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Total Synthesis

Total Synthesis of Antitumor Antibiotic Derhodinosylurdamycin A

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Abstract: The first total synthesis of derhodinosylurdamycin A, an angucycline antitumor antibiotic, has been described. The synthesis features a Hauser annulation followed by pinacol coupling to construct the tetracyclic angular aglycon, a Stille coupling of glycal stannane and tetracyclic aryliodide followed by stereoselective reduction to afford the 2-deoxy β-C-arylglycoside, and a late-stage stereoselective glycosylation for the preparation of derhodinosylurdamycin A. This synthetic strategy should be amenable to the chemical synthesis of analogs of derhodinosylurdamycin A bearing diverse 2-deoxy sugar subunits for structure and activity relationship studies.

Angucycline antibiotics are one type of bioactive natural products containing angularly assembled tetracyclic ring frame (cf. **1**–**4**, Figure 1) and possess diverse interesting biological activities.[1] Among angucycline natural products, the urdamycins including urdamycin A (**3**) and B–F were isolated from *Streptomyces fradiae* by Zeeck and co-workers in 1986.[2] Later, a number of other urdamycin family members were also discovered and characterized.[3] Derhodinosylurdamycin A (**4**), first obtained by methanolysis of urdamycin A (**3**), was reported as a bioactive natural product derivative[4] in 1989 and was later isolated as the main urdamycin metabolite from *S. fradiae* Tü2717 mutant lacking UrdGT1a.[5] Structurally, derhodinosylurdamycin A (**4**) contains an angular tetracyclic aglycon linked through a β-C-aryl glycosidic linkage[6] to a 2-deoxy trisaccharide subunit consisting of two D-olivoses and one L-rhodinose. Derhodinosylurdamycin A shows significant activity against L1210 leukemia cell lines (IC_{50} value of 0.75 μg mL^{-1}),[4] which is comparable to urdamycin A (IC_{50} value of 0.55 μg mL^{-1}).[2] The interesting structures and biological properties of the urdamycins have attracted a number of synthetic studies including synthesis of urdamycinone B (**2**)[7] and related molecules.[8] However, only limited studies were reported on the synthesis of urdamycinone A (aquayamycin, **1**)[9] or toward its tetracyclic core structure.[10] In 2000, Suzuki and co-workers reported the first total synthesis of urdamycinone A (aquayamycin, **1**)[9] in which Hauser annulation[11] and pinacol coupling were employed as key steps for construction of the angucycline skeleton. There is no total synthesis of urdamycin A or derhodinosylurdamycin A reported thus far. Because the actual mode of action of the urdamycins is not exactly known, it would be appealing to chemically prepare these molecules as well as their analogs[12] for structure and activity relationship (SAR) studies. In this Communication, we wish to report the first asymmetric synthesis of derhodinosylurdamycin A.

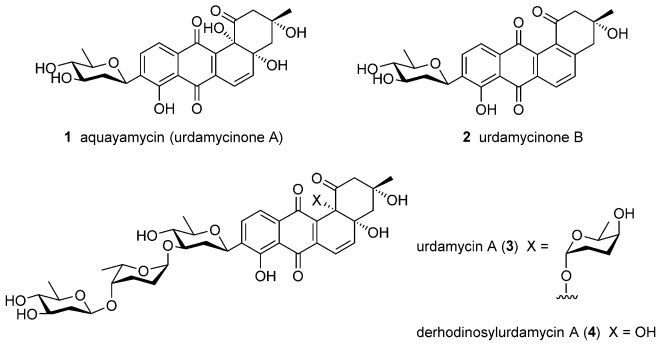

Figure 1. Representative urdamycin-family natural products.

Based on previous synthetic efforts,[7–10] especially the work reported by Suzuki and co-workers,[9] we designed a synthetic strategy that may enable us to prepare derhodinosylurdamycin A as well as its analogs bearing diverse 2-deoxy sugar subunits for structure and activity relationship studies, as shown in Scheme 1. Accordingly, derhodinosylurdamycin A (**4**) may be prepared through stereoselective α-glycosylation between disaccharide donor **5** and complex β-C-arylglycoside acceptor **6**. Stille coupling of glycal stannane **7** with tetracyclic aryliodide **8**, followed by stereoselective reduction[13] of the resulting enol ether and desilylation, should provide β-C-arylglycoside **6**. In turn, tetracyclic aryliodide **8** should be obtained through Hauser annulation[11] of cyanophthalide **9** and known complex enone **10**,[9b] followed by pinacol coupling and necessary functional-group manipulations.

