toluene was required to achieve any reactivity. Heterogeneous hydrogenation of **23** afforded a 3:1 mixture of aryl C-glycosides **26** favoring the desired α isomer (Scheme 6). The dimethyl ketal conferred stability during reduction of the glycal double bond as compared to substrates lacking this protecting group. Conversion of the dimethyl ketal into the corresponding carbonyl occurred cleanly when **26** was stirred with silica gel at elevated temperature for 34 h. Protection of the phenol with allyl bromide in the presence of cesium carbonate provided **15**. Alkylation yields were improved by employing a large excess of allyl bromide in order to avoid prolonged reaction times, which resulted in decomposition likely due to the formation of an unstable *ortho* quinone methide species.



Scheme 6. Stereoselective reduction of C-aryl glycal and oliose glycosylation. Reaction conditions: a) Pd/C (10%), H_2 (1 atm), toluene, 60% (3:1 α/β); b) SiO_2, C_6H_6, 40 °C, 83%; c) allyl bromide, Cs_2CO_3, DMF/acetone, 0 °C, 60%; d) **27** (4 equiv), $AgPF_6$, 2,6-*tert*-butyl-3-methyl pyridine, 4 Å MS, CH_2Cl_2, 0 °C, 83% (yield after desilylation to **33**).

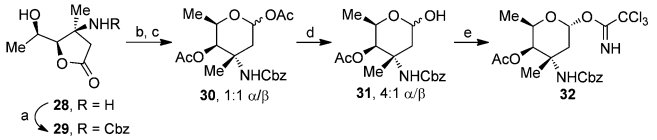
Up to this point in the synthesis, the epoxide side chain present in our synthetic intermediates posed no issues of adverse reactivity. For example, no byproducts derived from acid-catalyzed epoxide opening were observed in the oxidation/aromatization sequence in Scheme 3. However, when considering the possible glycosyl donors and modes of activation for the installation of the oliose residue, it became clear that chemoselective activation of a suitable donor would be advantageous to prevent degradation of our core structure. A report from the Hirama group came to our attention that appeared to address these concerns during the glycosylation of a particularly sensitive intermediate en route to kedarcidin.[28] Equally encouraging was the high stereoselectivity observed in this method, especially in the case of 2-deoxy glycosyl donors, a notoriously unselective class of substrates for a variety of common glycosylation methods.[29] Alcohol **15** appeared to be the ideal intermediate to attempt such a glycosylation. While chemoselectivity was assured due to the protecting group scheme, it was still unclear whether this method would afford

the desired α-oliose residue. Gratifyingly, glycosylation with thioglycosyl donor **27** promoted by silver hexafluorophosphate proceeded to give the desired O-glycoside **16** in 83% yield as a single diastereomer.

While an additional challenge remained in the conversion of the C-linked 2,6-dideoxy gulose into the native rhodosamine present in the natural product, the issue was postponed in order to take advantage of the ready deprotection of the primary TBS ether (HF·pyridine, 0 °C, 8 h, 83% yield, see Scheme 8) in the southeast region. This reactivity was seen to be highly convenient, as it would bias the chemoselectivity of the final glycosylation reaction to install the 3-*epi* vancosamine residue. We also required the identification of suitable glycosyl donors; although syntheses of 3-*epi* vancosamine have been published,[30] to the best of our knowledge, glycosylations of the monosaccharide have not been reported. Thus, our attention turned to the synthesis of a suitable glycosyl donor in the 3-*epi* vancosamine series and its evaluation in the glycosylation of primary alcohol glycosyl acceptors. An intermediate in Matsushima's synthesis (**28**)[30 g] was converted to glycosyl acetate **30** by *N*-Cbz formation, reduction of the lactone, and acetylation of the crude mixture of lactols (Scheme 7).

Glycosyl acetate **30** proved to be a versatile starting material for the synthesis of several glycosyl donors. Hydrolysis of the anomeric acetate yielded the free lactol **31**, which was converted to α trichloroacetimidate **32** by treatment with cesium carbonate and an excess of trichloroacetonitrile. Although the trichloroacetimidate was unstable to silica, this procedure provided material of sufficient purity to undergo productive glycosylation.

While glycosylations employing acetate **30** produced anomeric mixtures, treatment of a mixture of acceptor **33** and donor **32** in the presence of $BF_3{\cdot}OEt_2$ afforded the β glycoside



Scheme 7. Synthesis of 3-*epi* vancosamine glycosyl donors. Key: a) benzyl chloroformate, $NaHCO_3$ (aq.), THF, 82%; b) DIBAL, THF, −30 °C; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0–23 °C, 50% (over two steps); d) 5% HCl (aq.), THF, 62%; e) Cl_3CCN, Cs_2CO_3, CH_2Cl_2, 75%. Cbz = benzyloxycarbonyl, DIBAL = diisobutylaluminum hydride, DMAP = *N*,*N*-4-dimethylaminopyridine.

34 as a single diastereomer (Scheme 8).[31] Glycosylations conducted with an excess of $BF_3{\cdot}OEt_2$ resulted in better conversion than reactions carried out with TMSOTf or Bu_2BOTf. HF·pyridine was subsequently employed to aid in purification by desilylation of the glycosylation product and to prepare for the introduction of the azide by intermolecular displacement. The optimized sequence gave a 48% yield of **35** from **33**.

