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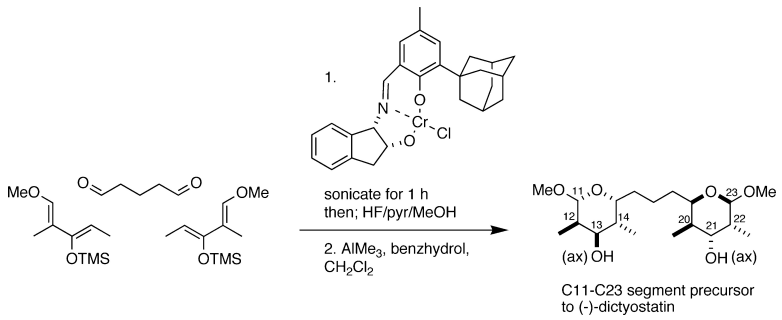
J. Am. Chem. Soc., **2007**, 129 (51), 16273-16277 • DOI: 10.1021/ja077336u



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A Two-Directional Approach to a (−)-Dictyostatin C11−C23 Segment: Development of a Highly Diastereoselective, Kinetically-Controlled Meerwein−Ponndorf−Verley Reduction

Andrew K. Dilger, Vijay Gopalsamuthiram, and Steven D. Burke*

Contribution from the Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706-1322

Received September 25, 2007; E-mail: burke@chem.wisc.edu

Abstract: A three-step synthesis of a precursor to the C11−C23 segment of (−)-dictyostatin is described. The sequence features a sonication-assisted, enantioselective double hetero Diels−Alder (HDA) reaction catalyzed by Jacobsen's Cr(III) Schiff base catalyst, followed by a novel, highly diastereoselective Meerwein−Ponndorf−Verley (MPV) reduction of the hydropyranone subunits under kinetic control to yield the bis-(axial alcohol) **4**. Generalized studies of both the HDA and MPV methodologies are also described.

Introduction

In the course of initiating a synthetic approach to the potent anticancer agent (−)-dictyostatin,[1] we found existing methodology to be inadequate for two of the first three steps. Development of an operational improvement in Jacobsen's powerful catalytic asymmetric hetero Diels−Alder method[2] and discovery of a kinetic Meerwein−Ponndorf−Verley protocol for selective reduction of hydropyran-4-ones to axial alcohols were required. Illustration of the strategic incentive provided by the dictyostatin C11−C23 segment and generalization of the methodological developments beyond that context are detailed herein.

(−)-Dictyostatin (**1**, Figure 1) was first isolated in 1994 by Pettit and co-workers[1] from a marine sponge *Spongia sp.* off the coast of Maldives and later by Wright and co-workers[3] from *Corralistidae* sponges. It was subsequently found to act as an efficient inhibitor of human cancer cell growth with GI_{50} values ranging from 50 pM to 1 nM. In addition, it retains activity against some taxol-resistant cell lines by stabilizing microtubules. This mode of action is analogous to that of the potential chemotherapeutic agent discodermolide, which is structurally similar.[4]

Dictyostatin comprises a 22-membered macrolactone with 11 stereogenic centers, 10 of which are in common with discodermolide. In addition, dictyostatin displays an endocyclic 2*Z*,4*E*-dienoate (C1−C5) and a *Z*-1,3-diene at C23. These interesting structural features coupled with its attractive biological profile have led to five total syntheses of dictyostatin[5] as well as significant synthetic efforts toward that end.[6]

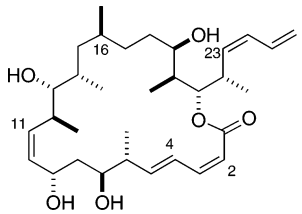

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Figure 1. Structure of (−)-dictyostatin.

