Studies Towards the Synthesis of Medermycin via Dötz Benzannulation

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ABSTRACT The *C*-arylglycosides are available in enantiomerically pure form via the Dötz benzannulation reaction between Fischer alkenyl chromium carbene complexes and alkynes; it also could be converted to a precursor of medermycin by *O*-carbamate directed *ipso* bromination and nitrile substitution in good overall yields. *Chirality 00:000–000, 2014.*

KEY WORDS: Streptomyces sp; Dötz benzannulation; C-arylglycoside; Fischer carbene complex; ipso bromination

INTRODUCTION

The *C*-arylglycosides are carbohydrate derivatives whose anomeric centers are directly bonded to a mono- or polycyclic aromatic moiety through a carbon–carbon bond.[1] The C-C bond in *C*-arylglycosides is stable to acid hydrolysis, which makes *C*-arylglycosides much more stable than *O*-arylglycosides. Up to now, more than 20 naturally occurring C-arylglycosides have been isolated.[2] Such compounds exhibit a diversity of biological activities including antitumor, antibacterial, and antifungal properties.[3–5] Their importance in medicinal chemistry and limited availability have brought enormous attention to their synthesis in the recent past.[6,7]

Medermycin (**1**) (Fig. 1) is a unique member of the pyranonaphthoquinone family of antibiotics containing a β-*C*-glycoside linkage to an aminosugar, D-angolosamine, which was first isolated from *Streptomyces* sp. by Takano et al. in 1976.[8] Biological evaluation of medermycin showed that it has strong activity against Gram-positive organisms including many species of *Staphylococcus* and *Bacillus*.[9] Medermycin can also inhibit human leukemia K-562 cells and platelet aggregation,[9] making it of interest as a leading target for synthesis. Since its reported isolation, several analog syntheses[10–15] and one total synthesis[16] of medermycin have appeared in the literature.

We have successfully developed a new methodology for the synthesis of *C*-arylglycosides via a Dötz benzannulation reaction.[17,18] The reaction of *C*-alkyne glycoside **2** with vinyl TMS carbene complex afforded *C*-arylglycoside **4** in 56% yield (Scheme 1). The results showed that regioselective oxidation for the larger group of an unsymmetrical alkyne *ortho* to the phenolic hydroxyl group is consistent with the orientation of the naturally occurring *C*-arylglycosides such as medermycin. We applied this Dötz benzannulation strategy, formally a [3 + 2 + 1] cycloaddition, to the total syntheses of (*S, S*)-isodityrosine[19] and shikonin.[20]

In an effort to expand the scope of this process, we decided to explore the synthesis of medermycin using our methodology to construct the core ring of the *C*-arylglycoside of the target. A retrosynthesis based on this approach is shown in Scheme 2.

MATERIALS AND METHODS

All air- and moisture-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Reactive liquid compounds were measured and transferred by gas-tight syringes and added to the reaction flask through rubber septa. Moisture-sensitive and hygroscopic solid compounds were transferred under a nitrogen atmosphere in a glove bag. The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residual solvents were usually removed under reduced pressure using a vacuum pump. Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel plates with an F_{254} indicator. Compounds were visualized under a UV lamp or by developing in iodine, vanillin, phosphomolybdic acid solution or with a potassium permanganate solution followed by heating on a hotplate to ~350 °C. Flash chromatography was performed on 230–400 mesh silica gel with technical grade solvents which were distilled prior to use. ^{1}H NMR spectra were recorded on a Brüker (Billerica, MA) AMX-250, Brüker AMX-300, Brüker AMX-500 at 250, 300, or 500 MHz, respectively, as $CDCl_3$ solutions with tetramethylsilane (δ = 0 ppm) as the internal standard. ^{13}C spectra were obtained on the same instruments at 62.5, 75, or 125 MHz, respectively, with $CDCl_3$ (δ = 77 ppm) as the internal reference. Chemical shifts are reported in parts per million (ppm). Multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), etc. Infrared spectra were recorded on a Thermo Nicolet NEXUX 670 FT-IR spectrometer as neat liquids with NaCl cells. Melting points were determined using a Fisher-Johns Hot Stage melting point apparatus and were uncorrected. Optical rotations were measured on a Jasco DIP-370 digital polarimeter.

