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Synthesis of the AB Subunit of Angelmicin B through a Tandem Alkoxy Radical Fragmentation-Etherification Sequence

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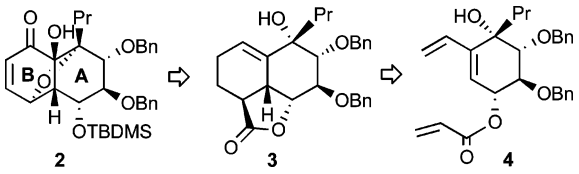
ABSTRACT



The synthesis of the tricyclic enone 2, corresponding to the AB subunit of the novel tyrosine kinase inhibitor angelmicin B, is described. The strategy centers on an intramolecular Diels–Alder (IMDA) reaction on triene 4 to provide the complex decalin 3, which is elaborated to 2. Other key steps are the formation of the THF ring in 2 through a tandem alkoxy radical fragmentation-etherification on the lactol derived from 3, and the synthesis of 4 via a ring-closing ene-yne metathesis (RCEYM).

Angelmicin B, was first isolated from *Microbispora rosea* by Uehara and co-workers in 1993, and later independently found with other congeners in a different subspecies, and named hibarimicin B (Figure 1).[1−3] Angelmicin B has attracted interest as a potential agent in differentiation therapy because it inhibits proliferation and induces differentiation in HL-60 human myeloid leukemia tumor cells (IC_{50}: 0.10 ± 0.02 μg/mL). It has been suggested that these effects might be linked to the specific inhibition of *src* tyrosine kinase. However, a more complex mechanism appears to be involved because both the antiproliferative activity and the induction of differentiation occur at about 100-fold lower concentration than *src* tyrosine kinase inhibiton.[4]

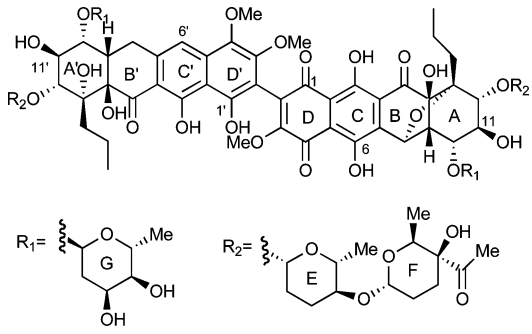


Figure 1. Angelmicin B (1).

Angelmicin B is pseudo-dimer comprised of similar anthraquinoid derived cyclitol segments ABCD and A′B′C′D′ segments, which are connected through the D−D′ biaryl

(1) Uehara, Y.; Li, P. M.; Fukazawa, H.; Mizuno, S.; Nihei, U.; Nishio, M.; Hanada, M.; Yamamoto, C.; Furumai, T.; Oki, T. *J. Antibiot.* **1993**, *46*, 1306.

(2) (a) Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett.* **1996**, *37*, 2785. (b) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 394.

(3) (a) Cho, S. I.; Fukazawa, H.; Honma, Y.; Kajiura, T.; Hori, H.; Igarashi, Y.; Furumai, T.; Oki, Y.; Uehara, Y. *J. Antibiot.* **2002**, *55*, 270. (b) Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 61. (c) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 53. (d) Hori, H.; Kajiura, T.; Igarashi, Y.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 46.

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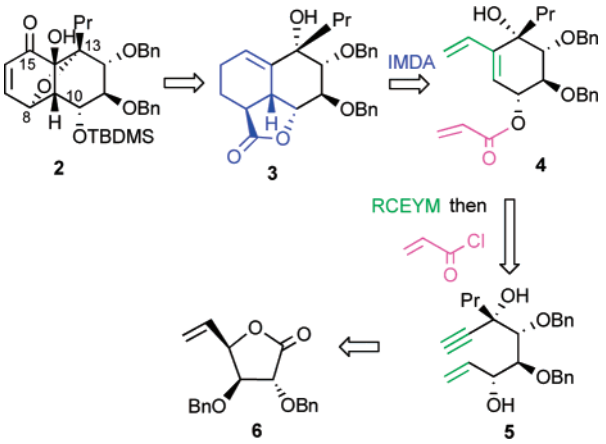
bond. The A and A′ cyclitol residues are glycosylated and the BCD and B′C′D′ segments vary in the oxidation states of the individual rings. The absolute configurations of the sugar units E, F, and G, the configuration at C13′, and the relative stereochemistry between distal rings A and A′ are unknown. In addition, it is unclear whether the natural structure represents a preferred atropisomer with respect to the D−D′ linkage. Contradicting results pertaining to this issue have been reported by Roush and Sulikowski.[5a,6b] The structural complexity and ambiguities combined with the intriguing biological properties make angelmicin B an important synthetic target.[5,6]

Sulikowski and co-workers have described an intermolecular Diels−Alder approach to a relatively simple model for the AB and A′B′ rings.[6] More recently, the Roush group has disclosed the synthesis of a derivative of the tricyclic enone **2**, which contained different alcohol protecting groups. This synthesis entails a key intramolecular aldol reaction on a stereochemically complex tetrahydrofuran substrate. Overall, the final product was obtained in 16 steps and less than 2% starting from a L-glyceraldehyde derivative and a chiral (*Z*)-γ-silyl-allylborane.[5]

