ORGANIC LETTERS
2011
Vol. 13, No. 24
6436–6439

Gram-Scale Synthesis of the A′B′-Subunit of Angelmicin B

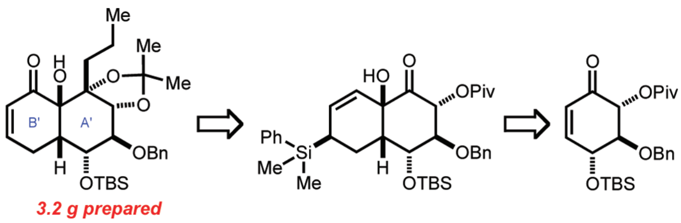
Benjamin C. Milgram, Brian B. Liau, and Matthew D. Shair*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

shair@chemistry.harvard.edu

Received October 11, 2011

ABSTRACT



A gram-scale enantiospecific synthesis of the A′B′-subunit of angelmicin B is reported. The synthesis involves a Lewis acid catalyzed contrasteric Diels–Alder reaction and a tandem silyl zincate 1,6-addition/enolate oxidation sequence.

Angelmicin B (**1**, Figure 1) was isolated in 1993 by Uehara, Oki, and co-workers from the rare actinomycete *Microbispora* subsp. AA9966.[1,2] Hibarimicin B, which was subsequently isolated along with hibarimicin A–G from the *Microbispora rosea* subsp. *hibaria* TP-A0121, shares an identical structure with **1**. Angelmicin B (**1**) was originally identified as an inhibitor of Src tyrosine kinase (IC_{50} > 5800 nM),[1a] and was later found to inhibit proliferation and induce differentiation of HL-60 human leukemia tumor cells (IC_{50} = 58 nM).[3] The discrepancy between these effective concentrations suggests that Src is perhaps not the target responsible for the anticancer activity of **1**, and to date, the cellular target of **1** remains unidentified.

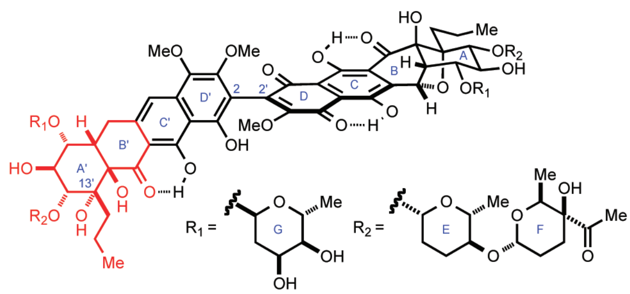


Figure 1. Structure of angelmicin B (**1**).

Angelmicin B (**1**) is a pseudo-C_2-symmetric glycosylated type II polyketide. The two halves of its fascinating pseudo-C_2-symmetric structure differ in the oxidation states of the B/B′, C/C′, and D/D′ rings. Several questions concerning the absolute and relative configuration of **1** remain to be addressed.[4] The absolute configuration of both halves of the aglycon and the carbohydrates as well as the relative stereochemistry of the C13′-carbinol are unknown. Additionally, it is unclear whether the compound

(1) (a) Uehara, Y.; Li, P. M.; Fukazawa, H.; Mizuno, S.; Nihei, Y.; Nishio, M.; Hanada, M.; Yamamoto, C.; Furumai, T.; Oki, T. *J. Antibiot*. **1993**, *46*, 1306–1308. (b) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 394–401. (c) Hori, H.; Kajiura, T.; Igarashi, Y.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **2002**, *55*, 46–52. (d) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **2002**, *55*, 53–60. (e) Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **2002**, *55*, 61–70. (f) Cho, S. I.; Fukazawa, H.; Honma, Y.; Kajiura, T.; Hori, H.; Igarashi, Y.; Furumai, T.; Oki, Y.; Uehara, Y. *J. Antibiot*. **2002**, *55*, 270–278.

(2) For structural elucidation of angelmicin B, see: (a) Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett*. **1996**, *37*, 2785–2788. (b) Hori, H.; Igarashi, Y.; Kajiura, T.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 402–417.