The synthesis commenced with the preparation of cyanophthalide **9**, as shown in Scheme 2. Magnesium bromide mediated deprotection of methoxymethyl ether of known complex trisubstituted benzene **11**[14] afforded corresponding phenol **12**, which was then subjected to electrophilic iodination. After a number of optimizations, it was found that treatment of phenol **12** with *N*-iodosuccinimide in the presence of aluminum chloride[15] as Lewis acid in dichloromethane afforded an

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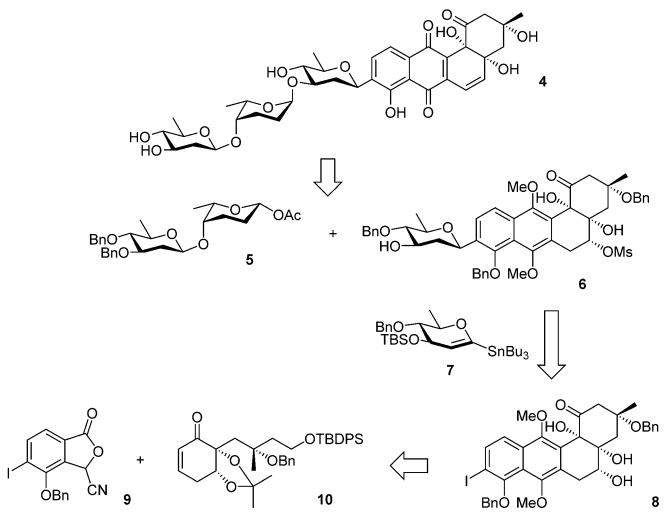
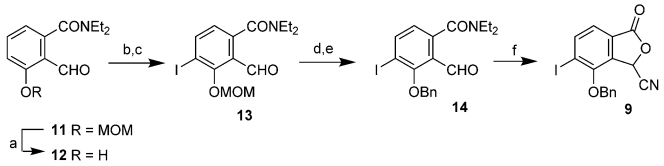


Scheme 1. Retrosynthesis of derhodinosylurdamycin A (**4**).