We envisaged an approach to **2** that centered on the elaboration of a complex decalin **3**, which could be obtained from the IMDA[7] reaction on triene **4** (Scheme 1). Triene **4**

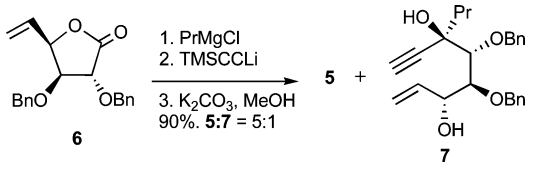
Scheme 1. Retrosynthetic Analysis of the AB Subunit



was expected from enyne **5** through a RCEYM strategy.[8,9] The known lactone **6**[10] appeared to be an appropriate precursor to **5**.

Treatment of lactone **6**[11] with nPrMgCl at −78 °C provided the hemiketal product, which was exposed in a separate step to TMSCCLi (Scheme 2). Desilylation of the

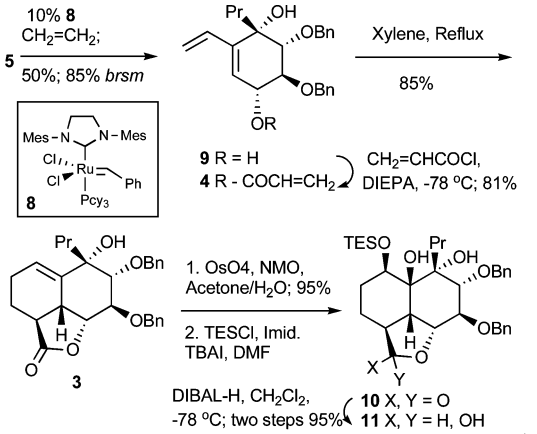
Scheme 2



crude product provided a 90% yield of **5** and its epimer **7** (respective ratio, *ca* 5:1). Similar selectivity has been observed for the addition of acetylide anions to related substrates.[12] The stereochemistry of **5** was confirmed by NOESY of later products (**3**, **9**, **15**) and single-crystal X-ray crystallography on **15** (vide infra).

RCEYM on enyne diol **5** was effected under Mori's conditions, using 10% Grubb's second generation catalyst under an ethylene atmosphere at room temperature in CH_2Cl_2 (Scheme 3).[13] Diene **9** was obtained in 50% isolated yield

Scheme 3



or 85% based on recovered **5**. Attempts to optimize this reaction by increasing the reaction temperature, varying the alcohol protecting groups or using the TMS protected acetylene were not successful. The ethylene atmosphere was also found to be essential. Selective esterification of diol **9** with acroyl chloride provided **4**, the triene substrate for the

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(6) (a) Lee, C. S.; Audelo, M. Q.; Reibenpies, J.; Sulikowski, G. A. *Tetrahedron* **2002**, *58*, 4403. (b) Maharoof, U. S.; Sulikowski, G. A. *Tetrahedron Lett.* **2003**, *44*, 9021. (c) Kim, K.; Maharoof, U. S.; Raushel, J.; Sulikowski, G. A. *Org. Lett.* **2003**, *5*, 2777−2780. (d) Lee, W.; Kim, K.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 1687.

(7) For recent reviews on IMDA see: (a) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820−849. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (c) Takao, K.-I.; Munakata, R.; Tadano, K.-I. *Chem. Rev.* **2005**, *105*, 4779−4807.

(8) For recent reviews on RCEYM see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2716−2203.

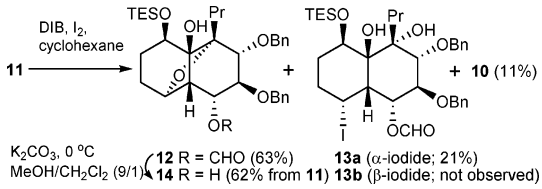
(9) For RCEYM on carbohydrate derivatives see: (a) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441−4449. (b) Dolhem, F.; Lièvre, C.; Demailly, G. *Eur. J. Org. Chem.* **2003**, 2336−2342. (c) Dolhem, F.; Lièvre, C.; Demailly, G. *J. Org. Chem.* **2004**, *69*, 3400−3407.

(10) Jia, C.; Zhang, Y.; Zhang, L. *Tetrahedron: Asymmetry* **2003**, *14*, 2195.

(11) The synthesis of **6** in ref 10 is achieved in eight steps from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose. In the present study, using a variation of this approach, **6** was obtained in six steps and ca 80% overall yield from methyl-α-D-glucopyranoside (supporting information).

