ORGANIC LETTERS

2013
Vol. 15, No. 10
2430–2433

Pd-Catalyzed Allylic Alkylation Cascade with Dihydropyrans: Regioselective Synthesis of Furo[3,2-*c*]pyrans

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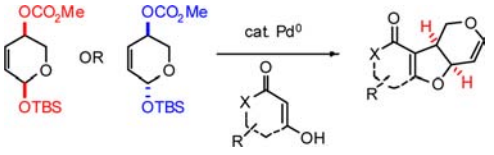
Received April 2, 2013

ABSTRACT



A regioselective palladium-catalyzed allylic alkylation cascade forms furo[3,2-*c*]pyrans from various cyclic β-dicarbonyl bis-nucleophiles and 3,6-dihydro-2*H*-pyran bis-electrophiles. The combination of allylic carbonate and anomeric siloxy leaving groups in the dihydropyran substrate allows control of the many regiochemical possibilities in this reaction. Annulation proceeds stereoconvergently to give *cis*-fused furopyrans from either *cis*- or *trans*-substituted starting material.

The construction of complex molecular architectures in a facile and efficient manner remains an overarching goal for the chemical sciences. Cascade (or domino) reactions allow improved atom and step economy in synthesis and therefore represent significant progress toward this goal.[1] Palladium-catalyzed allylic alkylation (Pd-AA) cascades involve the sequential addition of a bis-nucleophile (**B**) to an allylic bis-electrophile (**A**) (Figure 1).[2] Various combinations of nitrogen, oxygen, and carbon bis-nucleophiles (**B**) have been used for the preparation of a variety of vinyl-substituted ring systems (**C**).[3] A large number of possible regiochemical outcomes exist for a Pd-AA of a nonsymmetric allylic bis-electrophile with a nonsymmetric bis-nucleophile. Therefore, a major challenge of these annulation reactions is in differentiating the two nucleophilic and electrophilic centers so that a single product is formed regioselectively. Typically, this challenge has been avoided by employing symmetric electrophiles or nucleophiles, thereby obviating the need for regioselectivity. Thus, despite the synthetic efficiency of the Pd-AA cascade, it has found limited use in total synthesis.[4]

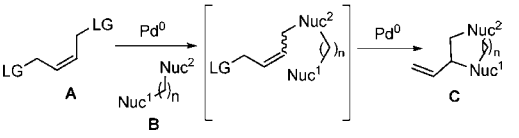


Figure 1. Generic Pd-AA Cascade Reaction.

(1) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. **Atom economy**: Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. **Step economy**: Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H *Acc. Chem. Res.* **2008**, *41*, 40.

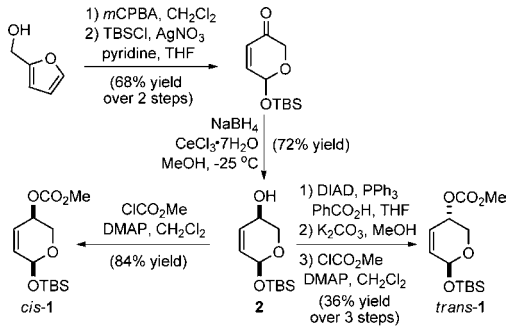
(2) For selected reviews on Pd-AA, see: Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley & Sons: New York, 1996; pp 290−399. Trost, B. M; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(3) For selected examples, see: **Piperazines**: Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826. Massacret, M.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 129. **Morpholines**: Thorey, C.; Wilken, J.; Hénin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5527. Nakano, H.; Yokoyama, J.; Fujita, R.; Hongo, H. *Tetrahedron Lett.* **2002**, *43*, 7761. **Dioxanes**: Massacret, M.; Lhoste, P.; Lakhmiri, R.; Parella, T.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 2665. **Oxazolidinones**: Tanimori, S.; Kirihata, M. *Tetrahedron Lett.* **2000**, *41*, 6785. Tanimori, S.; Inaba, U.; Kato, Y.; Kirihata, M. *Tetrahedron* **2003**, *59*, 3745. **Dihydrofurans**: Yoshida, M.; Nakagawa, T.; Kinoshita, K.; Shishido, K. *J. Org. Chem.* **2013**, *78*, 1687. Clavier, H.; Giordano, L.; Tenaglia, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8648. Tanimori, S.; Kato, Y.; Kirihata, M. *Synthesis* **2006**, 865. Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. **Cyclopropanes**: Burgess, K. *Tetrahedron Lett.* **1985**, *26*, 3049. Gaucher, A.; Dorizon, P.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **1995**, *36*, 2979.

