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Noteworthy observations accompanying synthesis of the apoptolidin disaccharide†

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A stereoselective synthesis of the apoptolidin disaccharide is reported. The key chemistry features a new transformation utilizing a highly selective tetramethylalkoxyalanate[v]-directed *syn*-methylation of a vinylogous ester, isolation of a hydrate of a 2-keto sugar, an eco-friendly radical cleavage of a bromomethyl group, and an efficient preparation of a fluorodisaccharide *via* the use of XtalFluor-E.

Apoptolidin A **1** is a complex natural product isolated from *Nocardiopsis sp.* by Seto and co-workers in 1997.[1,2] Apoptolidin A **1** shows anti-proliferative activity towards various cancer cell lines studied by the National Cancer Institute. Several structural congeners were isolated by Wender,[3] which demonstrated comparable biological activity. Three total syntheses[4] and several preparations of the disaccharide units have been reported.[5] Apoptolidin consists of a 20-membered macrolactone coupled with a side chain containing a cyclic hemiketal. 6-Deoxy-4-*O*-methyl-*l*-glucose is attached to O9 and a disaccharide consisting of *l*-olivomycose and *d*-oleandrose is linked to O27. Studies by Khosla revealed F0F1-ATPase as the possible biological target of Apoptolidin. Although oleandrose and olivomycose sugars in apoptolidin are not absolutely essential to the binding of apoptolidin to this target, they are crucial for cellular activity.[6] Apoptolidin D[3c] **2** is the C-6-*des*-methylated analogue of Apoptolidin A **1**. Our synthetic efforts are focused on the synthesis of Apoptolidin A and D and the SAR of the three additional C19,20 diastereomers thereof.[7]

Apoptolidins A and D were to be prepared from glycosylation of **3** using sugars **4** and **5** (Fig. 1). Sugar **4** is a synthon for 6-deoxy-4-*O*-methyl-*l*-glucose moiety found at O-9, and glycosyl fluoride **5** is a synthon for the disaccharide containing *l*-olivomycose and *d*-oleandrose, found at O-27. Glycosidic donor **5** was to be prepared from disaccharide **6**. The synthesis of **6** envisaged β-selective ester-directed glycosylation of sugars **7** and **8** (Fig. 2). Sugar **7** was to be prepared from L-rhamnose. Sugar **8** was envisioned to arise from methyl-D-glucopyranose which has three of the five required stereogenic centers.

L-Rhamnose was converted to known intermediate **9** in 3 steps and 95% yield.[8] Deacetylation provided diol **10** in 96% yield. Oxidation of **10** with pyridinium dichromate[9] afforded key vinylogous ester **11** (Scheme 1). Treatment of **11** with methyllithium generated a mixture of *syn*- and *anti*-methyl adducts in a 1.5 : 1 ratio. The combination of dimethylzinc and methyllithium improved the ratio to 3 : 1. Treating **11** with one equivalent of trimethylaluminium at −78 °C followed by *one equivalent* of methyllithium gave better selectivity (7.5 : 1 ratio). High yield and outstanding selectivity (50 : 1) for synthesis of **12-*syn*** were obtained by treating **11** with one equivalent of trimethylaluminium at −78 °C followed by *two equivalents* of methyllithium (Table 1). This new strategy is superior to the alternative methylation protocols employed by various groups[10] and later adopted by Koert[4a] and Roush[5c] in their syntheses of apoptolidin. The structure of **12-*syn*** was confirmed by X-ray crystallography.

Based upon the well-known delivery of hydride to proximal ketones *via* hydridoalkoxyalanate[IV] intermediates,[11] reaction of Me_3Al with alcohol **12-*syn*** to form the alkoxyalane[III] followed by addition one equivalent of MeLi to presumably formed trimethylalkoxyalanate[IV] **13a**[12,13] which intramolecularly transferred methyl to the ketone carbonyl from alpha face with 7.5 : 1 selectivity (Scheme 1). While pentaalkyl aluminium[V] species are known,[14] computer searches reveal

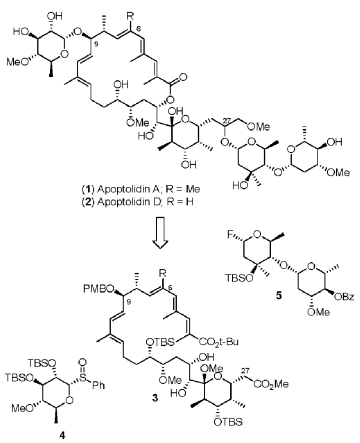

Fig. 1 Retrosynthesis for apoptolidin A and D.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds along with copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c1cc11448d