Curran recently reported that a synthetic analogue, 16-normethyldictyostatin, is a subnanomolar antiproliferative against human ovarian carcinoma 1A9 cells, making it equipotent to dictyostatin.[7] This observation, in combination with recent success in using a catalytic, enantioselective hetero Diels−Alder reaction in the context of synthesizing the C20−C32 subunit of the phorboxazoles,[8] stimulated us to evaluate a synthetic approach to both 16-normethyldictyostatin and the parent natural product. We noted the possiblity of employing a two-directional

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(2) (a) Chavez, D. E.; Jacobsen, E. N. *Org. Synth.* **2005**, *82*, 34−39. (b) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400.
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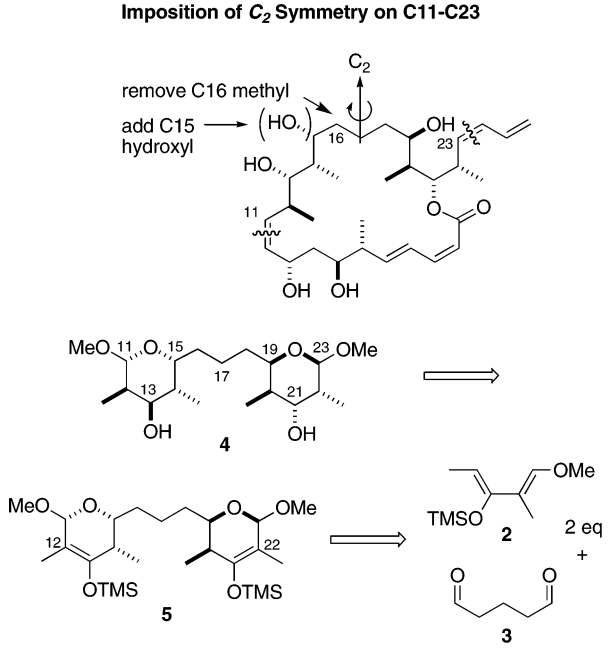
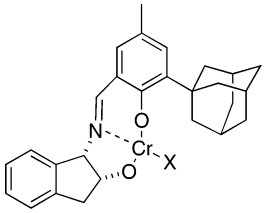
Scheme 1. Retrosynthesis of the C11−C23 Segment Precursor



strategy[9] for the C11−C23 subunit of dictyostatin and 16-normethyldictyostatin via C_2-symmetric intermediates upon imposing local symmetry by modifying C15 and C16 (Scheme 1). If a hydroxyl group is temporarily installed at C15 with (*R*)-configuration and the C16 methyl group is removed, the resultant region from C11−C23 exhibits C_2-symmetry about C17. In addition to its role in conferring symmetry to the C11−C23 subunit, the imposed oxygen functionality could also be used to install the C16 methyl group. Furthermore, we envisioned the stereotetrads[10] at C12−C15 and C22−C19 in **4** to be readily obtainable via an asymmetric double hetero Diels−Alder (HDA) reaction between 2 equiv of Danishefsky's diene (**2**)[11] and glutaraldehyde (**3**) under the influence of Jacobsen's Cr(III) Schiff base complex[2] (**6a**, Figure 2). Axial protonations of bis(silyl enol ether) **5** at C12 and C22 followed by unprecedented carbonyl reduction (*vide infra*) at C13 and C21 would afford diaxial diol **4**. Masked aldehydes at C11 and C23 in **4** are suited for eventual olefinations.



6a, X= Cl
6b, X=SbF_6

Figure 2. Jacobsen hetero Diels−Alder catalysts.

Results and Discussion

Initiation of the synthetic sequence by enantioselective double HDA immediately revealed a problem. Reaction of 2 equiv of Danishefsky's siloxy diene[9] **2** with glutaraldehyde (**3**) in the presence of 4 mol % of Cr(III)-catalyst **6a** afforded a complex mixture of products in variable yields. The standard conditions for this type of transformation involve a combination of aldehyde and diene neat, in the presence of powdered 4 Å molecular sieves, and the heterogeneous catalyst **6a**.[2] In this case, the dialdehyde **3** and diene **2** are only partially miscible, and the viscosity and heterogeneity of the reaction made efficient mixing and product formation monitoring difficult. The reaction was sluggish (>12 h, 45 °C), and attempts to achieve high conversion via elevated temperatures or longer reaction times led to decomposition of desired bis(cycloadduct) **5**, leading to significant amounts of elimination byproducts **7** and **8** (Figure 3). We thus sought to modify the reaction conditions described by Jacobsen.[2]

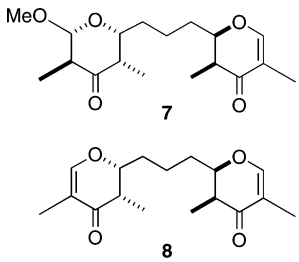


Figure 3. Elimination byproducts.