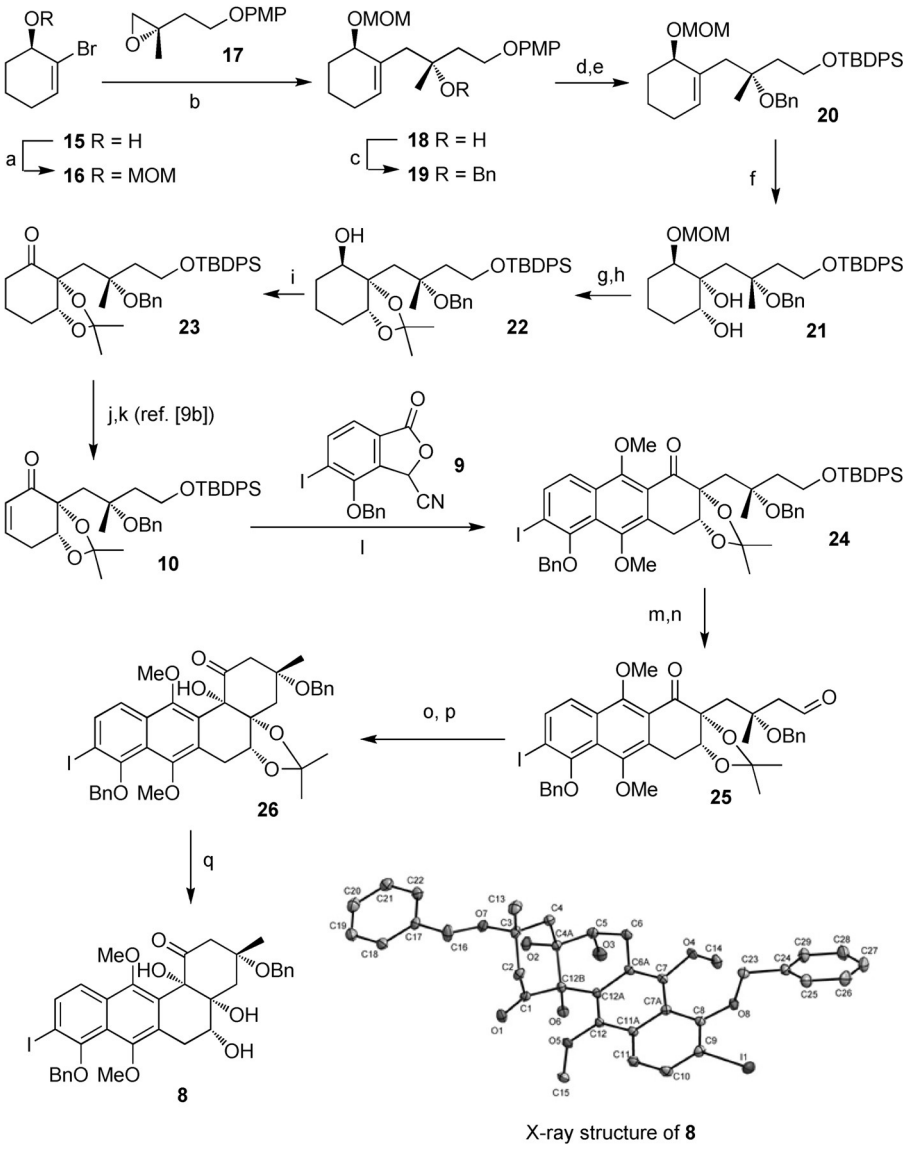
Scheme 2. Reagents and conditions: a) $MgBr_2$, ether/THF, 87%; b) $AlCl_3$, NIS, CH_2Cl_2, RT; c) MOMCl, iPr_2NEt, CH_2Cl_2, 56% for two steps; d) $MgBr_2$, ether/THF, 90%; e) K_2CO_3, BnBr, Acetone, 95%; f) TMSCN, KCN, 18-C-6, CH_2Cl_2, then AcOH, 92%. NIS = *N*-iodosuccinimide; MOMCl = chloromethyl methyl ether.

inseparable mixture that contained the desired *o*-iodophenol as the major product together with undesired *p*-iodophenol and *o,p*-bis-iodophenol, as well as some recovered starting material. Gratifyingly, converting this mixture of phenols to their corresponding MOM ethers gave a separable mixture[16] from which desired product **13** was isolated in 56% yield over two steps. Similarly, magnesium bromide mediated deprotection of methoxymethyl ether of **13**, followed by reprotection of the resulting phenol as its benzyl ether, provided desired product **14**. Finally, cyanophthalide **9** was prepared from **14** in 92% yield following a known two-step procedure.[17]

