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A *C*-Glycosidation Approach to the Central Core of Amphidinol 3: Synthesis of the C39–C52 Fragment

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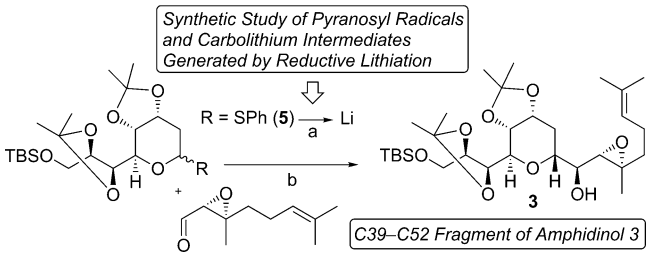
ABSTRACT



A concise route to an advance precursor (3) of the central core of amphidinol 3, a natural occurring polyketide, has been developed by applying a reductive lithiation as key step. The origin of the diastereoselectivity of this reaction was comprehensively studied for nucleophilic *C*-glycoside donor 5 and differently protected analogues.

The substance class of amphidinols are polyketide metabolites isolated from the marine dinoflagellate *Amphidinium klebsii* and *carterae*.[1−3] Dinoflagellates are protist unicellular algae and a rich source of structurally and biologically interesting natural products, e.g., brevetoxins,[4] maitotoxin,[5] and okadaic acid.[6] Amphidinols have shown potent hemolytic activity against human erythrocytes and antifungal activity against *Aspergillus niger*.[1] The dinoflagellate *A. klebsii* was initially isolated from washed seaweed collected from the Aburatsubu Bay in Kanagawa, Japan. Processing of 440 L of cell culture yielded 12 mg of amphidinol 3 with other amphidinol homologues, rendering extraction from natural sources impractical.[7] The structure of amphidinol 3 was elucidated by mass spectroscopic analysis and NMR spectroscopy[7] using a potentially powerful new *J*-based method.[8]

The novel architecture and the bioactive properties of amphidinol 3 led us to investigate its total synthesis[9] with special attention to the central core of amphidinol 3 (**2**, C31−C52 segment), which can be disconnected from the rest of the molecule by two olefination reactions.

Our approach to the central core of amphidinol 3 involves sequential addition of two glycosyllithium reagents to an aldehyde derived from alkene **3** and to the known epoxy aldehyde **6**[14] using the almost identical glycoside donors **4**

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(3) Houdai, T.; Matsuoka, S.; Murata, M.; Satake, M.; Ota, S.; Oshima, Y.; Rhodes, L. L. *Tetrahedron* **2001**, *57*, 5551.
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(12) Independent of our synthetic studies, Forsynth's group has extended the use of TEMPO oxidation of 1,5-diols to δ-lactones: Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.