The physical effects of sonication[12] on heterogeneous reactions have been of recent interest.[13] Ultrasonic agitation provides thermal and pressure effects due to cavitation. Performing the asymmetric double HDA reaction between **2** and **3** in an ultrasonic cleaning bath for 1 h at room temperature resulted in a significant improvement in rate, yield, and product purity (Scheme 2). It was not necessary to isolate and purify the Diels−Alder adduct **5**; immediate treatment with aqueous HF buffered in pyridine effected axial protonation of the silyl enol ether moieties and established the C12 and C22 equatorial methyl groups in the diketone **9**, which was obtained in 66% overall yield from **2** and **3**.[14,15]

For the desired stereochemistry at C13 and C21, both hydroxyls must be oriented axially. Original results by Danishefsky[14] suggested that bulky reducing reagents such as L-selectride[16] cease to favor equatorial hydride delivery in tetrahydro-4-pyranone systems such as **9** when the anomeric methoxy substituent is oriented equatorially. This result was rationalized by the Cieplak model,[17,18] although the reason for this result remains under debate.

In addition, synthetic efforts toward the axial alcohol 4-pyranol-containing natural products ratjadone A,[19] sorangicin A,[20] and lasonolide A[21] have faced difficulty in efficiently reducing the corresponding tetrahydropyran-4-one to the axial diastere-

(9) (a) Keller, V. A.; Kim, I.; Burke, S. D. *Org. Lett.* **2005**, *7*, 737−740. (b) Magnuson, S. R.; *Tetrahedron* **1995**, *51*, 2167−2213. (c) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17.
(10) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677−690.
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(17) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552.
(18) For reviews, see: (a) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263−5301. (b) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265−1336.
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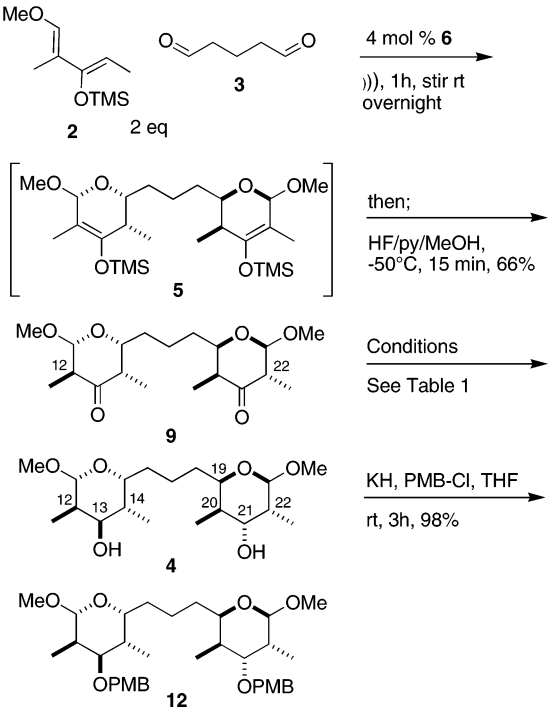
Scheme 2. Synthesis of the C11−C23 Subunit



omer. In all cases, extensive screening of reduction conditions led to equimolar quantities of axial and equatorial diastereomers, or worse.

This precedent presented us with the challenge to find a general method for accessing axial alcohols upon reduction of variously substituted hydropyran-4-ones. Thus, we explored methods of directly accessing the bis(axial alcohol) **4**. As expected, use of L-selectride failed, yielding a complex mixture of products, none of which was the desired diaxial diol. With no reason to expect equatorial hydride delivery using other aluminum hydrides or borohydrides, a mechanistically distinctive solution was sought. Our attention was drawn to the Meerwein−Ponndorf−Verley reduction[22,23] after recent reports of its use in highly diastereoselective transformations.[24] In particular, recent observations[24a] on the effect of solvent on axial/equatorial alcohol ratios in MPV reductions of substituted cyclohexanones with *i*-PrOAl(*i*-Bu)$_2$ were intriguing, with CH_2Cl_2 notably favoring axial alcohol formation.