Next, complex enone **10** was prepared through a modification of a previously reported synthetic approach.[9b] As shown in Scheme 3, halogen–lithium exchange of alkenyl bromide **16**, derived from known chiral (*R*)-2-bromo-cyclohex-2-en-1-ol **15**,[18] provided desired alkenyl lithium, which subsequently reacted with known chiral epoxide **17**[19] in the presence of boron trifluoride diethyl etherate to afford tertiary alcohol **18** in 71% yield.[20] Deprotonation of the tertiary alcohol of **18** by potassium hydride in DMF, followed by addition of benzyl bromide and a catalytic amount of tetra-*n*-butylammonium iodide, provided corresponding benzyl ether **19**, which underwent deprotection of *p*-methoxyphenyl (PMP) ether and reprotection of the resulting primary alcohol to furnish **20**. This change of protecting group was necessary to avoid the complication of oxidative deprotection of *p*-methoxyphenyl ether at a late stage. Next, osmium-catalyzed dihydroxlation[21] of **20** gave a mixture of diol **21** and its minor diastereomer (d.r. = 4.3:1) from which **21** was isolated in 75% yield. It is worth noting that, without quinuclidine as additive,[21] this dihydroxylation required prolonged reaction time and higher catalyst loading and afforded **21** in lower yield. Deprotection of the MOM ether of **21**[22] followed by selective protection of the *cis*-diol as the acetonide afforded alcohol **22**. Swern oxidation of the secondary alcohol of **22** provided desired ketone **23**, which was then converted to enone **10** following a well-established procedure[9b] that involves: 1) enolization of the ketone of **23** followed by addition of allyl chloroformate to form the corresponding allyl enol carbonate; and 2) a Saegusa-type palladium-mediated oxidation[23] of this carbonate to the enone **10**. Next, a Hauser annulation[9c,11] between cyanophthalide **9** and complex enone **10**, employing lithium *tert*-butoxide as a base, gave rise to the desired tricyclic hydroquinone, which was found to be unstable and immediately methylated to afford tricyclic compound **24**. Due to the instability of the tricyclic hydroquinone intermediate and difficulty in handling, tricyclic compound **24** was produced in a range of yields from 60–87% for two steps. Removal of the TBDPS ether of **24** followed by Swern oxidation of the resulting primary alcohol afforded the aldehyde **25**, which was quickly subjected to Pedersen-modified pinacol coupling[24] and subsequent Swern oxidation of the resulting secondary alcohol to provide tetracycle **26**. It is worth noting that our attempts to directly convert **25** to **26** using *N*-heterocyclic carbene-catalyzed intramolecular aldehyde–ketone benzoin condensation[25] were unfruitful. Finally, deprotection of the acetonide of **26** gave rise to the complex tetracyclic aryliodide **8**. The structure of tetracycle **8** was unambiguously confirmed by single-crystal X-ray crystallographic analysis (Scheme 3).[26]

With tetracyclic aryliodide **8** in hand, we sought to prepare its cross-coupling partner, glycal stannane **7**. As shown in Scheme 4, known D-rhamnal-derived glycal stannane **27**[13a] was subjected to silyl ether deprotection followed by regioselective silyl protection to provide mono-silyl ether **28**. Benzylation of the C4-OH of compound **28** afforded desired glycal stannane **7** in 70% yield over three steps. In order to obtain disaccharide donor **5**, stereoselective glycosylation[27] between 2,6-dideoxy-2-iodo-D-glucopyranosyl trifluoroacetimidate donor **29**[28,29] and L-rhodinose-derived acceptor **30**[30] was first carried out to furnish desired β-linked disaccharide **31** in 93% yield. Next, radical-mediated reductive deiodination of disaccharide **31** followed by DDQ-mediated oxidative removal of PMB ether and subsequent acetylation of the anomeric hydroxy group afforded desired disaccharide donor **5**.

With all the fragments in hand, we executed the remaining studies for the completion of synthesis of derhodinosylurdamycin A. Thus, standard Stille coupling of glycal stannane **7** and aryl iodide **8** followed by mesylation of the secondary alcohol afforded desired product **32** (Scheme 5). Next, a one-pot stereoselective reduction[13] of the cyclic enol ether of **32** using $NaCNBH_3$ and HCl under carefully controlled pH and concomitant removal of the TBS ether afforded desired complex β-C-arylglycoside acceptor **6**.[31] Next, *tert*-butyldimethylsilyl trifluor-