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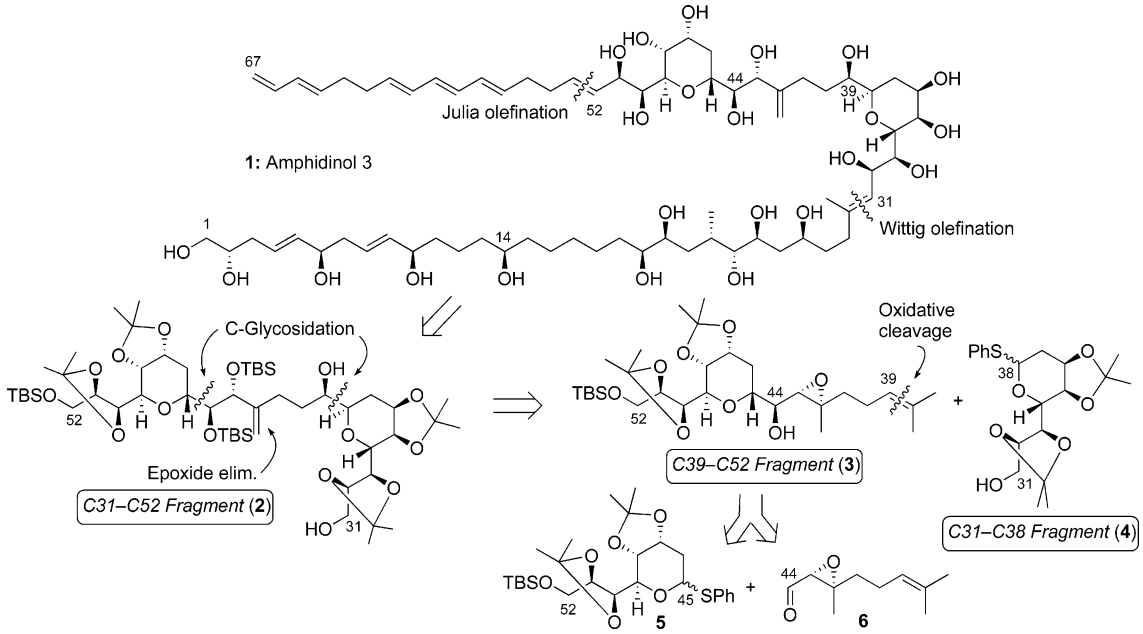
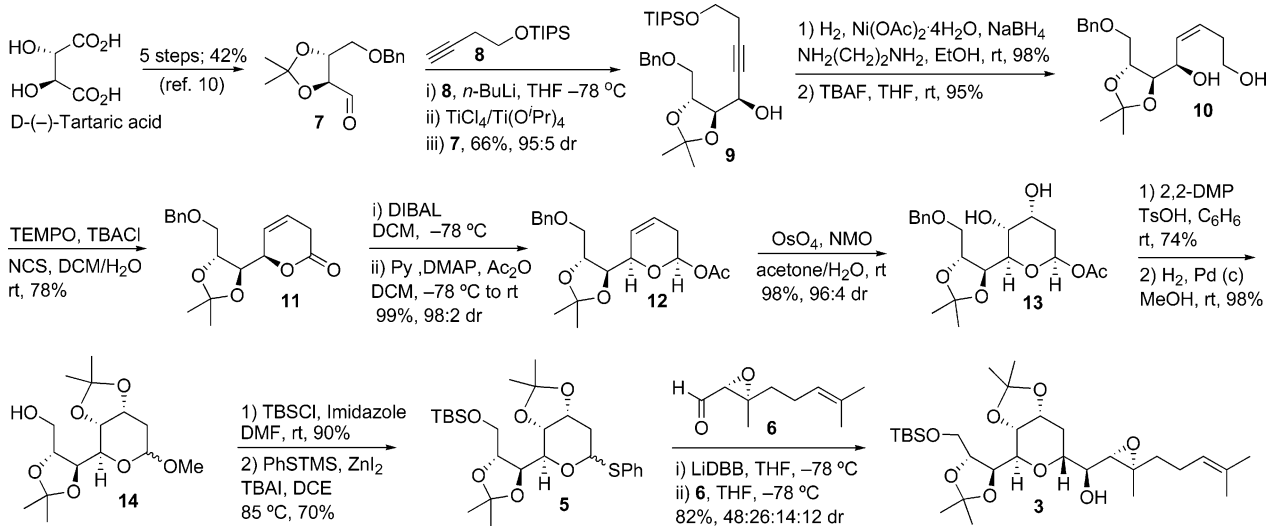
Scheme 1. Retrosynthetic Analysis of Amphidinol 3 (**1**)



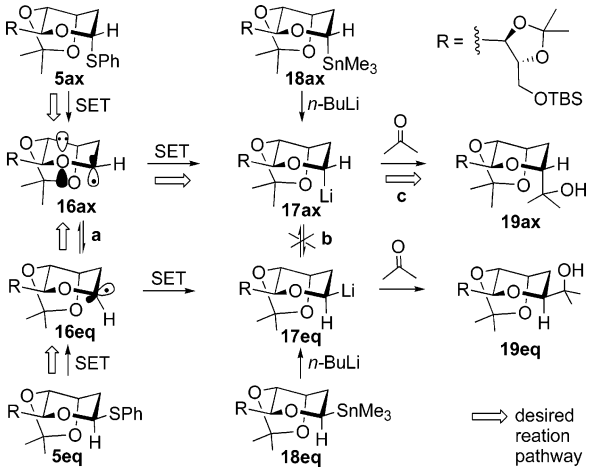
and **5,** respectively (Scheme 1). This convergent approach takes maximum advantage of the partial symmetry of amphidinol 3.