(3) Yokoyama, A.; Okabekado, J.; Uehara, Y.; Oki, T.; Tomoyasu, S.; Tsuruoka, N.; Honma, Y. *Leuk. Res*. **1996**, *20*, 491–497.

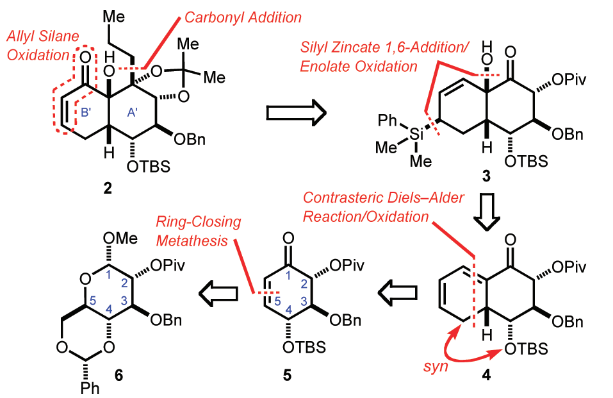
(4) For more information, see: ref 6e.

(5) Romaine, I. M.; Hempel, J. E.; Shanmugam, G.; Hori, H.; Igarashi, Y.; Polavarapu, P. L.; Sulikowski, G. A. *Org. Lett*. **2011**, *13*, 4538–4541.

10.1021/ol202728v
Published on Web 11/15/2011

exhibits atropisomerism as a result of potential hindered rotation about its C2–C2′ bond.[5] A total synthesis of **1** or its aglycon would elucidate these stereochemical uncertainties but has yet to be achieved.[6] Intrigued by the biological properties, stereochemical ambiguities, and structural complexity of **1**, we initiated a program aimed at its total synthesis. Herein we report a highly scalable enantiospecific synthesis of the orthogonally protected A′B′-subunit of angelmicin B (**2**, Scheme 1).

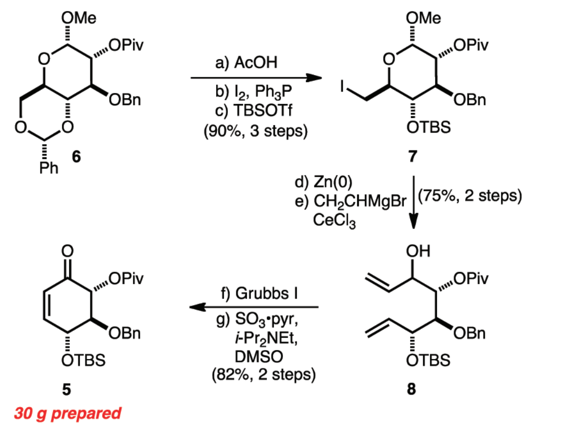
Scheme 1. Proposed Synthesis of **2**



Our retrosynthesis of **2** is outlined in Scheme 1. We anticipated that the enone functionality in **2** could be generated by oxidation of allylic silane **3**. Additionally, we envisioned that introduction of the *n*-propyl substituent in **2** could be accomplished through a diastereoselective organometallic addition to α-hydroxy ketone **3** from the convex face of the rigid *cis*-decalin carbon framework. Next, **3** would be accessed by means of a regio- and diastereoselective 1,6-addition of a silyl zincate to dienone **4**, followed by in situ oxidation of the resultant extended zinc enolate. A Lewis acid catalyzed contrasteric Diels–Alder reaction between cyclohexenone **5** and 1,3-butadiene would then set the relative stereochemistry in **4**, wherein the newly formed C–C bonds and the C4–OTBS substituent reside in a *syn* orientation. Finally, suitably protected **5** would be prepared through ring-closing metathesis of a linear precursor accessed from readily available D-glucose derivative **6**. The type and position of the hydroxyl protecting groups were chosen with respect to two criteria. First, a C4–OTBS group was deemed necessary for *syn* selectivity in the key Lewis acid catalyzed contrasteric Diels–Alder reaction. Second, orthogonally deprotectable groups were selected to facilitate sequential introduction of the sugar residues surrounding angelmicin B. The ability to produce gram quantities of late-stage intermediates is essential for a successful total synthesis of angelmicin B, one of the largest and most complex aromatic polyketides known. Recognition of the common stereochemical elements shared by **2** and D-glucose helped enable the realization of this requirement.