Preparation of aryl bromide 15e. To a solution of **9e** (380 mg, 0.59 mmol) in 12 mL distilled DMF, NBS (350 mg, 1.97 mmol) was added. The solution was stirred for 12 h. Then the reaction mixture was put on the vacuum to remove DMF and purified via flash chromatography (10% EtOAc/Hexane) which gave 288 mg (75%) of the aryl bromide **15e**. $[\alpha]^{20}_D = -2.63$; ^{1}H NMR (300 MHz, $CDCl_3$):

Contract grant sponsor: National Natural Science Foundation of China; Contract grant numbers: 81373254 and 21390402
Contract grant sponsor: National Institutes of Health (SP), NIGMS; Contract grant number: GM59350-01
Contract grant sponsor: National Science and Technology Major Project of the Ministry of Science and Technology of China; Contract grant number: 2012ZX10004801-003-011
Contract grant sponsor: Key Project of Chinese Ministry of Education; Contract grant number: 313040
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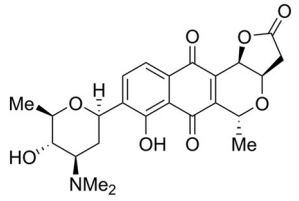
Dedicated to the memory of Professor Richard Loeppky. Deceased April 21, 2012.
Received for publication 3 April 2014; Accepted 4 August 2014
DOI: 10.1002/chir.22383
Published online in Wiley Online Library (wileyonlinelibrary.com).



Medermycin (**1**)

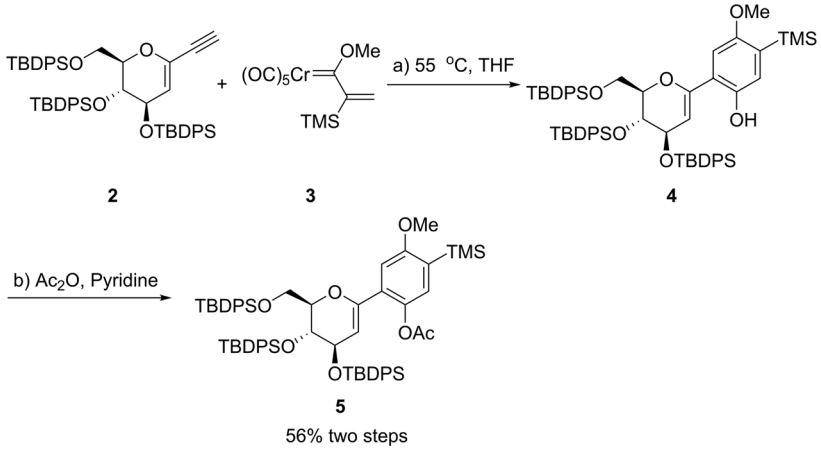
Fig. 1. Structure of medermycin.

δ = 7.29 (s, 3H), 7.00 (s, 1H), 4.63 (d, *J* = 11.2 Hz, 2H), 3.79 (s, 3H), 3.73-3.48 (m, 1H), 3.48-3.34 (m, 5H), 3.20 (t, *J* = 3.1 Hz, 1H), 2.30 (dd, *J* = 12.9 Hz, 1H), 1.46-1.84 (m, 10H), 0.91-0.89 (m, 18H), 0.12-0.07 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 152.9, 142.6, 131.2, 121.3, 114.5, 114.4, 78.3, 77.1, 74.7, 71.2, 55.7, 42.2, 41.8, 41.4, 26.2, 26.0, 19.0, 18.2, 18.0, 14.1, 13.2, -2.8, -3.0, –4.0, –4.3 ppm. IR (neat): 2945, 2841, 2337, 1770, 1543, 1482, 1102. HRMS: m/z calc'd for $C_{30}H_{54}NO_6Si_2{}^{79}BrLi$, $[M+Li]^+$ 666.2833, found 666.2862.