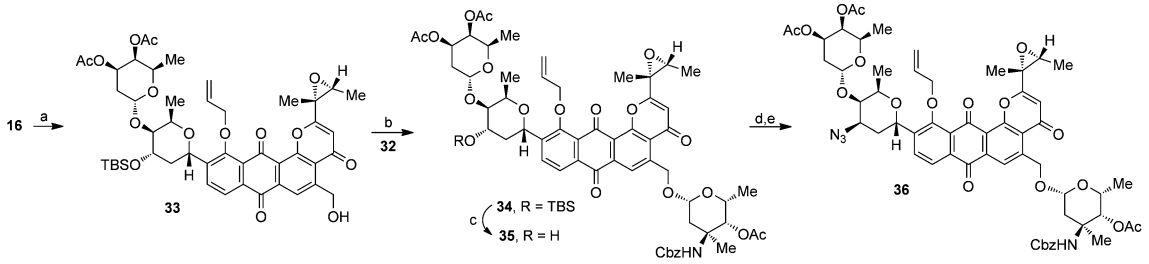
With product **35** in hand, we attempted the introduction of the dimethylamino group present in pluraflavin A. Triflation of the free alcohol proceeded cleanly, requiring 10 min at 0 °C for completion (Scheme 8). Addition of 3 equivalents of tetrabutylammonium azide to the crude triflate in benzene at room temperature afforded the desired azide **36** in 4 h and 96% yield. Although introduction of the azide was facile, its reduction to the primary amine posed a considerable challenge. No reaction was observed with many known reducing agents, such as propanedithiol,[32] dithiothreitol, $[Et_3NH][SnSPh_3]$,[33] $SnCl_2{\cdot}2H_2O$,[34] $HSnBu_3$, and H_2SnBu_2.[33] Reduction did occur with H_2 in the presence of Pd/C or Lindlar's catalyst[35] and zinc/acetic acid[36] but these conditions were incompatible with the pluraflavin core, resulting in decomposition.

We sought recourse to the highly chemoselective Staudinger reduction.[37] However, treatment of **36** with triphenylphosphine in wet tetrahydrofuran did not provide the desired amine. This was attributed to the slow rate of hydrolysis of the iminophosphorane intermediate. Indeed, peaks corresponding to the mass of the iminophosphorane were observed in mass spectral analysis of the crude reaction mixture.

We reasoned that hydrolysis of the iminophosphorane produced during Staudinger reduction of the azide with triphenylphosphine was difficult and could be accelerated by reducing the steric bulk imposed by the phosphine substituents. In accord with this hypothesis, reduction with methyldiphenylphosphine provided some primary amine, which was reductively methylated with sodium triacetoxyborohydride and formalin to provide the dimethylamino compound in low yield (30% NMR). Future work on the total synthesis will be directed at the optimization of the azide reduction and the optimal procedure for protecting group removal.

Conclusion

In summary, an approach to the synthesis of pluraflavin A has been developed that succeeded in installing the C- and O-



Scheme 8. Synthesis of azide **36**. Reaction conditions: a) HF·pyridine, THF, 0 °C, 8 h, 83%; b) **32** (1.5 equiv), $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40 °C; c) HF·pyridine, THF, 23 °C, 48% (over two steps); d) Tf_2O, pyridine, CH_2Cl_2, 0 °C; e) Bu_4NN_3, C_6H_6, 96% (over two steps). Tf = trifluoromethanesulfonyl.

linked sugar residues in a stereo- and regioselective manner. Stille coupling proved to be a robust method for the functionalization of the pluraflavin bromo "aglycone." Experimental evidence supports the hydroxyl directed hydrogenation of the *C*-aryl glycal to form the synthetically challenging α glycoside linkage present in pluraflavin A.

Ongoing efforts are focused on the installation of the dimethylamino group of the rhodosamine residue and the global deprotection of the resulting product. While initial attempts at Staudinger reduction of the azide and subsequent methylation have met with measureable success, we are optimistic that further experimentation will result in a successful route to the potent anti-cancer agent.

Acknowledgements

This work was financially supported by the NIH grant R01 HL025848. The authors thank the Guthikonda family for their generous support (fellowship to J.H.), Rebecca Wilson for help in editing the manuscript, Arthur Han for experimental assistance, and John Decatur and Yasuhiro Itagaki for NMR and mass spectrometric assistance, respectively.

Keywords: anti-cancer agents · C-glycoside · glycosylation · pluraflavin A · pluramycins

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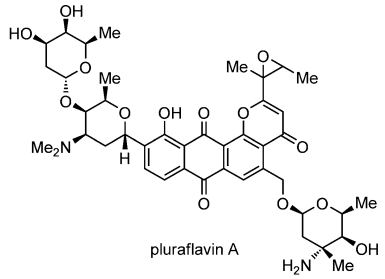
Received: February 19, 2014
Published online on ■■ ■■, 0000

FULL PAPER

A synthetic strategy towards the potent anti-cancer agent pluraflavin A (see figure) has been developed. Formation of the halogenated aromatic core enabled the installation of the α C-aryl glycoside linkage, which was forged by the Stille coupling of a stannyl glycal and subsequent hydrogenation of the cross-coupling product.



pluraflavin A

Natural Product Synthesis

*J. Hartung, B. J. D. Wright, S. J. Danishefsky**

■■ – ■■

Studies Toward the Total Synthesis of Pluraflavin A