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Lactol-Directed Osmylation. Stereodivergent Synthesis of Four C-19,20 Apoptolidin Diols from a Single Allylic Hemiacetal

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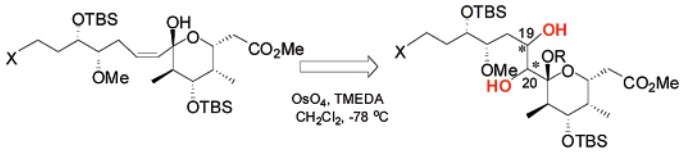
ABSTRACT



Four C-19, 20 Apoptolidin diols

A synthetic approach to prepare four Apoptolidin C-19,20 diastereomeric diol derivatives was developed. Two diastereomers were obtained from the (*Z*)-form, which is converted to the (*E*)-form, followed by dihydroxylation to deliver two more diastereomers. The (*E*)-allylic hemiacetal and methoxyacetal showed opposite diastereoselectivity.

Apoptolidin A (**1A**) is a 20-membered macrocyclic lactone that was isolated from *Norcardiopsis* sp. by Seto and co-workers in 1997, and **1A** induced apoptotic cell death in rat gila cells transformed with the E1A oncogene at ng/mL but did not cause cell death in normal gila cells or fibroblasts at μg/mL.[1] In 2000, Khosla and co-workers correlated its activity with inhibition of mitochondrial F_0F_1-ATPase.[2] Significantly, **1A** is in the upper 0.1% of agents screened using the NCI's 60 human tumor cell line panel with respect to differential cytotoxicity. The selective biological activity and complex structure have made it a challenging target for the synthetic community.[3] Apoptolidin A (**1A**) and D (**1D**) undergo ring expansion from the C-19 to the C-20 hydroxyl group to produce Isoapoptolidin A and D (Figure 1) that are over 10-fold less active than the precursor lactones.[4,6c]

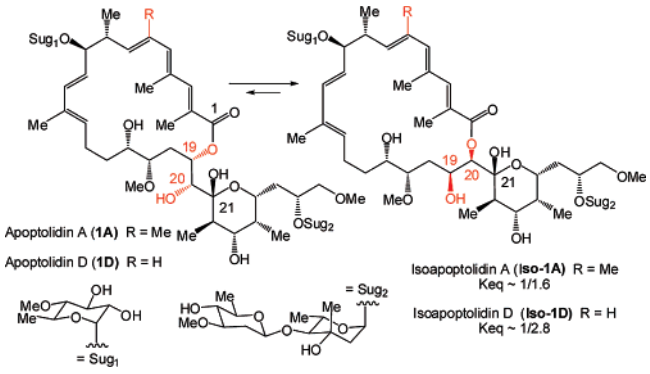


Figure 1. Ring expansion equilibrium of Apoptolidin A and D.

Furthermore, Wender probed the Apoptolidin structure−activity relationship and biological mode of action and, more recently, isolated three additional Apoptolidins (Apoptolidin B, C, and D).[5]

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(2) (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 14766. (b) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71. (c) Salomon, A. R.; Zhang, Y.; Seto, H.; Khosla, C. *Org. Lett.* **2001**, *3*, 57.

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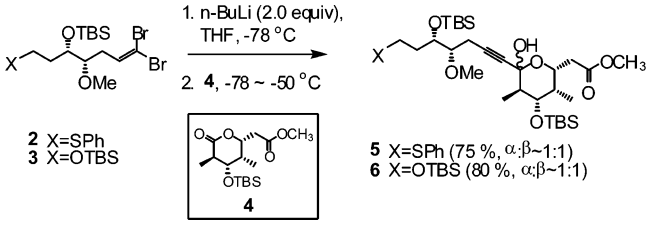
In order to explore the anticancer activity/selectivity of Apoptolidin analogues, we report preparation of four C-19,20 diols to test the possibility of avoiding the undesirable trans-acylative ring expansion equilibrium which attends the natural isomer.[5a]

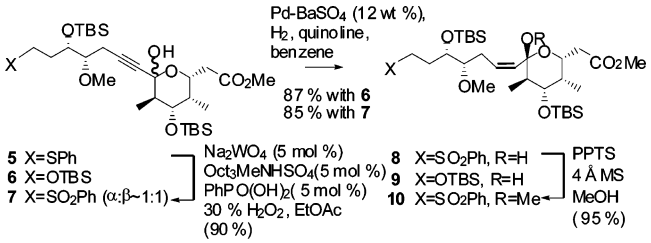
The synthesis[6] of hemiacetals **5** and **6** begins with 1,2-addition of the lithium acetylides prepared by the method of Corey *et al.*[7] on dibromides **2**[8] and **3**[8] to lactone ester **4**.[8,9] The reaction affords inseparable ~1:1 anomeric hemiacetals **5** and **6** in 75 and 80% yields, with ~15−20% unreacted **4** and proton quenched acetylene being recovered (Scheme 1). Careful control of reaction temperature and reagent stoichiometry is essential to avoid β-elimination of the silyloxy group and/or addition to the methyl ester.