Our synthesis commenced with **6**, which was obtained in three steps from methyl α-D-glucopyranoside on a multigram scale according to a modified literature protocol (Scheme 2).[7] A three-step procedure for the conversion of **6** to iodide **7** began with AcOH-mediated hydrolysis of the benzylidene acetal, followed by selective Wittig iodination of the resultant primary hydroxyl group and TBS protection of the remaining secondary carbinol in 90% overall yield. Sonication of **7** with activated zinc powder promoted reductive fragmentation to generate an aldehyde intermediate,[8] which upon treatment with an organocerium reagent derived from vinylmagnesium bromide furnished allylic alcohol **8** as an inconsequential diastereomeric

Scheme 2. Synthesis of Diels–Alder Substrate **5**[a]



[a] Reagents and conditions: (a) 80% aq AcOH, 80 °C, 1 h, 94%; (b) Ph_3P (1.3 equiv), imidazole (3.0 equiv), I_2 (1.3 equiv), PhMe, 23 to 45 °C, 1 h, 97%; (c) TBSOTf (2.0 equiv), 2,6-lutidine (1.0 M), 0 to 23 °C, 30 min, 99%; (d) Zn(0) (10 equiv), THF/H_2O (4:1), sonication, 40 °C, 2 h; (e) $CH_2CHMgBr$ (1.2 equiv), $CeCl_3$ (1.2 equiv), THF, −78 °C, 2 h, 75% (3:1 dr) for two steps; (f) Grubbs I (5 mol %), CH_2Cl_2, 23 °C, 18 h, 85%; (g) SO_3•pyr (3.0 equiv), *i*-Pr_2NEt (5.0 equiv), DMSO (10.0 equiv), CH_2Cl_2, 0 °C, 1.5 h, 97%. Abbreviations: TBS = *tert*-butyldimethylsilyl, Grubbs I = bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride, DMSO = dimethyl sulfoxide, pyr = pyridine.

(6) For studies towards angelmicin B or its related natural products, see: (a) Lee, C. S.; Audelo, M. Q.; Reibenpies, J.; Sulikowski, G. A. *Tetrahedron* **2002**, *58*, 4403–4409. (b) Maharoof, U. S. M.; Sulikowski, G. A. *Tetrahedron Lett*. **2003**, *44*, 9021–9023. (c) Kim, K.; Mahroof, S. M.; Raushel, J.; Sulikowski, G. A. *Org. Lett*. **2003**, *5*, 2777–2780. (d) Narayan, S.; Roush, W. R. *Org. Lett*. **2004**, *6*, 3789–3792. (e) Lambert, W. T; Roush, W. R. *Org. Let*. **2005**, *7*, 5501–5504. (f) Lee, W.; Kim, K.; Sulikowski, G. A. *Org. Lett*. **2005**, *7*, 1687–1689. (g) Li, J.; Todaro, L. J.; Mootoo, D. R. *Org. Lett*. **2008**, *10*, 1337–1340. (h) Li, J.; Todaro, L.; Mootoo, D. R. *Eur. J. Org. Chem*. **2011**, 6281–6287.

(7) Franais, A.; Urban, D.; Beau, J. M. *Angew. Chem., Int. Ed*. **2007**, *46*, 8662–8665.

(8) (a) Skaanderup, P. R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem*. **2002**, *133*, 467. (b) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016. (c) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2400–2410. (d) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2411–2431. (e) Nakane, M.; Hutchinson, C. R.; Gollman, H. *Tetrahedron Lett*. **1980**, *21*, 1213–1216. (f) Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem*. **1991**, *56*, 2213–2217.

(9) Compound **8** was generated as a 3:1 mixture of diastereomers. See Supporting Information for more details.

(10) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc*. **2000**, *122*, 8444–8452.

(11) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed*. **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100–110.