Traditionally, the MPV reduction is an equilibrium process, yielding the thermodynamically more stable equatorial alcohol product from six-membered cyclic ketones. However, we felt that design of a kinetically controlled reaction in which equatorial hydride delivery was favored by a very bulky hydride donor and reversibility was disfavored by slow aluminum alkoxide exchange might allow efficient access to **4**. Excess bulky MPV reagent and a hydride donor that afforded a ketone with a low reduction potential[25] were also incorporated as reaction design elements to disfavor equilibration.

Several conditions were screened to optimize for the production of bis(axial alcohol) **4** (Table 1). The MPV reagents were preformed by adding the alcohol hydride donor to a solution of the aluminum source at 0 °C and stirring for 1 h at room temperature, followed by addition of diketone **9**. Using conditions analogous to those of Snaith,[24a] the MPV reagent derived from DIBAL-H and isopropanol proved disappointing, affording desired diaxial alcohol **4** (25%) and the undesired diastereomers **10** (45%) and **11** (23%) as shown in Table 1 (entry 1). This low level of selectivity was changed only modestly with *i*-PrOAl(*i*-Bu)$_2$ in toluene, but use of diphenylmethanol (benzhydrol) as the hydride source gave an enhanced yield ratio of 40:14:3 for **4**/**10**/**11**, substantially favoring the diaxial diol **4**.

Optimal conditions utilized tris(diphenylmethoxy)aluminum, preformed from 12 equiv of benzhydrol and 4 equiv of $AlMe_3$ in dichloromethane at 0 °C. Crystalline diaxial diol **4** was produced in 73% yield, with 12% of the axial, equatorial diastereomer and no observable formation of bis(equatorial) diol **11**. Prolonged reaction times did not increase the yields or change the ratio of **10** and **11**, suggesting that this reaction is kinetically controlled. This conclusion is further supported by two additional experiments. Resubjection of bis(equatorial) diol **11** to the reaction conditions ($AlMe_3$, benzophenone, CH_2Cl_2) slowly yields diketone **9** and diols **4** and **10**, whereas resubjection of bis(axial) diol **4** only yields diketone **9**, **4**, and minor amounts of half-oxidized (monoketone) material.

An X-ray crystal structure of **4** (Figure 4) was obtained to confirm the relative stereochemistry generated in the double hetero Diels−Alder reaction, the enol ether protonations, and the MPV reductions. In addition, the enantiomeric purity of **4** was very high[26] as a consequence of two enantioselective hetero Diels−Alder reactions on a single substrate, illustrating the Horeau principle or the Eliel effect.[9c,27,28]

With optimized conditions in-hand for the production of **4**, the generality of these methods was evaluated by preparing and reducing a variety of monocyclic tetrahydropyran-4-ones. Reactions of the highly activated siloxy diene **2a** (Table 2) proceeded smoothly at room temperature under the influence of Jacobsen catalyst **6a**. Notably, the electron-rich *p*-anisaldehyde (entry c) reacted to completion in 19 h using sonication, whereas after 5 days of stirring at room temperature the reaction had still not reached completion. All other aldehydes reacted to completion with diene **2a** in 5 h or less. The less activated diene **2b** required a longer reaction time even in the presence of the more active Jacobsen catalyst **6b**. These reactions were complete in 19−27 h, a slight improvement over previously reported results.[2b] Entries e and h−j were aimed at systematically determining the effect of various steric requirements about the carbonyl as well as the nature of the R^2 substituent on the diastereoselectivity of the MPV reduction.[29]

The Meerwein−Ponndorf−Verley reductions proceeded with good to excellent stereoselectivities (Table 3). Diastereoselectivities as high as 14:1 can be obtained regardless of the nature