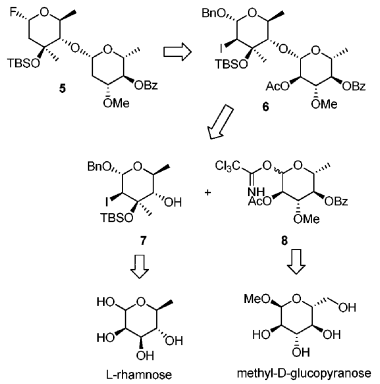
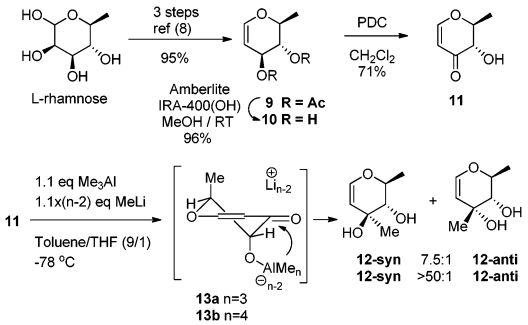


Fig. 2 Acetate-directed glycosylation strategy for the synthesis of **5**.

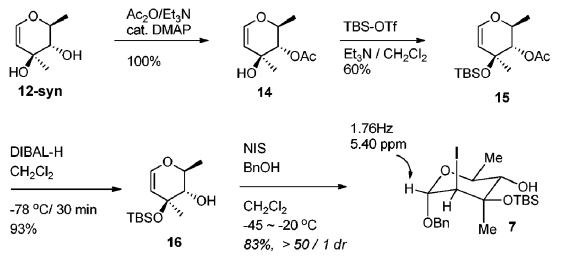


Scheme 1 Synthesis and methylation of vinylogous ester **11**.

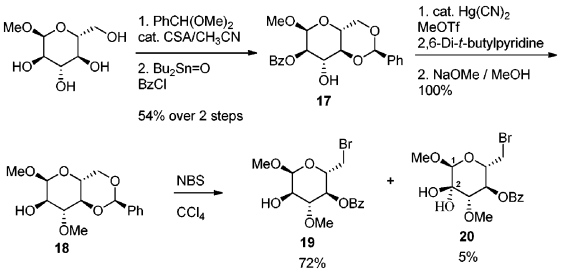
no examples of dianionic alkoxyteteraalkyl species such as **13b** which is tentatively proposed to explain the exquisite $>50:1$ **12-*syn*/12-*anti*** selectivity observed in the reaction adding two equivalents of methyl lithium to the alkoxyalane preformed from **11**.

Diol **12-*syn*** was converted to acetate **14** in quantitative yield. Tert-alcohol **14** was protected as silyl ether **15**. Acetate **15** was reduced to alcohol **16** using DIBAL-H.[4a] Finally, iodoglycosylation of **16** with benzyl alcohol provided **7** in 83% yield and excellent α-selectivity, completing the synthesis of olivomycose sugar in 24% yield over 10 steps from L-rhamnose (Scheme 2).[15]

Synthesis of *d*-oleandrose sugar began from methyl D-glucopyranoside. Protection of 1,3-diol followed by benzoylation provided **17** in 67% over 2 steps (Scheme 3). Methylation of free alcohol in **17** followed by the deprotection of benzoyl ester gave **18** in quantitative yield over 2 steps. Hanessian-Hullar reaction[16] of benzylidene **18** provided bromide **19**[17] along with ketone-hydrate **20** which is produced *via* hypobromide oxidation[18] and hydration. The literature reveals that other 2-oxo-sugars are susceptible to forming hydrates.[19] The propensity of hydrate formation is likely due to ring strain relief in



Scheme 2 Synthesis and iodo-glycosylation of **16**.



Scheme 3 Preparation of bromosugar **19**.

conjunction with hydrogen bonding to the C-1 oxygen moiety. The structure of **20** was characterized by ^{1}H, ^{13}C-NMR (C-2 appearing at 108.9 ppm) and MS.