10.1021/ol400902d © 2013 American Chemical Society
Published on Web 04/26/2013

We have discovered that certain dihydropyran substrates serve as nonsymmetric bis-electrophiles for Pd-AA cascades with cyclic β-dicarbonyl compounds. This methodology provides rapid access to unsaturated furo-[3,2-*c*]pyran ring systems with excellent regio- and diastereoselectivity. The Pd-AA cascade was investigated using *cis*-**1**, which was prepared in four steps from furfuryl alcohol *via* known alcohol **2**[5] (Scheme 1).

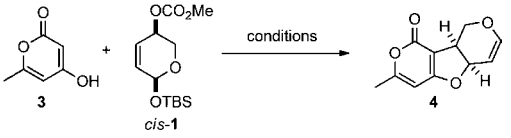
Scheme 1. Synthesis of Pyran Substrates, *cis*-**1** and *trans*-**1**



Initial solvent screening experiments employed 4-hydroxy-6-methyl-α-pyrone (**3**) as the β-dicarbonyl compound and provided modest yields of furopyran **4** (Table 1, entries 1−3). Interestingly, the use of excess **3** was detrimental to the reaction (entry 4), leaving unreacted *cis*-**1** and producing the undesired *O*-alkylation side product, *cis*-**5** (Scheme 2). The negative effects of excess 4-hydroxy-α-pyrone could be countered by adding triethylamine to the reaction mixture (entry 5). Toluene was found to be the optimal reaction solvent, and when used in conjunction with 5 mol % of $Pd(PPh_3)_4$, the desired product **4** was obtained in 83% yield (entry 9).

Pd-AA with soft nucleophiles typically proceeds through a double inversion of configuration;[6] however, the Pd-AA cascade of *trans*-**1** with **3** also produced the *cis*-fused furopyran, **4** (Table 2). The *cis*-stereochemistry of **4** was confirmed by X-ray crystallographic analysis (Scheme 2).[7] This is presumably a consequence of the prohibitively large amount of strain energy present in the *trans*-fused furopyran product, **6**,[8] since the relative energy difference

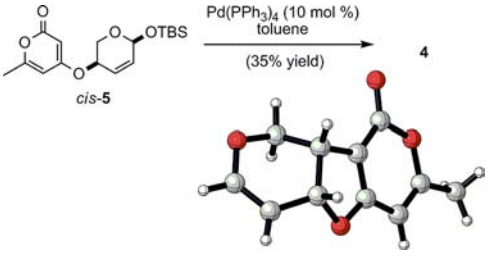
Table 1. Optimization of the Pd-AA Cascade with *cis*-**1**



entry	catalyst (mol %)	solvent	equiv **3**	yield[a]
1	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	CH_2Cl_2	1.0	30%
2	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	CH_3CN	1.0	12%
3	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	THF	1.0	44%
4	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	CH_2Cl_2	2.2	5%[c]
5	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	CH_3CN/NEt_3[d]	2.2	42%
6	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	CH_3CN/NEt_3[d]	1.0	40%
7	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	toluene	1.0	65%
8	$Pd(PPh_3)_4$ *(10)*	toluene	1.0	71%
9	**$Pd(PPh_3)_4$ *(5)***	**toluene**	**1.0**	**83%**
10	$Pd(PPh_3)_4$ *(5)*	toluene/NEt_3[d]	1.0	71%
11	$Pd(PPh_3)_4$ *(1)*	toluene	1.0	56%[e]

[a] Isolated yield. [b] 2:1 ratio of P/Pd was used. [c] 39% recovered *cis*-**1** and 4% *O*-alkylation product *cis*-**5** were also isolated. [d] 1.0 equiv of NEt_3 was added. [e] 9% *O*-alkylation product *cis*-**5** was also isolated.

Scheme 2. Conversion of *cis*-**5** into **4** and ORTEP Drawing of **4** with Thermal Ellipsoids at 50% Probability



between the *cis*- and *trans*-fused products was calculated to be 51 kJ/mol.[9] While an inner-sphere process could be invoked to explain the overall retention of configuration, the higher catalyst loading required for efficient transformation of *trans*-**1** into **4** (Table 2, entry 3) suggests that the initial *syn*-palladium complex, **7**, is isomerized by intermolecular nucleophilic attack of a transient Pd(0) species (step **VI**, Scheme 3).[10] To validate this hypothesis we investigated the Pd-AA cascade of cyclohexene-based substrate *trans*-**8**[11](Scheme 4). This substrate provides an opportunity to evaluate the putative π-allyl-Pd isomerization without the possibility of the reaction proceeding through an oxonium intermediate, as may be the case for *trans*-**1**. Ultimately,