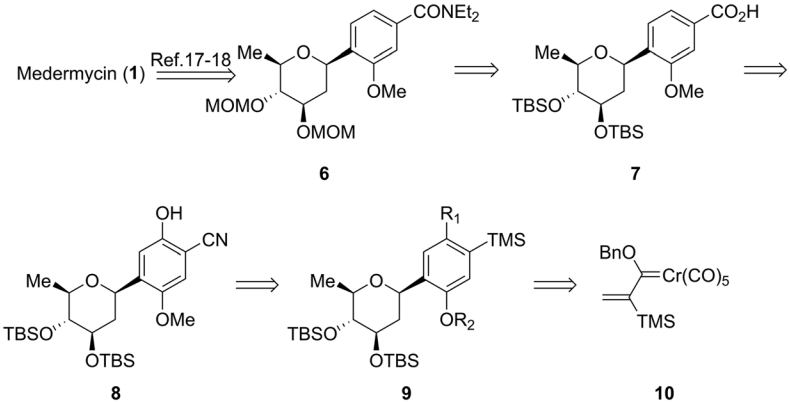
Preparation of *o*-carbamate protected aryl nitrile 21. Compound **15e** (50 mg, 0.76 mmol) was dissolved in 5 mL distilled DMF. Then 16 mg CuCN was added. The solution was heated to 160 °C and kept at that temperature for 12 h. After the solution was cooled, the reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with $MgSO_4$, Flash chromatography gave 45 mg of the desired product **21** (98%). $[\alpha]^{20}{}_D$ = 7.32; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (s, 1H), 6.99 (s, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 3.82 (m, 4H), 3.50-3.38 (m, 5H), 3.21-3.19 (m, 1H), 2.42 (d, *J* = 12.0 Hz, 1H), 1.31-1.22 (m, 1H), 0.91-0.88 (m, 18H), 0.12-0.1 (m, 12H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 153.0, 152.3, 147.7, 137.8, 121.4, 115.7, 112.9, 105.2, 78.2, 77.2, 74.6, 71.3, 55.8, 42.5, 42.1, 41.1, 26.2, 26.1, 19.0, 18.3, 18.0, 14.1, 13.2, –2.8, –3.0, –4.0, –4.3 ppm. IR (neat): 2947, 2861, 2236, 1736, 1400, 1123. HRMS: m/z calc'd for $C_{31}H_{54}N_2O_6Si_2Li$, $[M+Li]^+$ 613.3680, found 613.3673.

Preparation of phenol 8. *O*-Carbamate protected aryl nitrile **21** (45 mg) was dissolved in 8 mL of EtOH and then 40 mg of NaOH was added. The solution was heated to reflux and stirred for 14 h. After the solution was cooled, the solvent was evaporated. Then water (5 mL) was added and CH_2Cl_2 (5 mL) was added to the residue and separated. The water layer was extracted with another three portions of CH_2Cl_2, and the organic layer was combined and dried with $MgSO_4$ and then concentrated. Flash chromatography gave 25 mg of the desired product **8** (67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (s, 1H), 6.85 (s, 1H), 4.66 (d, *J* = 11.0 Hz, 1H), 3.78-3.73 (m, 4H), 3.42-3.37 (s, 1H), 3.18 (t, *J* = 8.4 Hz, 1H), 2.32 (dd, *J* = 12.8, 7.1 Hz, 1H), 1.37-1.23 (m, 4H), 0.91-0.89 (m, 18H), 0.12-0.08 (m, 12H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) : δ = 152.9, 149.3, 138.8, 114.6, 112.4, 97.2, 78.3, 77.2, 74.6, 71.2, 55.8, 41.2, 26.2, 26.0, 19.0, 18.3, 18.0, –2.7, –3.0, –4.0, –4.3 ppm. HRMS: m/z calc'd for $C_{26}H_{44}NO_5Si_2^-$, $[M-H]^-$ 506.2764, found 506.2784.