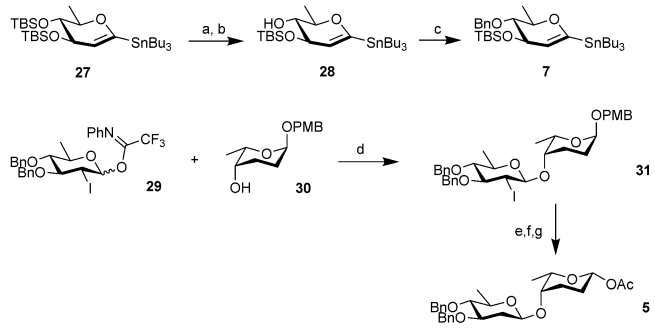
X-ray structure of **8**

Scheme 3. Reagents and conditions: a) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 99%; b) *n*BuLi, −70 °C, THF, then **17**, BF_3·Et_2O, −78 °C, 71%; c) KH, BnBr, cat. Bu_4NI, DMF, 0 °C, 90%; d) CAN, CH_3CN, −15 °C; e) TBDPSCl, imidazole, DMF, 93% for two steps; f) K_2OsO_4·2H_2O, K_2CO_3, $K_3Fe(CN)_6$, methane sulfonamide, quinuclidine, 75%; g) $ZnCl_2$, octane thiol, CH_2Cl_2; h) dimethoxypropane, cat. CSA, 69% for two steps; i) $(COCl)_2$, DMSO, −78 °C, then Et_3N, CH_2Cl_2, 81%; j) KHMDS, −78 °C to −40 °C, 30 min; then allyl chloroformate, −78 °C, THF; k) $Pd(OAc)_2$, CH_3CN, 73% for two steps; l) i) **9**, *t*BuOLi, THF, −78 °C, then **10**, −78 °C to 45 °C; ii) K_2CO_3, $(MeO)_2SO_2$, acetone, reflux, 60–87% for two steps; m) TBAF, THF; n) $(COCl)_2$, DMSO, −78 °C, then Et_3N, CH_2Cl_2, 76% for two steps; o) $VCl_3(thf)_3$, Zn, DMF, CH_2Cl_2, 84%; p) $(COCl)_2$, DMSO, −78 °C, then Et_3N, CH_2Cl_2, 86%; q) 5% H_2SO_4, 1,4-dioxane, quantitative. CAN = cerium ammonium nitrate; CSA = camphorsulfonic acid; DMF = *N*,*N*-dimethylformamide; KHMDS = potassium hexamethyldisilazide; TBDPS = *tert*-butyldiphenylsilyl.

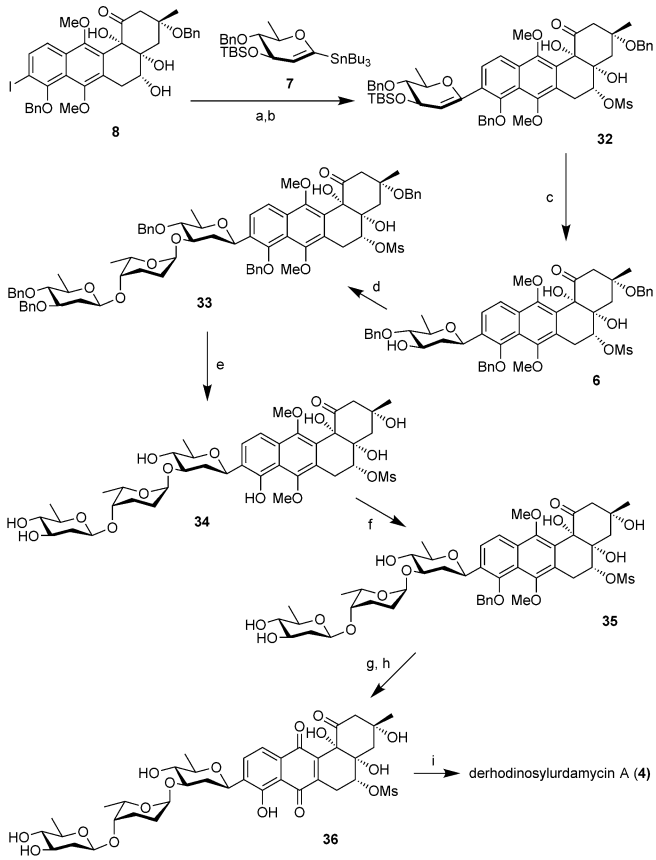
omethanesulfonate-catalyzed stereoselective glycosylation between disaccharide-derived donor **5** and complex acceptor **6** gave rise to the partially protected derhodinosylurdamycin A skeleton **33**. However, subsequent global deprotection of benzyl ethers of **33** was found not to be an easy task. In fact, hydrogenolysis of **33** under hydrogen balloon in the presence of high-loading catalyst Pd/C (up to 50 mol%) did not go to completion even after a week and afforded desired product **34** in poor yield. After several attempts, finally it was found that, by increasing the hydrogen pressure to 40 psi, this palladium-catalyzed hydrogenolysis of **33** in EtOAc/MeOH co-solvent was completed in two days and desired product **34** was produced in 91% yield. To prepare the final target, derhodinosylurdamycin A, the methylated hydroquinone moiety of **34** had to be oxidized to the corresponding quinone. Due to the susceptibility of phenol of **34** to oxidation,[9c] this phenol was first selectively benzylated in the presence other aliphatic alcohols to afford **35** in 91% yield. Treatment of compound **35** with cerium ammonium nitrate at 0 °C for eight minutes followed by simple work-up using ice-cold sodium bicarbonate afforded corresponding quinone, which was found to be unstable. This quinone was then immediately subjected to a quick Pd/C-catayzed hydrogenation to remove the phenolic benzyl ether.[26] During this hydrogenolysis the quinone was also reduced to hydroquinone, which was readily oxidized back to quinone **36** after exposure to the air. Finally, *N*,*N*-diisopropylethylamine-mediated elimination of the mesylate of complex intermediate **36** afforded the final target, derhodinosylurdamycin A (**4**) in 77% over three steps.[26]