(4) **Agelastatin A**: Trost, B. M.; Dong, G. *Chem.—Eur. J* **2009**, *15*, 6910. **Huperzine A**: Campiani, G.; Sun, L.-Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660. Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron* **1998**, *54*, 5471. He, X.-C.; Wang, B.; Yu, G.; Bai, D. *Tetrahedron: Asymmetry* **2001**, *12*, 3213. **Neosarpagine**: Liao, X.; Huang, S.; Zhou, H.; Parrish, D.; Cook, J. M. *Org. Lett.* **2007**, *9*, 1469. **Carbovir/Aristeromycin**: Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745.

(5) Achmatowicz, O., Jr.; Buckowski, P.; Szechner, B.; Zierchowska, A.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4529.

(6) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215.

(7) Crystal data: monoclinic, space group $P2_1/c$ (No. 14), (*a*) 7.7627(3) Å, (*b*) 11.0574(4) Å, (*c*) 11.2765(4) Å, (β) 103.614(2)°, (*V*) 940.73(6) Å^3, (*Z*) 4.

(8) For examples of strain energy in 5,6-ring systems, see: Velluz, L.; Valls, J.; Nominé, G. *Angew. Chem., Int. Ed.* **1965**, *4*, 181.

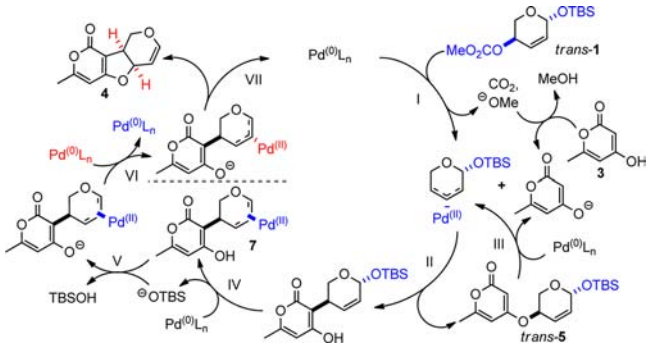
(9) DFT calculations (B3LYP/6-31G*) were performed with Spartan '08. See Supporting Information for computational details.

(10) The isomerization of π-allyl-Pd complexes by Pd(0) has been previously implicated in the loss of stereospecificity in Pd-AA reactions: Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921. Granberg, K. L.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.

(11) Tsarev, V. N.; Wolters, D.; Gais, H.-J. *Chem.—Eur. J.* **2010**, *16*, 2904.

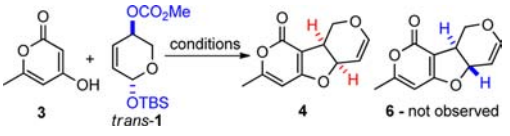
(12) The relative stereochemistry of **9** was assigned using NOE correlation and comparison to the $^3J_{HH}$ values of **4**.

Scheme 3. Proposed Mechanism for the Palladium-AA Cascade of *trans*-**1** with Pyrone **3**[a]



[a] (**I**) Selective ionization of the allylic carbonate, giving a π-allyl Pd complex. (**II**) *C*-3 alkylation with net retention of configuration. (**III**) Reversion of the *O*-alkylation product *trans*-**5** to a π-allyl Pd complex. (**IV**) Formation of the second π-allyl Pd complex. (**V**) Deprotonation of the 4-hydroxy-α-pyrone nucleophile by *tert*-butyldimethylsiloxide. (**VI**) Isomerization of the π-allyl Pd complex by Pd(0). (**VII**) Annulative *O*-attack at *C*-5 to form the *cis*-fused product and regenerate the Pd(0) catalyst.

Table 2. Pd-AA Cascade with *trans*-**1**



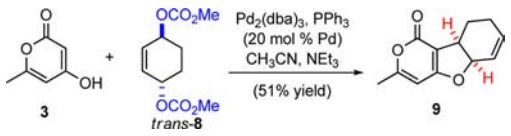
entry	catalyst (mol %)	solvent	equiv **3**	yield[a]
1	$Pd_2(dba)_3/PPh_3$ *(10)*[b]	CH_3CN/NEt_3[c]	1.0	38%
2	$Pd(PPh_3)_4$ *(5)*	toluene	1.0	10%
3	$Pd(PPh_3)_4$ *(20)*	toluene	1.0	74%

[a] Isolated yield. [b] 2:1 ratio of P/Pd used. [c] 1.0 equiv of NEt_3 added.