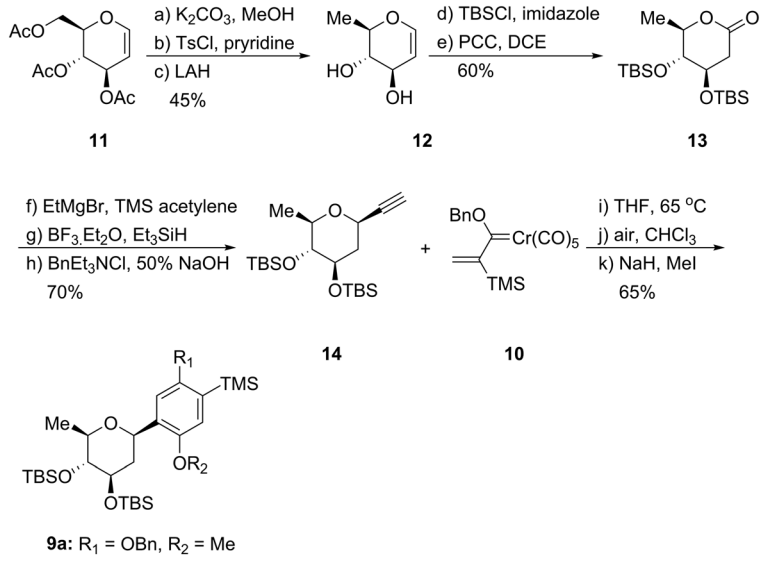
Preparation of deoxygenated nitrile 22. A solution of phenol **8** (13 mg, 0.04 mmol) in 1 mL CH_2Cl_2 at 0 °C was treated with pyridine (10 μL) and the solution was stirred for 15 min, after which was added Tf_2O (30 μL). The reaction was monitored by TLC and completed after half an hour, at which time it was poured into sat. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was combined and dried with $MgSO_4$, then concentrated. Flash chromatography gave 11 mg of the desired triflate (66.9% yield). To a solution of the triflate (10 mg, 0.0156 mmol)



Scheme 1. *C*-Arylglycosides via a benzannulation mediated by Fischer chromium carbene complexes.



Scheme 2. Retrosynthesis of medermycin.



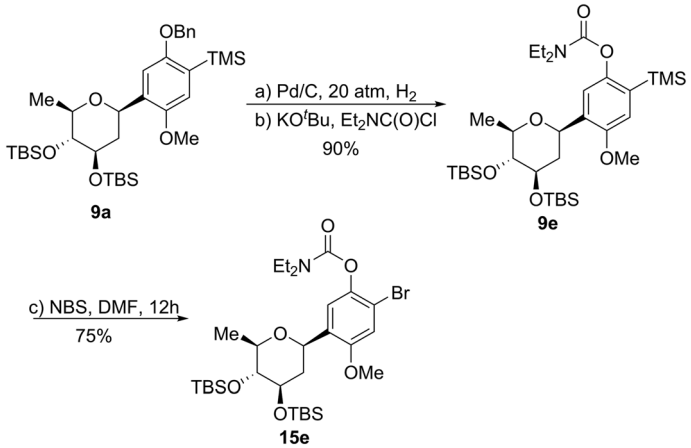
Scheme 3. Synthesis of *C*-arylglycoside **9a**.