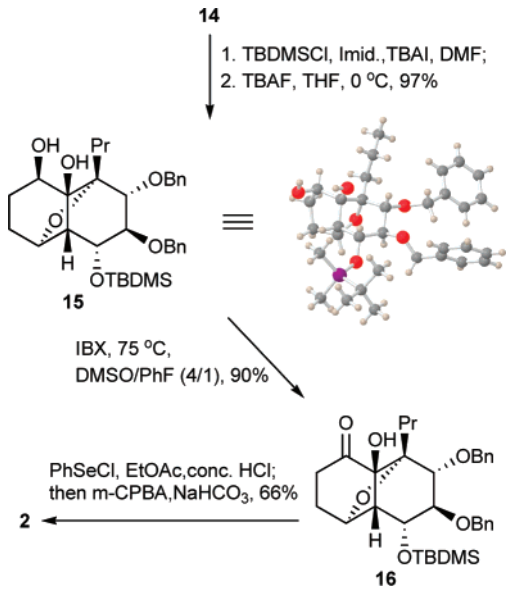
key IMDA reaction. The reaction of **4** in xylene at reflux afforded the exo adduct **3** with the desired configuration at the ring junction (C9), as the sole DA product. The structure of **3** was confirmed by 2D COSY, NOESY, and HSQC experiments (Supporting Information). High exo selectivity in IMDA reactions of related substrates has been previously noted.[14]

Scheme 4



The IMDA product **3** appeared exquisitely suited for elaboration to the desired target **2**. Thus the convex topography of **3** suggested that stereoselective dihydroxylation of the alkene would facilitate the introduction of the C14,15 acyloin moiety, and oxidative fragmentation of the lactol derived from **3** should pave the way for tetrahydrofuran formation. Accordingly, treatment of **3** under standard dihydroxylation conditions afforded a single triol diastereomer (Scheme 3), in which the stereoselectivity of the dihydroxylation was deduced in a later derivative (cf **15**, Scheme 5). After selective protection of the secondary alcohol as the triethylsilyl ether, the resulting lactone **10** was treated with DIBAL-H to give lactol **11** in 90% yield from **3**. The overall yield of the highly substituted decalin **11** from enyne diol **5** was 53% based on recovered **5** (31% isolated).

Scheme 5



In preparation for the introduction of the THF ring in the final product, lactol **11** was treated with diiodosobenzene diacetate/I_2 following the conditions developed by Suárez (Scheme 4).[15] Although we had anticipated a mixture of epimeric iodides **13a** and **13b**, we isolated the cyclic ether **12** directly as the major product in 63% yield. Iodide **13a** (21%) and a small amount of lactone **10** (11%) were also obtained but there was no evidence for **13b**. Lactone **10** was inseparable from **12** and product separation was facilitated by treatment of the mixture with K_2CO_3 in MeOH/CH_2Cl_2. This reaction gave the tricylcic diol **14** and recovered lactone **10**, which were easily separated. The overall yield of **14** from **11** was 62%. The structure of **14** was confirmed through X-ray crystallography of the later derivative, **15** (vide infra, Scheme 5). Iodide **13a** was assigned from 2D COSY, NOESY, and HSQC experiments (Supporting Information).

The mechanism for the formation of THF **12** is at this point unclear. It is possible that the reaction proceeds through fragmentation of an initial alkoxy radical, thence a mixture of **13a** and **13b**. The absence of **13b** in the reaction mixture could be an indication that this compound is rapidly converted to **12** via an intramolecular displacement pathway, whereas **13a** is not. Although related radical pathways to cyclic acetals have been reported, the analogous transformation to cyclic ethers is unusual.[15] Notwithstanding the mechanistic underpinings, this reaction provides simultaneous entry to potential precursors to both the AB and A′B′ subunits of Angelmicin B, that is, THF **12** and iodide **13a**, respectively. In this vein, elaboration of **12** to a more advanced precursor for the AB subunit was next investigated.

Accordingly, **14**, the aforementioned diol derivative of **12** was subjected to standard alcohol protecting group changes, to give diol **15**. Treatment of **15** with *o*-iodoxybenzoic acid (IBX) in DMSO/PhF at 75 °C for 20 h according to the Nicolaou procedure gave cyclohexanone **16** in 90% yield.[16] In contrast to the reported reactivity of this reagent, a prolonged reaction time, higher temperatures, or treatment of **16** with IBX in a separate step, did not effect further oxidation to the cyclohexenone **2**. Eventually, using the Sharpless-Reich protocol[17] that was applied to a similar intermediate in the Roush synthesis,[5b] **16** was converted to **2** in 66% isolated yield (80% brsm). The ^{1}H and ^{13}C NMR data for **2** was very similar to the data for the Roush derivative, which was different with respect to the alcohol protecting groups.

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In summary, the AB ring subunit of angelmicin B (hibarimicin B) was prepared in 15 steps and 9% yield (17% *brsm*) from the known carbohydrate lactone **6**. The synthetic strategy, which sequences a RCEYM/IMDA protocol and an unusual tandem alkoxy radical fragmetation-etherification, is conceptually very different from an earlier synthesis of a closely related target. Application of this approach to the A′B′ subunit of angelimicin B and congeners is being pursued and will be reported in due course.

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Supporting Information Available: Procedures and characterization of all new compounds, NMR charts for selected intermediates, and X-ray data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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