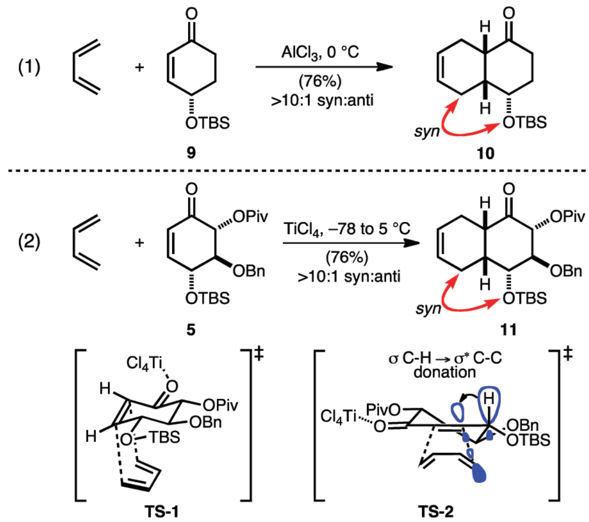
mixture in 75% yield over two steps.[9,10] Finally, exposure of **8** to a first-generation Grubbs olefin metathesis catalyst[11] in dilute CH_2Cl_2 followed by Parikh−Doering oxidation[12] of the resulting diastereomeric cyclohexenols produced **5** in 82% yield over two steps. Over 30 g of **5** were prepared through this method.

Following our synthesis of **5**, we next attempted the key Lewis acid catalyzed contrasteric Diels−Alder reaction depicted in eq 1 of Scheme 3. Danishefsky et al. had previously demonstrated that 2-cyclohexenone **9**, bearing a γ-OTBS group, participates in a contrasteric intermolecular Diels−Alder reaction with 1,3-butadiene when catalyzed by $AlCl_3$ to provide *cis*-decalin **10** in 76% yield (eq 1, Scheme 3).[13] In this transformation, the β-C−C bond is formed *syn* relative to the γ-OTBS group in high diastereoselectivity (> 10:1 *syn*/*anti*). We anticipated similar stereoselectivity in our proposed Diels−Alder reaction, despite the additional Lewis basic groups in our substrate. Gratifyingly, treatment of **5** with 1,3-butadiene in the presence of $TiCl_4$ at 5 °C for 3.5 h afforded a > 10:1 mixture of adducts, favoring the desired *syn* diastereomer **11**. This reaction, which can be performed on a multigram scale with high diastereoselectivity, is to our knowledge the most complex example of a contrasteric Diels−Alder yet reported.

The stereoselectivity of this reaction is likely governed by subtle steric and stereoelectronic effects. Approach of 1,3-butadiene to **5** *syn* to the γ-OTBS substituent is sterically occluded by both the γ-OTBS and α-OPiv groups and thus counterintuitive (transition state 1, Scheme 3). However, stereoelectronic considerations suggest that pseudoaxial approach of 1,3-butadiene to the β-carbon of the chairlike ground state conformation of **9** is kinetically favored.[14] Additionally, the Cieplak model has been invoked to rationalize the stereochemical outcome for the aforementioned Diels−Alder reaction.[15] In accordance with this line of reasoning, formation of the β-C−C bond *syn* with the electron-withdrawing γ-OTBS group stabilizes the forming σ^*-C−C orbital through hyperconjugation with the electron-donating σ-C−H bond (transition state 2, Scheme 3). It is plausible that a synergism of individually small stereoelectronic effects bias the reaction pathway toward the observed product diastereomer **11**.