The preparation of *C*-glycoside donor **5** commenced from aldehyde **7**,[10] a known chiral synthon conveniently obtained by standard refunctionalization of D-(−)-tartaric acid (Scheme 2). Aldehyde **7** was coupled with a titanium acetylide leading to alcohol **9** with high diastereoselectivity (95:5 dr).[10] Partial reduction of the triple bond under P-2 nickel reduction conditions[11] and alcohol desilylation afforded diol **10**. Primary-selective TEMPO alcohol oxidation followed by subsequent lactol oxidation efficiently provided lactone **11**.[12] Reductive acetylation of lactone **11** diastereoselectively produced acetoxy ether **12**,[13] which was then subjected to dihydroxylation conditions. Osmium tetraoxide oxidation of lactol acetate **12** afforded the desired diastereomeric diol **13** (96:4 dr) by a selective approach of the oxidant to the less sterically hindered face of the alkene. This reductive acetylation/dihydroxylation sequence was more efficient than reversing the order of steps, as osmium tetraoxide oxidation of lactone **11** provided a 4:1 mixture of 1,2-*cis* diols. After a strategic reprotection sequence, chemoselective phenylthio acetal installation provided *C*-glycoside donor **5**. Reductive lithiation of phenylthio acetals **5** and subsequent coupling to known epoxy aldehyde **6**[14] led preferentially to the C31−C52 segment of amphidinol 3 (**3**) but with poor diastereoselectivity (48:26:14:12 dr). The addition showed modest

Scheme 2. Synthesis of the C39−C52 Fragment of Amphidinol 3 (**3**)



Scheme 3. Mechanism of the Reductive Lithiation Reaction



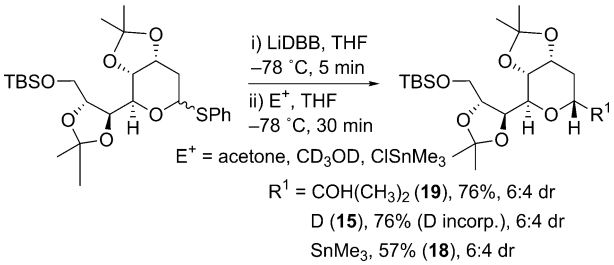
Felkin−Ahn selectivity.[15] Unexpectedly, the selectivity for axial lithiation of the 2-thiophenyl tetrahydropyrans **5** was very low.[16,17]

Lithium di-*tert*-butylbiphenylide (LiDBB)[18] reacts with 2-thiophenyltetrahydropyrans by a single-electron transfer (SET) normally producing a dynamic mixture of anomeric radicals, which equilibrate toward the thermodynamically more stable axial radical.[19] The preferred axial radical is then reduced by a second SET providing a thermodynamically less stable axial organolithium.[16a]

The loss of selectivity in the overall reductive lithiation of **5** and coupling with an electrophile could have been caused by (a) nonselective axial radical formation, (b) poor configurational stability of the organolithium intermediates, or (c) nonstereospecific electrophilic addition (Scheme 3). Reductive lithiation of a mixture of phenylthio acetals **5** and trapping with different electrophiles such acetone, CD_3OD, or Me_3SnCl led to a ca. 6:4 mixture of adducts independent of the identity of the electrophile (Scheme 4). Apparently, the alkyllithium is formed with poor selectivity but reacts with retention of configuration.

Alternative preparation of the organolithium intermediates (**17ax** and **17eq**) via tin−lithium exchange and trapping with acetone confirmed their configurational stability and their stereospecific reaction with acetone as electrophile (Scheme 3). The configurational stability of the organolithium intermediates generated by reductive lithiation at −78 °C was

Scheme 4. Reductive Lithiations of Phenylthio Acetals **5**

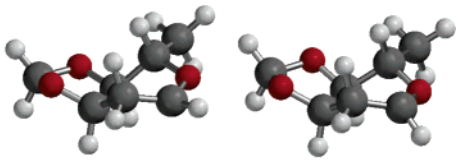


also tested at −50 °C for 30 min without any change of selectivity after acetone trapping. Reductive lithiation of each individual phenylthio acetal, **5ax** and **5eq**, in the presence of a large excess of LiDBB (inverse addition) and subsequent trapping with acetone gave again a ca. 6:4 mixture of adducts, confirming the lack of selective formation of axial radical intermediate **16ax** or its subsequent reduction.