Scheme 1. Addition of Acetylenic Anions to Lactone **4**



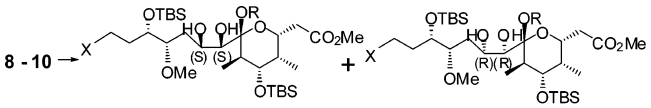
Numerous efforts[10] at semi-hydrogenation of alkyne **5** failed, presumably due to catalyst poisoning by the phenyl sulfide moiety. Therefore, **5** was oxidized[11] to sulfone **7**, which is easily reduced to allylic hemiacetal (*Z*)-**8** in 85% yield under a hydrogen balloon using catalytic Pd−$BaSO_4$ and quinoline. Benzene and cyclohexane were good solvents, but hexane gave a much slower reaction rate, while ethyl acetate and methanol favored over-reduction. Interestingly, the 1:1 anomeric mixtures of hemiacetals **6** and **7** largely isomerized to β-anomers (*Z*)-**8** and **9** during the hydrogenation. Protection of hemiacetal **8** led to methoxyacetal **10** by the action of PPTS in methanol (Scheme 2).

Scheme 2. Sulfide Oxidation and Semi-hydrogenation



Seminal contributions of the Donohoe group at Oxford,[12] describing the ability of allylic and homoallylic alcohols to direct osmylation, inspired our extension of this effect to the chemistry of allylic hemiacetals. Treatment of (*Z*)-allylic lactol **8** using the Oxford stoichiometric OsO_4/TMEDA/CH_2Cl_2 protocol[13] at low temperature provided a 9:1 mixture of diols **11/14** in near quantitative yield. Upjohn dihydroxylation[14] using *catalytic* OsO_4 and NMO in aqueous acetone at *room temperature* for 12 h produced 95% yield of diols **11/14** in a less selective 3:1 ratio. Attempts to employ the Sharpless alkaloid catalyzed AD protocol on the hemiacetals led to no reaction, even after several days at room temperature.[15] By way of comparison, methoxyacetal **10** afforded less than 25% of dihydroxylated methoxyacetals **13/16** with minimal selectivity under both conditions. The stereochemistry of diol **11** was verified by X-ray.[8] As anticipated, the effect of the side chain terminus was minimal, with TBS ether (*Z*)-**9** showing a 4:1 preference in favor of diol **12** using the Upjohn method (Table 1). Stereochemistry of this

Table 1. Dihydroxylation of (*Z*)- **8**, **9**, and **10**



substrate	R	conditions[a]	% yield[b]	ratio[c]
8	H	A	quant	9:1 (**11/14**)
8	H	B	95	3:1 (**11/14**)
9	H	B	95	4:1 (**12/15**)
10	CH_3	A	<25[d]	1.5:1 (**13/16**)
10	CH_3	B	<25[d]	1.5:1 (**13/16**)

[a] Condition A: OsO_4 (1 equiv), TMEDA (1.1 equiv), CH_2Cl_2, −78 °C to rt, 12 h. Condition B: OsO_4 (5 mol %), NMO (3 equiv), acetone−H_2O (4:1), rt, 12 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] The remainder of the mixture is recovered starting material.

(3) (a) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchelle, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. (b) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchelle, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443 and references cited therein. (c) Wehlan, H.; Dauber, M.; Fernaud, M. T. M.; Schuppan, J.; Mahrwald, R.; Ziemer, B.; Garcia, M. E. J.; Koert, U. *Angew. Chem., Int. Ed.* **2004**, *43*, 4597. (d) Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 872 and references cited therein. (e) Wu, B.; Liu, Q.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6673 and references cited therein. (f) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810. (g) Chen, Y.; Evarts, J. B.; Torres, E.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 3571. (h) Abe, K.; Kato, K.; Arai, T.; Rahim, M. A.; Sultana, I.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2004**, *45*, 8849. (i) Chang, S. S.; Xu, J.; Loh, T. P. *Tetrahedron Lett.* **2003**, *44*, 4997. (j) Paquette, W. D.; Taylor, R. E. *Org. Lett.* **2004**, *6*, 103.

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(8) See Supporting Information for additional information. An improved preparation of lactone **4** is provided.