in 1 mL DMF was added $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), dppf (8.8 mg, 0.016 mmol), TEA (15 μL, 0.106 mmol), HCO_2H (3.0 μL, 0.091 mmol). Then the solution was warmed to 70 °C and stirred for 0.5 h. Filtration through SiO_2 to remove baseline material gave 7 mg (91%) of the desired deoxygenated nitrile **22**. $[\alpha]^{20}_D$ = 27.06. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.8 Hz, 1H), 7.28 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.05 (d, *J* = 1.4 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 3.84 (s, 1H), 3.82-3.74 (m, 1H), 3.50-3.34 (m, 1H), 3.2 (t, *J* = 8.38 Hz, 1H), 2.13 (ddd, *J* = 13.0, 6.0, 3.0 Hz, 1H),1.37-1.30 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.92-0.90 (m, 18H), 0.13-0.08 (m, 12H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 137.3, 127.6, 119.8, 113.8, 112.1, 79.1, 75.5, 72.1, 56.3, 42.1, 27.1, 26.9, 19.9, 19.1, 10.9, –1.9, –2.2, –3.1, –3.4. IR (neat): 2966, 2907, 2861, 2242, 1729, 1584, 1477, 1400, 1255, 1104 ppm. HRMS: m/z calc'd for $C_{26}H_{47}NO_4Si_2H$, $[M+H]^+$ 492.2965, found 492.2979.

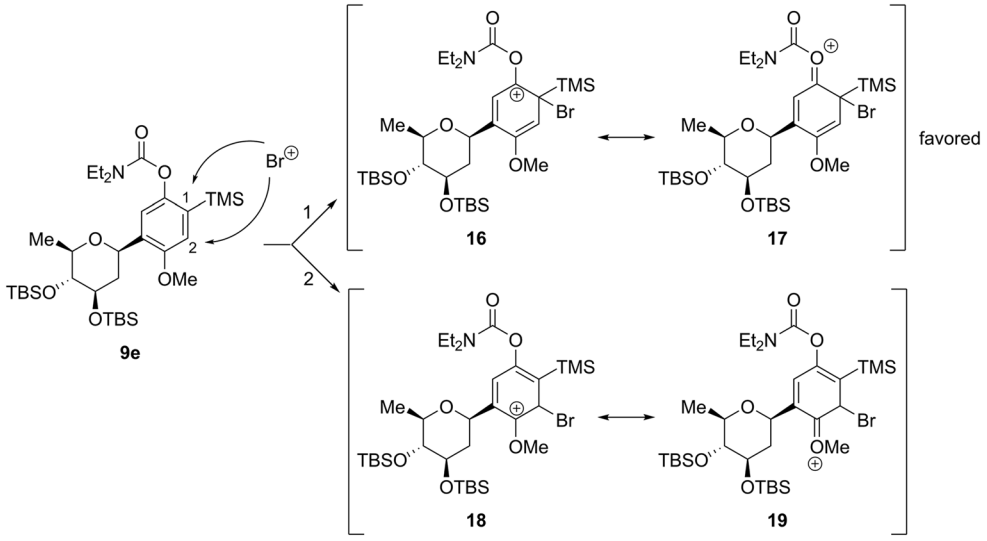
TABLE 1. *Ipso* Bromination of compound 9

Entry	Aryl TMS (**9**)	R_1	R_2	Bromide(**15**)	Yield (%)
1	**9a**	OBn	Me	**15a**	12
2	**9b**	H	Me	**15b**	Trace
3	**9c**	H	Ac	**15c**	40
4	**9d**	OH	Ac	**15d**	31