The synthesis of **2** continued with a series of carefully controlled oxidations of the *cis*-decalin carbon skeleton of **11** (Scheme 4). Exposure of **11** to TMSI, generated in situ from TMSCl and NaI, promoted thermodynamic enolization

Scheme 3. Lewis Acid Catalyzed Contrasteric Diels−Alder Reaction[a]



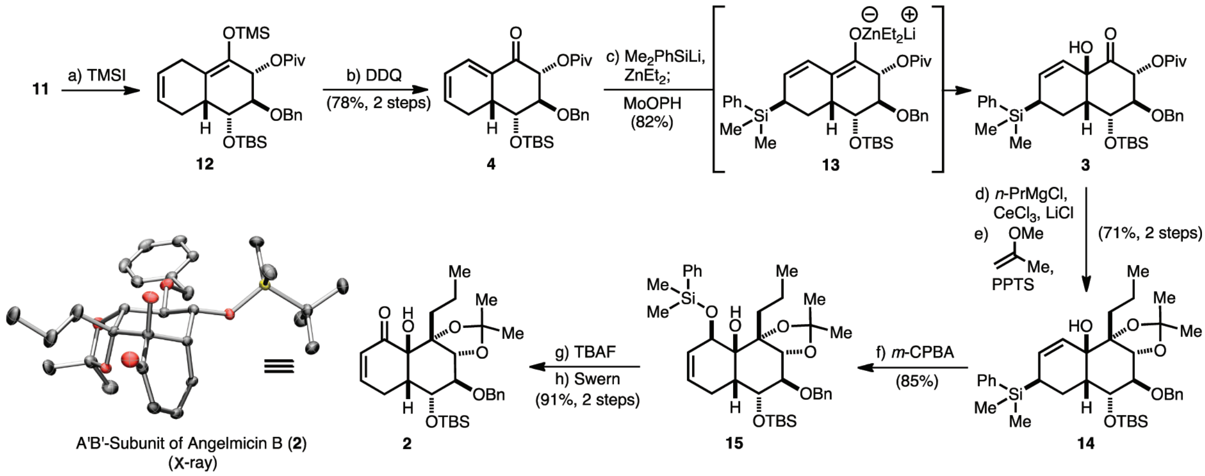
[a] Reagents and condtions: (a) 1,3-butadiene (20 equiv), $AlCl_3$ (0.9 equiv), PhMe, 23 °C, 1 h, 76% (> 10:1 *syn*/*anti*). (b) 1,3-butadiene (8.0 equiv), $TiCl_4$ (1.0 equiv), PhMe, −78 to 5 °C, 3.5 h, 76% (> 10:1 *syn*/*anti*). Abbreviations: TS = transition state.

of the ketone at C6 rather than at C2 to generate enol silane **12** as a single regioisomer.[16] This regioselection is particularly noteworthy since C2−H is presumably more acidic than C6−H. Chemoselective oxidation of **12** was accomplished upon treatment of **12** with DDQ to afford dienone **4** in 78% overall yield, again as a single regioisomer.[17] The mild nature of this procedure prevented overoxidation of the dienone moiety. Next, regio- and diastereoselective addition of dimethylphenylsilyl zincate to the δ-position of **4** generated extended zinc enolate intermediate **13**.[18] In situ α-oxidation of **13** with MoO_5•pyr•HMPA (MoOPH) delivered *cis*-decalin **3** as a single regio- and diastereoisomer in 82% yield. The one-pot 1,6-conjugate addition/enolate oxidation sequence was amenable to a variety of oxidants including Davis oxaziridine and DMDO; however, MoOPH proved to be the most efficient oxidant on a large scale.[19] Overall, the tandem reaction sequence generated the sterically congested C6-tertiary carbinol and an allylic silane, which was planned to serve as a latent enone surrogate.

Exposure of **3** to excess organocerium reagent derived from *n*-propylmagnesium chloride led to carbonyl addition exclusively from the convex face of the molecule and

(12) Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
(13) Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387–395.
(14) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642–2649.
(15) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552. (b) Ohkata, K.; Tamura, Y.; Shetuni, B. B.; Takagi, R.; Miyanaga, W.; Kojima, S.; Paquette, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 16783–16792. (c) Carreño, M. C.; González, M. P.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 9128–9137.
(16) (a) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, *9*, 730–732. (b) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764–2765. (c) Krafft, P. A.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345–1348.
(17) (a) Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, *19*, 3455–3458. (b) Corey, E. J.; Guzman−Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611–3612.
(18) (a) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658–5661. (b) Vaughan, A.; Singer, R. D. *Tetrahedron Lett.* **1995**, *36*, 5683–5686. (c) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. *J. Am. Chem. Soc.* **1998**, *120*, 4021–4022. (d) Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701–706. (e) Tckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581–1593.
(19) (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944–5946. (b) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127–132 and references therein.