The thermodynamic preference of the radical intermediates did not favor the formation of an axial radical stabilized by pseudoanomeric effect. This preference is probably due to a twist-boat conformation of the pyranosyl radicals generated. Conformational analysis of the *C*-glycosidation adducts (**3**, **19ax**, and **18ax**) by ^{1}H NMR suggested that protected pyranosides with such substitution patterns have a tendency to adopt twist-boat-like conformations.[20]

Conformational analysis of anomeric radical intermediate **16** would be helpful in understanding the stereochemical outcome of its reductive lithiation and coupling reactions with electrophiles. Computational studies of a model radical intermediate **26**, analogue to radical **16**, revealed a preference for boat conformations (Scheme 5). The calculated low

Scheme 5. Conformational Analysis of Model Pyranosyl Radical Intermediate **26** at UB3LYP/6-31G*



trans configuration (0.0 kcal/mol) cis configuration (0.2 kcal/mol)

energy difference between *trans* and *cis* boat radicals was only 0.2 kcal/mol and was in agreement with all our experimental results.

To increase the diastereoselectivity on the reductive lithiation of **5** and coupling with **6**, we investigated a conformational restriction strategy. The conformational influence of the protecting groups installed on the *C*-glycoside

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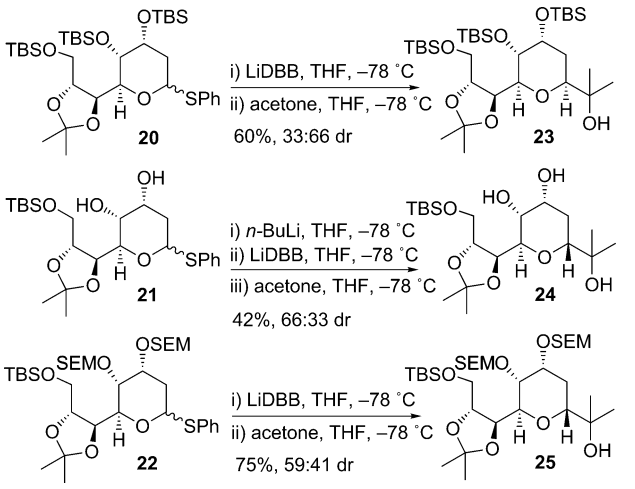
(18) LiDBB is an arene radical anion reducing agent first described by Freeman: Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
(19) Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375.
(20) See Supporting Information.

Scheme 6. Reductive Lithiation of Phenylthio Acetals **20**, **21**, and **22**



donor should affect the stereoselectivity.[21] We identified the cyclic acetal of **5** as potentially responsible for the lack of selectivity on its reductive lithiation. Thus, we studied three differently protected *C*-glycoside donors (**20**, **21**, and **22**) that did not incorporate bridging protecting groups on the glycoside (Scheme 5), all conveniently prepared from α-acetoxy ether **13**.[20] Reductive lithiation of diol **21** and bis-SEM analogue **22** followed by coupling with acetone provided mixtures similar to those observed with bis-acetonide **5**. The exception was bis-TBS ether **20** that led to a 33:66 ratio favoring the equatorial isomer. This exception was probably due to a ring inversion of the pyranosyl ring caused by a 1,2-diequatorial interaction of the OTBS groups and the alkyl chain substituent of the THP ring.[21] Variation in the protecting groups did influence the stereoselectivity, but none of the protecting groups led to useful levels of selectivity.

In summary, we have designed a convergent synthesis of the central core of amphidinol 3. Our strategy was implemented on the preparation of the C39−C52 fragment (**3**) in 16 steps, which also constitutes a formal synthesis of the C31−C38 segment (**4**). The synthesis includes the use of a cyclic α-acetoxy ether **12** as a transient intermediate capable of directing a diastereoselective dihydroxylation reaction. The nucleophilic *C*-glycosidation reaction of phenylthio acetal **5** and key coupling with aldehyde **6** was studied in order to increase its diastereoselectivity. The anomalous conformational behavior of the derived radical intermediates was influenced but not improved by alternate protecting group patterns.

The modest selectivity in the key coupling reaction led us to investigate nucleophilic additions to an oxocarbenium ion derived from the lactol acetate **13**. These oxocarbenium ion additions are highly diastereoselective and form the crux of our revised approach to amphidinol 3.

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Supporting Information Available: Experimental procedures and characterization data of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Matsuda has described a conformational restriction strategy for controlling the stereochemical outcome of pyranosyl radical reactions: (a) Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870. (b) Abe, H.; Terauchi, M.; Matsuda, A. Shuto, S. *J. Org. Chem.* **2003**, *68*, 7439.