As described above, converting **33** to **36** required repetitive protection/deprotection and redox reactions. A potentially more efficient route to transform **33** to **36** may involve: 1) oxidation of the methylated hydroquinone to quinone; 2) global debenzylation through Pd/C-catalyzed hydrogenolysis followed by reoxidation of the in situ formed hydroquinone. In fact, oxidation of methylated hydroquinone of **33** did furnish the desired corresponding quinone; however, this quinone was highly susceptible to facile elimination of the mesylate.[9c] In addition, global debenzylation of this quinone under forcing hydrogenolysis conditions was found to be problematic.

In conclusion, we have reported the first total synthesis of antitumor antibiotic derhodinosylurdamycin A (1.8% overall yield, calculated based on 29 linear steps from commercially available starting materials). Key reactions involve a Hauser an-



Scheme 4. Reagents and conditions: a) TBAF, THF; b) TBSCl, Et_3N, CH_2Cl_2; c) BnBr, NaH, DMF, 70% over three steps; d) TBSOTf, CH_2Cl_2, −78 °C, 93% e) AIBN, Bu_3SnH, toluene, 85%; f) DDQ, pH 7 buffer, CH_2Cl_2, 65%; g) Ac_2O, Et_3N, CH_2Cl_2, 96%; DMF = *N*,*N*-dimethylformamide; AIBN = azobisisobutyronitrile; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



Scheme 5. Reagents and conditions: a) 20 mol% $Pd(PPh_3)_2Cl_2$, toluene, 85%; b) MsCl, pyridine, 95%; c) 0.5 M HCl in MeOH, $NaCNBH_3$, bromocresol green, EtOH, 69%; d) **5**, TBSOTf, −78 °C, CH_2Cl_2, 81%; e) Pd/C, H_2 (40 psi), EtOAc/MeOH, 91%; f) Cs_2CO_3, BnBr, DMF, 91%; g) CAN, CH_3CN, 0 °C; h) Pd/C, H_2, EtOAc/MeOH, then air; i) iPr_2NEt, 1,4-dioxane, 80 °C, 77% over three steps; DMF = *N*,*N*-dimethylformamide; CAN = cerium ammonium nitrate.

nulation to construct the tricyclic core, a Pinacol coupling to close the fourth angular ring, a Stille coupling of glycal stannane and aryl iodide followed by stereoselective reduction to access the β-C-arylglycoside, and a late-stage stereoselective glycosylation for the preparation of derhodinosylurdamycin A. Application of this synthetic strategy to the synthesis of derhodinosylurdamycin A analogs bearing diverse sugar subunits and evaluation of their structure and activity relationship are currently under way and will be reported in due course.

Acknowledgements

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Keywords: 2-deoxy sugars · antitumor antibiotic · derhodinosylurdamycin A · total synthesis · urdamycin

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[31] We also prepared a disaccharide-derived glycal stannane containing an additional α-L-rhodinose on the O-3 of glycal stannane **7**. Although the corresponding Stille coupling worked well, subsequent stereoselective reduction of the cyclic enol ether using $NaCNBH_3$ and HCl caused severe cleavage of the L-rhodinose.

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