Scheme 4. Completion of the Synthesis of the A′B′-Subunit of Angelmicin B (**2**)[a]



[a] Reagents and conditions: (a) TMSCl (10 equiv), NaI (15 equiv), HMDS (20 equiv), MeCN, 82 °C, 3 h; (b) DDQ (3.0 equiv), CH_2Cl_2, 23 °C, 3 h, 78% for two steps; (c) $Me_2PhSiLi$ (1.0 M in THF, 1.5 equiv), $ZnEt_2$ (1.0 M in PhMe, 1.5 equiv), THF, −78 °C, 30 min; then **4**, −78 to 0 °C, 30 min; then MoOPH (2.6 equiv), −78 to −20 °C, 20 min, 82%; (d) $CeCl_3$ (15 equiv), LiCl (30 equiv), THF, 23 °C, 12 h; then *n*-PrMgCl (1.6 M in Et_2O, 12 equiv), −78 °C, 3 h; then **3**, −78 to 0 °C, 2 h, 85%; (e) 2-methoxypropene (10 equiv), PPTS (10 mol %), PhH, 23 °C, 4.5 h, 84%; (f) *m*-CPBA (1.3 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, −78 to −5 °C, 7 h, 85%; (g) TBAF (1.0 M in THF, 1.5 equiv), THF, −78 °C, 1.5 h, 99%; (h) $(COCl)_2$ (8.0 equiv), DMSO (16 equiv), CH_2Cl_2, −78 °C, 1 h; then diol, −78 °C, 4 h; then Et_3N (32 equiv), −78 to 0 °C, 30 min, 92%. Abbreviations: TMS = trimethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, MoOPH = oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), PPTS = pyridinium *p*-toluenesulfonate, *m*-CPBA = *meta*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride.

concurrent cleavage of the pivoyl ester (Scheme 4).[20] The use of a mixed organocerium reagent was required to avoid ketone enolization and reduction.[21] The resultant 1,2-diol was protected as an acetonide, affording **14** in 71% yield over two steps. Treatment of **14** with *m*-CPBA led to epoxidation of the allylic silane with in situ 1,5-silyl migration of silicon and concomitant epoxide opening to provide compound **15** in 85% yield.[22] Chemoselective removal of the dimethylphenylsilyl group with TBAF at −78 °C and Swern oxidation[23] of the resulting allylic alcohol delivered **2** in 91% yield over two steps on a gram scale, completing our synthesis of the protected A′B′-subunit of angelmicin B.

In summary, a scalable and enantiospecific synthesis of the protected A′B′-subunit of angelmicin B (**2**) has been accomplished starting from methyl α-D-glucopyranoside. This sequence has been utilized to prepare 3.2 g of **2** to date. The synthesis features a Lewis acid catalyzed contrasteric Diels–Alder reaction between cyclohexenone **5** and 1,3-butadiene. Additionally, the synthesis further demonstrates the utility of silyl zincate reagents in organic synthesis through their application in a tandem 1,6-conjugate addition/enolate oxidation sequence. Reports of our progress toward a total synthesis of angelmicin B will be forthcoming.

(20) (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc*. **2010**, *132*, 4894–4906. (b) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc*. **2008**, *130*, 16424–16434. (c) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett*. **1996**, *37*, 6787–6790.

(21) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4392–4398.

(22) Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 2898–2900.

(23) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.

Acknowledgment. We thank Dr. Shao-Liang Zheng (Harvard University) for his assistance with X-ray crystallography. Financial support from the NIH (R01GM090068) is acknowledged. B.C.M. acknowledges AstraZeneca and Eli Lilly for financial support. B.B.L. acknowledges an NSF predoctoral fellowship for financial support.

Supporting Information Available. Experimental procedures, physical data, X-ray data for **2**, and copies of ^1H and ^{13}C spectra for **2**–**5**, **7**, **8**, **11**, **14**, **15**, and all synthesis intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.