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(23) For a review, see: (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007−1017. (b) Nishide, K.; Node, M. *Chirality* **2002**, *14*, 759−767.
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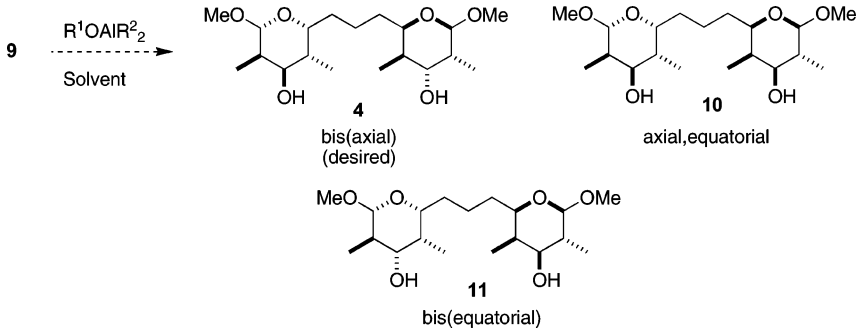
(25) Adkins, H.; Cox, F. W. *J. Am. Chem. Soc.* **1938**, *60*, 1151−1159.
(26) The enantiomeric ratio was determined by chiral HPLC to be >200:1 by synthesizing the bis(PMB ethers) **12** and *ent*-**12** from **4** and *ent*-**4** and injecting against a mixture of both enantiomers on a Chiralcel OD-H column.
(27) (a) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576−578.
(28) Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515−524.
(29) A lack of stereocontrol over the silyl enol ether geometry in diene **2c** (entry i, Table 1) and lack of regiocontrol for the formation of diene **2d** resulted in low yields of **13i** and **13j**, although sufficient quantities were generated for use in evaluating the subsequent kinetic MPV reductions.

Table 1. Examination of MPV Reductions on Diketone **9**



entry	Al source	R^1	R^2	solvent	% yield **4**	% yield **10**	% yield **11**
1[a]	DIBAL-H	*i*-Pr	*i*-Bu	CH_2Cl_2	25	45	23
2[a]	DIBAL-H	*i*-Pr	*i*-Bu	toluene	33	25	24
3[a,b]	DIBAL-H	$CH(Ph)_2$	*i*-Bu	CH_2Cl_2	40	14	3
4[b,c]	$AlMe_3$	$CH(Ph)_2$	$OCH(Ph)_2$	CH_2Cl_2	73	12	0

[a] Reactions were carried out using 4 equiv of DIBAL-H and 4 equiv of the alcohol. [b]Minor amounts of half-reacted (mono-axial alcohol, mono-ketone) material were also observed. [c]4 equiv of $AlMe_3$ and 12 equiv of benzhydrol were used.

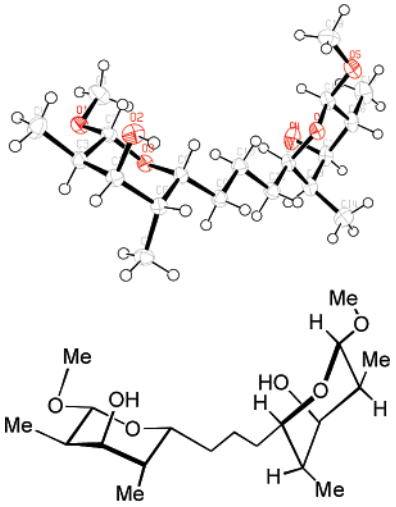
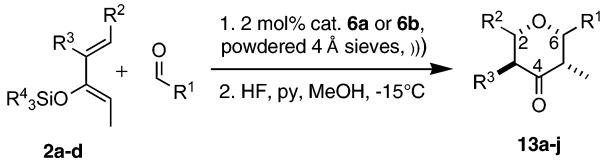


Figure 4. X-ray crystal structure and line drawing of diol **4**.

Table 2. Study of Sonicated Hetero Diels–Alder Reactions



2a-d **13a-j**

2a, R^2=OMe, R^3=R^4=Me
2b, R^2=Me, R^3=H, R^4=Et
2c, R^2=OMe, R^3=H, R^4=Et
2d, R^2=R^3=Me, R^4=Et

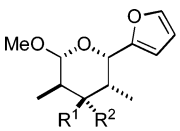
entry	diene	R^1	R^2	R^3	catalyst	time (h)	% **13**
a	**2a**	Ph	OMe	Me	**6a**	3	69
b	**2a**	$(CH_2)_2OPMB$	OMe	Me	**6a**	5	79
c	**2a**	PMP[a]	OMe	Me	**6a**	19	64
d	**2a**	CH_2PH	OMe	Me	**6a**	3.5	63
e	**2a**	2-furyl	OMe	Me	**6a**	4	73
f	**2b**	Ph	Me	H	**6b**	19	66
g	**2b**	$(CH_2)_2Ph$	Me	H	**6b**	27	60
h	**2b**	2-furyl	Me	H	**6b**	22	82
i	**2c**	2-furyl	OMe	H	**6a**	3	nd
j	**2d**	2-furyl	Me	Me	**6b**	12	nd

[a] PMP = *p*-methoxyphenyl.