Preparation of aryl carboxylic acid 7. To a solution of deoxygenated nitrile **22** (49.6 mg, 0.101 mmol), 1 M DIBAL-H solution in hexane (400 μL, 0.4 mmol) was added at the temperature of –70 °C. It was then allowed to warm up slowly to room temperature for 2 h and stirred for another 12 h. NH_4Cl solution (2 mL) was added and the reaction mixture was stirred for another 2 h. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was combined and dried with $MgSO_4$, and then concentrated to give the crude aldehyde. The crude aldehyde was taken up in 10 mL of a 1:1 solution of CH_3CN and *t*-BuOH and 40 drops of 2-methyl-2-butene was added. To this solution, 50 mg of NaH_2PO_4 and 40 mg of $NaClO_2$ in 2 mL of water were added. The mixture was vigorously stirred for 20 min at room temperature and then extracted with EtOAc (15 mL) three times. The organic layer was dried by $MgSO_4$ and concentrated. Flash chromatography gave 42 mg of the desired acid **7** (82% yield). $[\alpha]^{20}_D$ = 28.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.9, 1.5 Hz, 1H), 7.59-7.55 (m, 2H), 4.75 (d, *J* = 12.5 Hz, 1H), 3.88 (s, 3H), 3.50-3.35 (m, 1H), 3.22 (t, *J* = 8.3 Hz, 1H), 2.40-2.29 (m, 1H),1.40-1.20 (m, 4H), 0.92-0.90 (m, 18H), 0.13-0.08 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 136.9, 128.7, 125.9, 123.0, 111.1, 78.4, 77.2, 74.7, 71.5, 55.3, 41.4, 26.2, 26.0, 19.1, 18.3, 18.0, –2.8, –3.0, –4.0, –4.3 ppm. IR (neat): 3421, 2967, 2866, 1693, 1584, 1466, 1116. HRMS: m/z calc'd for $C_{26}H_{48}O_6Si_2$, $[M-H]^-$ 511.2911, found 511.2887.



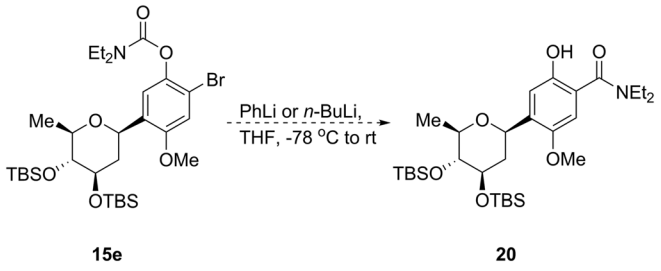
Scheme 4. *Ipso* Bromination of compound **9e**.



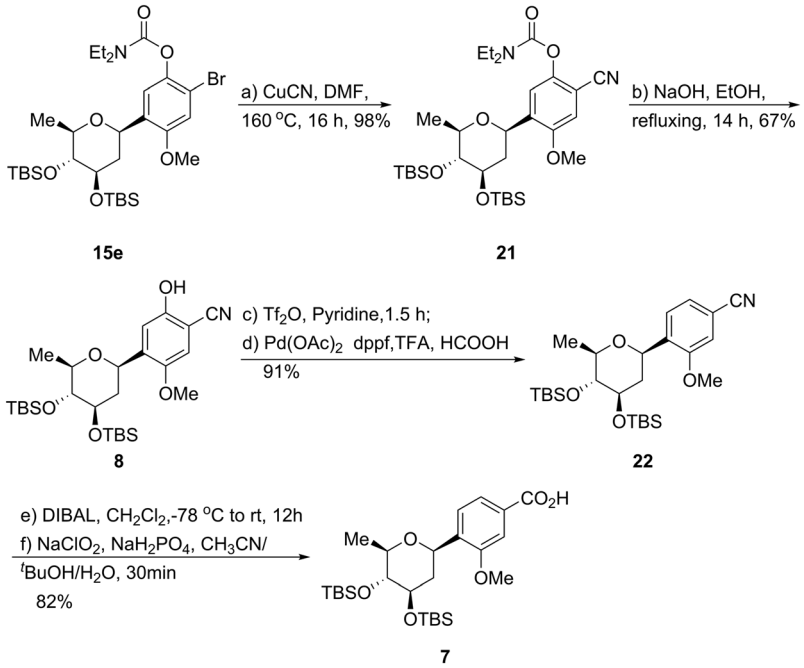
Scheme 5. Explanation of the regioselectivity.