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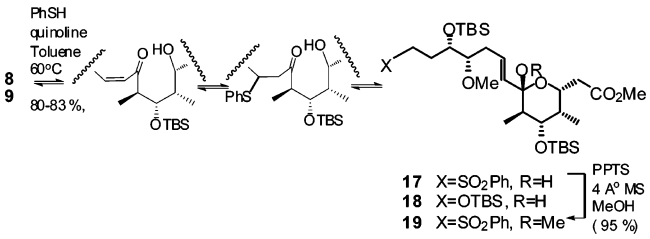
Scheme 3. Conversion of the (*Z*)- to (*E*)-hemiacetal

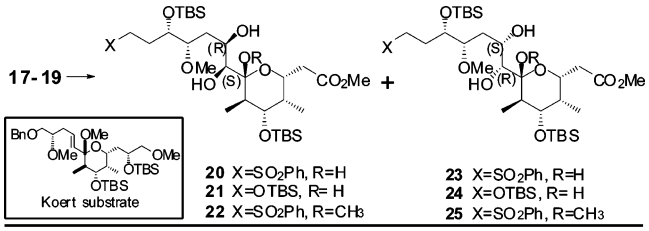


reaction was assigned by comparison of the ^{1}H NMR and ^{13}C NMR spectra with those of diols **11** and **14**.

In order to secure the isomeric *trans*-hemiacetals (*E*)-**17** and **18** (Scheme 3), we resorted to thermodynamic equilibration of the (unobservable) enone via Michael addition−elimination using thiophenol and quinoline or pyridine in toluene at 60 °C. Significantly, employing pyridine or quinoline effectively affords (*E*)-**17** and **18**, but stronger bases, such as triethylamine, generated substantially more impurities. Crude (*Z*)-**8** and **9** can be taken directly into the equilibration reaction when quinoline is used for the hydrogenation reaction. Other olefin equilibration reagents, such as Bu_3P[16] and I_2,[17] were not successful, and AIBN-mediated radical processes generated many unwanted products. Access to allyl methoxyacetal **19** was again assured by acid-catalyzed methanolysis of **17** in 95% yield.

Directed dihydroxylation of **17** was completed in 12 h to quantitatively give a 5:1 ratio of **20**/**23**. Substrates **17** and **18** give 2−2.5:1 stereoselectivity under the Upjohn conditions. Allyl methoxyacetal **19** affords the opposite selectivity, favoring the "natural" diastereomer **25**, consistent with Koert, who obtained 6:1 selectivity with his (*E*)-allylic methoxyacetal substrate (box, Table 2).[18] As with the *cis*-series of

Table 2. Dihydroxylation of (*E*)-**17**, **18**, and **19**



substrate	R	conditions[a]	% conv[b]	ratio[b]
17	H	A	quant	5:1 (**20/23**)
17	H	B	90	2:1 (**20/23**)
18	H	B	90	2.5:1 (**21/24**)
19	CH_3	A	80	1:7 (**22/25**)
19	CH_3	B[c]	50	1:2 (**22/25**)

[a] Condition A: OsO_4 (1 equiv), TMEDA (1.1 equiv), CH_2Cl_2, −78 °C to rt, 12 h. Condition B: OsO_4 (5 mol %), NMO (3 equiv), acetone−H_2O (4:1), rt, 12 h. [b] Determined by ^{1}H NMR. [c] Condition: OsO_4 (10 mol %), NMO (3 equiv), acetone−H_2O (4:1), rt, 2 days.

Table 1, the milder (but stoichiometric) hemiacetal-directed dihydroxylation using condition A gave better selectivity and yields than condition B.

Stereochemistry of the above diastereomers was assigned by comparison with the NMR spectra of compounds sharing similar core structures.[18] Additionally, **26**[8] was confirmed by X-ray (see Supporting Information).

Useful trends are observed from the ^{13}C NMR shifts available from the diols produced in this study (Table 3),[8]

Table 3. ^{13}C NMR Shifts

	X = SO_2Ph					X = OTBS			
	C-17	C-19	C-20	C-21		C-17	C-19	C-20	C-21
11	81.1	*S* 70.6	*S* 76.9	100.3	**12**	81.5	*S* 70.4	*S* 75.5	100.8
14	84.7	*R* 73.0	*R* 74.0	101.8	**15**	85.5	*R* 73.0	*R* 74.7	101.9
20	81.4	*R* 67.3	*S* 73.3	101.1	**21**	81.5	*R* 67.5	*S* 73.2	101.2
23	80.4	*S* 65.5	*R* 73.0	102.9	**24**	80.7	*S* 66.1	*R* 73.0	102.7
22	82.5	*R* 68.9	*S* 75.8	102.1					
25	80.5	*S* 67.4	*R* 74.9	103.6					

for example: (1) C-20(*S*) > C-20(*R*), C-19(*R*) > C-19(*S*) for all pairs, more importantly (2) *the chemical shift of C-21* appears further downfield for C-20(*R*) than C-20(*S*), and *the chemical shift of C-17* is further downfield for C-19(*R*).