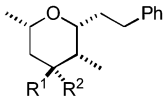
of the R^2 substituent, suggesting steric effects are controlling, rather than stereoelectronic effects.[14,17,18] These results illustrate the generality of this method and suggest that it will be useful in other natural product syntheses.

The observed stereoselectivity can be explained on the basis of several contributing factors. The requirement in an MPV reduction that complexation and hydride transfer occur simultaneously in a six-membered transition state suggests that this transition state would be late and productlike.[30] This should allow for a correlation of the structure and energy of the intermediate aluminum alkoxides resulting from axial versus equatorial hydride delivery and the corresponding transition states. We have thus concluded that this MPV reduction proceeds with product development control and that its stereochemical course is driven by the stability of the aluminum alkoxide species rather than the product alcohols. Molecular mechanics calculations using Gaussian at the PM3 level of theory on energy-minimized structures of the corresponding aluminum alkoxides of **14**/**15e** and **g** (**14**/**15e*** and **g***, Figure 5) reveals that the equatorial aluminum alkoxides are less stable than the axial diastereomers. Furthermore, these calculations also suggest that the energy differences parallel the observed stereoselectivities. The equatorial alkoxide of **15e** is ~8.7 kcal/mol less stable than that of **14e**, the alcohols being obtained in a 12:1 ratio in favor of the **14e**. Alcohols **14g** and **15g** are, however, closer in energy. These alcohols are isolated in a 1.7:1 ratio of axial to equatorial alcohols.

Qualitatively evaluating the structures of the transition states (Figure 6) leading to equatorial and axial aluminum alkoxides also provides evidence for this proposal. **TS1** depicts axial



14e*, R^1 = OAl[OCH(Ph)$_2$]$_2$, R^2 = H
15e*, R^1 = H, R^2 = OAl[OCH(Ph)$_2$]$_2$



14g*, R^1 = OAl[OCH(Ph)$_2$]$_2$, R^2 = H
15g*, R^1 = H, R^2 = OAl[OCH(Ph)$_2$]$_2$

Figure 5. Aluminum alkoxides for molecular modeling calculations.

(30) Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 11552–11568.

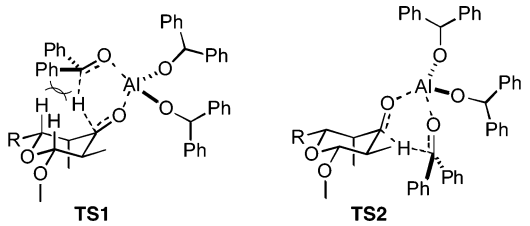
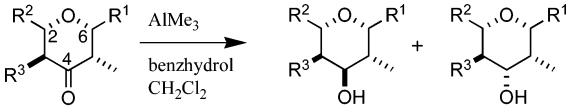


Figure 6. Transition state drawings leading to equatorial and axial alcohols.

Table 3. Results of MPV Reductions



entry	R^1	R^2	R^3	% **14**	% **15**	ax/eq
a	Ph	OMe	Me	76	16	4.2:1
b	$(CH_2)_2$OPMB	OMe	Me	71	18	3.9:1
c	PMP	OMe	Me	78	18	4.3:1
d	CH_2PH	OMe	Me	65	6.5	10:1
e	2-furyl	OMe	Me	69	5.7	12:1
f	Ph	Me	H	55	19	2.7:1
g	$(CH_2)_2$Ph	Me	H	61	36	1.7:1
h	2-furyl	Me	H	73	14	5.2:1
i	2-furyl	OMe	H	79	6	13:1
j	2-furyl	Me	Me	79	6	14:1

hydride delivery, leading to equatorial aluminum alkoxides, and **TS2** shows the transition state leading to axial aluminum alkoxides. Significant flattening of substituted pyrans relative to cyclohexanes causes a near-eclipsing interaction between the equatorial aluminum alkoxide and the flanking equatorial substituents (H or Me). In addition, **TS1** encounters severe steric interactions between the two axial hydrogens flanking the ring oxygen and the phenyl rings of the benzhydryloxy group delivering the hydride. No such interaction exists in **TS2**, suggesting a reason for the significant preferences for axial alcohol production. The reaction is then rendered slow to reverse by virtue of the formation of benzophenone, which is known to undergo slow MPV reduction,[25] thereby preventing deterioration of the axial/equatorial product ratio.