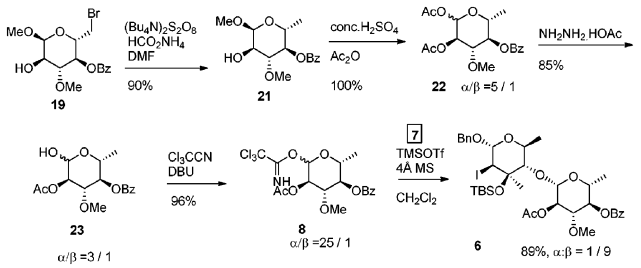
The dehalogenation of bromide **19** was explored next. Subjecting compound **19** to dehalogenation conditions developed by Fu,[20] led to only 25% conversion. Dehalogenation under typical AIBN/tributyltin hydride[21] conditions improved the conversion to 66%. Reaction with triethylboron/tributyltin hydride[22] led to complete conversion and 87% isolated yield. Parallel attempts with the eco-friendly Kim combination of peroxydisulfate mediated[23] conditions offered good conversions. Ideally, quantitative conversion and 90% isolated yield of the benzoyl ester **21** were obtained when ammonium formate and tetrabutylammonium peroxysulfate was used in DMF at 60 °C. It appears that this is the first application of the Kim reagent for radical reductive cleavage of a C–Br bond.

Sugar **21** was converted to glycosyl acceptor **8** in 3 steps and 74% yield. Acetylation of **21** provided anomeric acetates **22** in 5 : 1 *dr*. Regioselective hydrolysis of anomeric acetate in **22** provided lactol **23** as a 3 : 1 anomeric mixture. Treatment of lactol **23** with trichloroacetonitrile[24] and DBU afforded the chloroacetimidate **8** in excellent yield and high selectivity (Scheme 4). Gratifyingly, acetate-directed glycosylation of **8** with alcohol **7** afforded β-glycoside **6** in 89% yield and 9 : 1 selectivity.

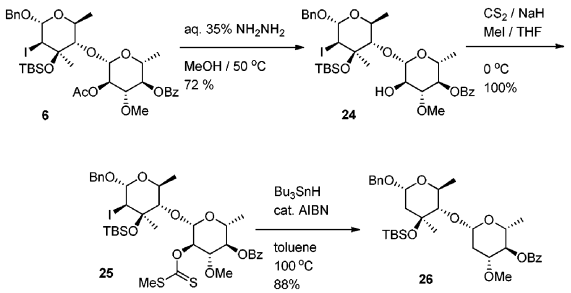
The acetate of **6** was cleaved under aqueous hydrazine conditions, and the resulting alcohol **24** was converted to xanthate **25** in 72% yield over two steps (Scheme 5). The xanthate

Table 1 Methylation of **11**

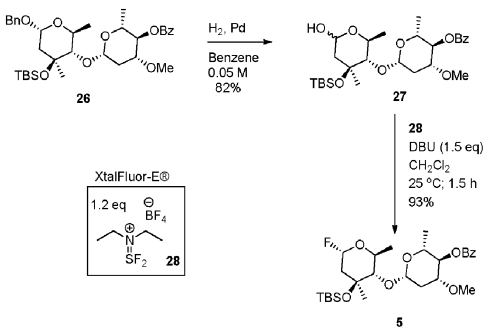
Reagent	**12-*syn*/12-*anti***	Yield of **12-*syn***	Yield of **12-*anti***
MeLi (1.1 eq.)	1.5 : 1	55%	35%
Me_2Zn (1.1 eq.), then MeLi (1 eq.)	3 : 1	60%	20%
Me_3Al (1.1 eq.), then MeLi (1.1 eq.)	7.5 : 1	75%	10%
Me_3Al (1.1 eq.), then MeLi (2.2 eq.)	50 : 1	85%	Trace
Me_4Zr[10c]	N/A	64%	N/A



Scheme 4 Preparation of **6**.



Scheme 5 Preparation of sugar **26**.



Scheme 6 Synthesis of glycosyl donor **5**.

and the iodo groups were removed in one pot using tributyltin hydride to provide **26** in 88% yield.[25]

Reduction of **26** under Pd/H_2 conditions followed by the fluorination of lactol **27** with diethylamino sulfur trifluoride[26] (DAST) provided the glycosidic donor **5** in 81% yield but required chromatography (Scheme 6). A more effective fluorinating agent, XtalFluor-E® **28** was recently reported.[27] Fluorination of lactol **27** by this reagent provided the fluoride **5** in excellent yield with no side products, thus eliminating the need for chromatography.

The synthesis of **5** was completed in 10% yield over 16 linear steps. Studies on O-27 glycosylation of the glycosyl fluoride **5** are currently under investigation.

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