As expected, osmylation reactivity and selectivity are related to both the anomeric stereochemistry and the olefin geometry. The products obtained support a Donohoe-type H-bond-directed dihydroxylation mechanism for the allylic hemiacetals. As shown in Figure 2, both the (*Z*)- and (*E*)-

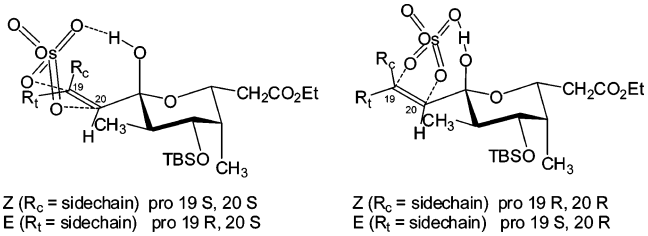


Figure 2. Proposed transition states of **8** (or **9**) and **17** (or **18**).

olefins prefer *Si* face directed osmylation, while the preference is diminished with the (*E*)-hemiacetals and reversed with the (*E*)-methoxy acetals, consistent with the Koert

(11) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X. Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469.
(12) (a) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946. (b) Donohoe, T. J. *Synlett* **2002**, *8*, 1223 and references therein.
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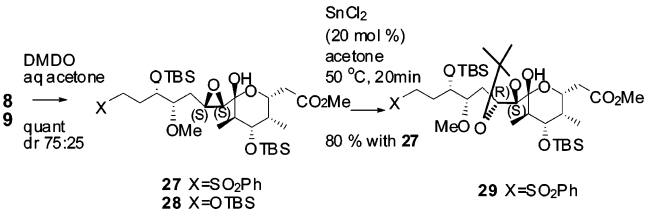
findings.[18] As expected, the effect is greatest at low temperature in the stoichiometric osmylation, parallel to that seen in the Donohoe studies.[12,13]

An alternative approach to the C-19,20 diols explored epoxide opening (Scheme 4). Epoxidation of **8** and **9** by

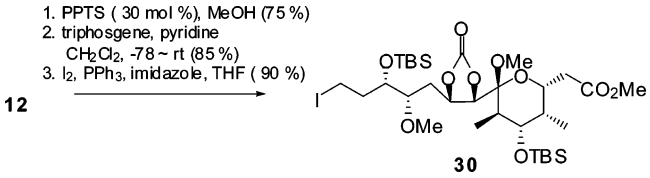
Scheme 4. Alternative Oxidation via Epoxide **27**



DMDO (dimethyldioxirane)[19] afforded a mixture of two epoxides of 75:25 dr in essentially quantitative yield. Stereochemistry of the two diastereomers was hypothesized based upon the above ^{13}C NMR trends with C-19(*S*),20(*S*) as the major epoxide.[8] Intramolecular epoxide opening protocols with derivatives of major diastereomer **27** from the dioxirane reaction bearing esters,[20] carbamates,[21] or carbonates[22] at the anomeric position failed.[23] Unsatisfactory intermolecular epoxide openings included $Sc(OTf)_3$,[24] $RuCl_3$,[25] $Cu(OTf)_2$,[26] $AlCl_3$,[27] and $BF_3{\cdot}OEt_2$.[28] However, reaction with 20 mol % of anhydrous $SnCl_2$ in acetone[29] at 50−55 °C for 20 min provided dioxolane **29** in 80% yield. Although the stereochemistry at C-19,20 is tentative, it is assigned as C-19(*R*),20(*S*) based upon mechanism and ^{13}C NMR shift values (cf. Table 3).[8]

Simultaneous primary desilylation and protection of the C-21 anomeric position of **12** can be effected using PPTS in methanol. Treating the crude methoxyacetal with triphosgene gives the cyclic carbonate which is further converted to iodide **30**, ready to couple (Scheme 5).[8]

Scheme 5. Preparation of Iodocarbonate **30**



Hydrogen-bond-directed osmylation enables synthesis of four diastereomeric diols from a single (*Z*)-allylic hemiacetal. These materials will be converted to C-19,20 analogues of apoptolidin for SAR studies. Further reports on this endeavor will be reported in due course.

Acknowledgment. We thank Dr. Karl Wood and Dr. Phillip Fanwick of Purdue University for MS and X-ray data.

Supporting Information Available: Experimental procedures, spectroscopic and analytical data for new compounds, ^{1}H and ^{13}C NMR spectra of key compounds, including X-ray data for **11** and **26** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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