trans-**8** was also found to provide *cis*-fused **9**, adding weight to the proposed inversion by Pd(0).[12]

Throughout these investigations, double alkylation was observed in almost all instances. Single *O*-alkylation was only observed in two cases where reactivity was impaired, either through low catalyst loading (Table 1, entry 11) or by the presence of excess pyrone **3** (Table 1, entry 4). 4-Hydroxy-6-methyl-α-pyrone (**3**) has a pK_a of 6.83 (80% (w/w) DMSO/H_2O),[13] and therefore, under effective reaction conditions, the *O*-alkylation product, **5**, can act as an allyl acetate equivalent, reacting with Pd(0) to reform the previous π-allyl complex (Scheme 3, step **III**).[14] Indeed, the *O*-alkylated byproduct *cis*-**5** was converted into **4** upon treatment with 10 mol % palladium catalyst (see Scheme 2). This suggests that the excellent regioselectivity observed in most cases is a consequence of the first substitution operating under thermodynamic control. The use of an anomeric siloxy group is key to the success of this chemistry as the relatively low reactivity of the OTBS group allows preferential ionization of the allylic carbonate.[15] The resulting π-allyl-Pd species is regioselectively alkylated at C-3 as a result of both steric and electronic factors inherent to pyran-based substrates.[16]

Scheme 4. Mechanistic Validation Using *trans*-**8**



The scope of this reaction was explored with *cis*-**1** using a variety of cyclic β-dicarbonyl bis-nucleophiles **3**, **11**–**20** (Table 3). In general, nucleophiles with high enol content, such as α-pyrones, **3**, and coumarins, **11**–**14**, produced the highest yields of the desired furopyrans (i.e., **4**, **21**, **22**, **31**, **32**). In contrast, substrates that are predisposed to the keto form, such as 1,3-indandione (**19**) and Meldrum's acid (**20**), are prone to the formation of α-disubstituted β-dicarbonyl side products (e.g., **29**). The Pd-AA cascade with **20** produced the ring-opened lactone **30**, which presumably results from extrusion of acetone from the initial dioxinone, followed by trapping of the resulting acylketene intermediate with methanol liberated from the carbonate.[17] While only a 39% yield of **30** was obtained

(13) Tan, S. F.; Ang, K. P.; Jayachandran, H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 471. The pK_a of 6-methyl-4-hydroxy-α-pyrone in H_2O is 4.94: Ang, K.; Tan, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1525.

(14) Moreno-Mañas and coworkers have shown this experimentally, by reacting a 4-allyloxy-6-methyl-α-pyrone with a Pd(0) catalyst to obtain a C-3 alkylated 4-hydroxy-α-pyrone: Moreno-Mañas, M.; Ribas, J.; Virgili, A. *J. Org. Chem.* **1988**, *53*, 5328.

(15) In contrast, the analogous hemiacetal substrate produced a complex mixture of undesired products. See Supporting Information for details.

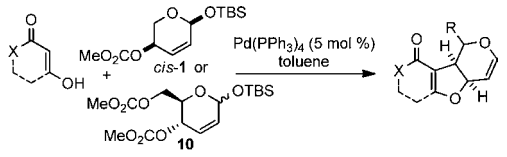
(16) Brescia, M.-C.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **1997**, *62*, 1257.

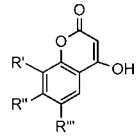
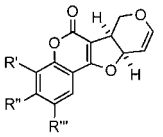
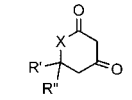
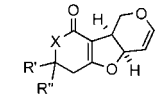
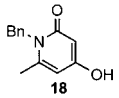
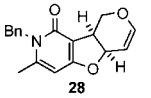
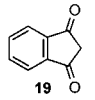
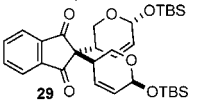
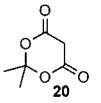
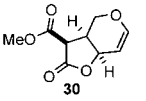
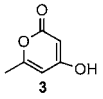
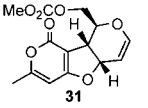
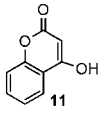
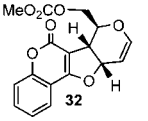
(17) Related processes have been noted previously: (a) Fillion, E.; Carret, S.; Mercier, L. G.; Trépanier, V. É. *Org. Lett.* **2008**, *10*, 437. (b) Basson, M. M.; Holzapfel, C. W.; Verdoorn, G. H. *Heterocycles* **1989**, *29*, 2261.