Conclusion

In summary, a high-yielding, three-step synthesis of a C11–C23 segment **4**, applicable to (−)-dictyostatin and (−)-16-normethyldictyostatin, has been developed. The sequence of a double enantioselective hetero Diels–Alder reaction, axial-selective silyl enol ether protonations, and kinetically controlled axial-selective Meerwein–Ponndorf–Verley reductions efficiently installs 10 stereogenic centers, including those at C12, C13, C14, C19, C20, C21, and C22 present in (−)-dictyostatin. Studies directed at desymmetrization and elaboration of this C_2-symmetric intermediate are currently in progress. The newly developed MPV reagent tris(diphenylmethoxy)aluminum allows for a general method of efficiently reducing hydropyran-4-ones **13** to axial alcohols with a variety of substituents equatorially oriented at the C2 and C6 positions. This represents a general solution to a problem which has hampered the otherwise attractive use of the HDA reaction in polypropionate synthesis.[10,11a,14]

Experimental Methods

General Procedure for Hetero Diels–Alder Reactions: Ketone 13b: To a 250 mL round-bottom flask were added diene **2a** (2.94 g, 14.70 mmol, 1.2 equiv), aldehyde (2.38 g, 12.25 mmol, 1 equiv), Jacobsen catalyst **6a** (0.119 g, 0.245 mmol, 0.02 equiv), and powdered 4 Å molecular sieves (1.23 g, 100 mg/mmol aldehyde). The mixture was sonicated for 5 h (see Supporting Information), keeping the sonicator bath water at room temperature. To 150 mL of a 1:1 mixture of methanol–pyridine was added 50% aqueous HF (2 equiv). This mixture was cooled in a methanol/ice bath (−15 °C). The hetero Diels–Alder adduct was dissolved in methanol (10 mL) and slowly added to the HF/pyridine. Upon completion as determined by TLC, saturated aqueous $NaHCO_3$ (100 mL) was added and then solid Na_2CO_3 (2 g). The mixture was diluted with ether (500 mL), and the layers were separated. The aqueous layer was saturated with NaCl and extracted with ether (3 × 150 mL). The combined organic layers were washed with saturated $CuSO_4$, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexanes–ether) yielded 3.11 g (79%) of pure 4-pyranone (**13b**).

General Procedure for Meerwein–Ponndorf–Verley Reductions of Tetrahydropyran-4-ones 13a–j: To a clean and dry round-bottom flask was added benzhydrol (9 equiv) under an atmosphere of nitrogen and dissolved in dichloromethane (0.25 M). The resulting solution was cooled to 0 °C, and trimethylaluminum [2 M in toluene, 3 equiv] was added dropwise via a syringe. The reaction was continued at room temperature for 1 h at which time visible evolution of methane had subsided, leading to the formation of tris(benzhydryloxyalane). The ketone **13** (1 equiv) was then added either neat or as a solution in dichloromethane into the above flask so that the overall concentration was 0.07 M, and the progress of the reaction was monitored by TLC for completion. The reaction was quenched with 2 N hydrochloric acid (until aqueous solution was acidic) and extracted with anhydrous ether (100 mL × 2). Drying the organic layer over anhydrous sodium sulfate was followed by evaporation of the solvent under reduced pressure to afford the crude product which was purified by silica-gel chromatography to give the axial alcohol **14** and the equatorial alcohol **15**.

Acknowledgment. We gratefully acknowledge Dr. Ilia Guzei for elucidation of the X-ray crystal structure of **4** and NIH Grants CA74394 and CA108488 for generous support. The NSF (CHE-0342998, CHE-9629688, and CHE-8813550) and the NIH (1 S10 RR04981-01) are acknowleged for support of the NMR facilities at the University of Wisconsin–Madison Department of Chemistry. We thank Mr. Xin Wei (UW–Madison) for initial experiments in this study, Mr. Grant Geske (UW–Madison) for performing calculations on the aluminum alkoxides of **14**/**15e*** and **g***, and Dr. Brian S. Lucas for advice.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **4** and **9**–**15**, chiral HPLC traces of **12** and *ent*-**12**, and .cif file for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA077336U