RESULTS AND DISCUSSION

The *C*-arylglycoside **9a** (R_1 = OBn, R_2 = Me) needed for this process was prepared as shown in Scheme 3. The synthesis started with 3, 4, 6-*O*-acetyl D-glucal **11**. Nicolaou's method was employed to synthesize the D-rhamnal **12** in three steps in 45% overall yield.[21] The D-rhamnal **12** is protected by TBS group under standard conditions. Then PCC oxidation gives lactone **13**. Addition of the Grignard acetylide to lactone and the subsequent reductive deoxygenation and selective desilylation under phase transfer conditions gave the desired the C-alkyne glycoside **14** in 70% yield in stereocontrol. With the desired C-alkyne glycoside **14** in hand, the Dötz benzannulation reaction proceeded under standard conditions to give the chromium arene complex, which was air-oxidized to the desired free phenol. The standard Williamson conditions (NaH, MeI) successfully methylated the phenol to give the *C*-arylglycoside **9a** in 65% yield.



Scheme 6. "Metallo-Fries" attempt of 2-lithio-phenol derivatives.



Scheme 7. Final steps for the synthesis of core intermediate **7**.

The next challenge involved the *ipso* halogenation of the TMS-group in compound **9**. Bromination of **9a** and deoxygenated aryl TMS **9b** using NBS in DMF gave the desired aryl bromide product **15a** and **15b** in 12% yield and a trace amount, respectively (Table 1, entries 1–2). The major product isolated is the electrophilic bromination product without the desilylation. When the acetyl group was chosen as the protective group for the phenol to decrease the *ortho* directing effect of OR_2 group the best yield was improved to 40% (Table 1, entries 3–4). A possible way to improve the yields of *ipso* bromination is to increase the directing ability of the R_1 group of compound **9** to compete with methoxy group. Possibly, H, OH, and OBn are not very strong *ortho* directing groups, which is responsible for the low yield.[22] Thus, the *O*-carbamate was chosen as the protecting group for the hydroxyl group *meta* to the sugar. Fortunately, bromination of *O*-carbomate protected aryl TMS compound **9e** with NBS (3.0 equiv.) in 12 h resulted in the formation of the expected aryl bromide **15e** in 75% yield (Scheme 4).

A reasonable explanation is that the large conjugate π system gave extra stability for the intermediate **16** compared to **18** (Scheme 5); therefore, the reaction prefers to go through pathway 1 to get the *ipso* bromination/desilylation product **15e**. Also, the other *ortho* position is sterically hindered by the sugar moiety and the carbamate so that it cannot be attacked by bromine cation (Scheme 6). The metallation reaction on *O*-carbamate protected aryl bromide **15e** was attempted. The dehalogenated product was obtained as the major product along with a trace amount of **20** by crude NMR analysis.

The completion of the desired intermediate **7** is outlined in Scheme 7. The aryl bromide **15e** reacted with CuCN in refluxing DMF to afford the nitrile **21** in 98% yield. The basic condition was used to deprotect the carbamate group of the nitrile **21** with 67% yield. The corresponding phenol **8** reacted with Tf_2O and pyridine to give the aryl triflate, which can be deoxygenated by Pd catalyst, affording aryl nitrile **22** in 91% yield. The direct transformation of the aryl nitrile **22** to acid **7** failed. A possible reason is that the acid conditions under high temperature caused the decomposition of the pyran ring. Finally, the core acid **7** was synthesized in 82% yield with a reduction-oxidation two-step sequence which could be converted to medermycin.

CONCLUSION

In conclusion, we have successfully completed the optically purity core intermediate **7** of medermycin. The present synthesis features a novel benzannulation strategy to construct the C-O ether linkage. The amicable reaction conditions make it a versatile approach to the synthesis of other related naturally occurring C-aryl glycosides.

ACKNOWLEDGMENTS

This work was supported, in part, by the National Natural Science Foundation of China 81373254 and 21390402 (XH), the National Institutes of Health (SP), NIGMS Grant GM59350-01, the University of Missouri, Monsanto, the National Science and Technology Major Project of the Ministry of Science and Technology of China No. 2012ZX10004801-003-011 (XH), Key Project of Chinese Ministry of Education No. 313040 (XH),the Fundamental Research Funds for the Central Universities (CQ) and Innovation Seed Fund of Wuhan University School of Medicine (XH).

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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