(18) For related processes with sugar-derived bis-electrophiles, see ref 17b and: Al-Tel, T. H. *Z. Naturforsch., B: Chem. Sci.* **2000**, *55*, 657.

(19) See Supporting Information for details of these experiments.

Table 3. Pd-AA Cascade Substrate Scope

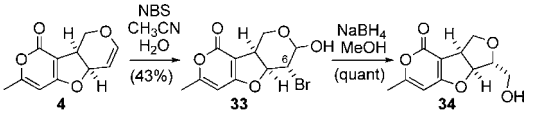


bis-nucleophile	product	yield[a]
		
11 R',R'',R'''=H	**21** R',R'',R'''=H	77%
12 R',R'''=H, R''=OMe	**22** R',R'''=H, R''=OMe	68%[b]
13 R',R''=H, R'''=Me	**23** R',R''=H, R'''=Me	47%[b,c]
14 R'=Me, R'',R'''=H	**24** R'=Me, R'',R'''=H	49%[b,c]
		
15 R'-R''=$(CH_2)_5$, X=O	**25** R'-R''=$(CH_2)_5$, X=O	56%
16 R',R''=CH_3, X=CH_2	**26** R',R''=CH_3, X=CH_2	57%
17 R'=*p*-BrC_6H_4,R''=H, X=O	**27** R'=*p*-BrC_6H_4,R''=H, X=O	61%
 **18**	 **28**	37%[c]
 **19**	 **29**	52%
 **20**	 **30**	39%[d,e] 69%[b,d,f]
 **3**	 **31**	77%[g]
 **11**	 **32**	90%[g]

[a] Isolated yields are quoted. [b] 10 mol % $Pd(PPh_3)_4$ was used. [c] Toluene/DMF (3:1) was used as solvent. [d] *ca.* 14:1 dr. [e] 53% of the α-disubstituted side product was also obtained. [f] 5 equiv of Meldrum's acid and THF/MeOH (10:1) were used. [g] 15 mol % $Pd(PPh_3)_4$ was used.

under the previously optimized conditions, the use of excess **20** and a THF/MeOH (10:1) solvent mixture reduced the formation of the α-disubstituted side product and provided an improved 69% yield of **30**. Bis-nucleophile solubility is an important consideration, and the use of DMF as a cosolvent was required for the generation of

Scheme 5. Synthetic Utility of Furopyrans



23, **24**, and **28** in reasonable yield. Additionally, the use of a sugar-derived bis-electrophile, **10**, provided good yields of the more substituted furopyrans **31** and **32**.[18] In these cases, the dihydropyran starting material contained a mixture of anomers; thus a higher catalyst loading was used to facilitate these stereoconvergent reactions. The latter examples serve to probe the impact of steric factors on the excellent regiochemical control of these Pd-catalyzed reactions.[16] Overall, the parameters that define an effective bis-nucleophile proved relatively complex, and enol content alone does not seem to guarantee high yield. For example, tetronic and tetramic acids, which both exist predominantly in the enol form, provided complex mixtures devoid of the desired products.[19]

The synthetic utility of the furopyran products was demonstrated through the bromohydroxylation of **4** (Scheme 5).[20] Treatment of the resulting bromohydrin **33** with sodium borohydride effected both hemiacetal reduction and cyclization, forming the fused bis-furan **34**. This bicyclic motif is present in a number of bioactive natural products.[21]

In summary, a palladium-catalyzed allylic alkylation cascade of cyclic β-dicarbonyl bis-nucleophiles with nonsymmetric pyran-based bis-electrophiles was used to regioselectively and stereoconvergently prepare a range of *cis*-fused furo[3,2-*c*]pyrans. This methodology affords a number of versatile chemical structures, whose exploitation in several synthetic endeavors is currently being pursued.

Acknowledgment. Victoria University is gratefully acknowledged for funding, the provision of a Ph.D. scholarship (M.J.B.) and a Curtis-Gordon Scholarship (C.A.T.). We also thank Dr. Jan Wikaira (University of Canterbury) for obtaining the X-ray data for **4** and Ian Vorster, Dr. Robert Keyzers, and Assoc. Profs. Paul Teesdale-Spittle and Peter Northcote (VUW) for NMR assistance and helpful discussions.

Supporting Information Available. Experimental procedures, spectroscopic data and spectra for all new compounds. X-ray crystallographic data (CIF) for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) The 6-*epi* diastereomer of **33** was also isolated (19% yield).

(21) For example: Atienza, J.; Hernandez, E.; Primo, J. *Appl. Microbiol. Biotechnol.* **1992**, *37*, 298.

The authors declare no competing financial interest.