

Org Lett. Author manuscript; available in PMC 2009 June 8.

Published in final edited form as:

Org Lett. 2008 April 3; 10(7): 1337–1340. doi:10.1021/ol703036y.

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

Jialiang Li, Louis J. Todaro, and David R. Mootoo\*

Department of Chemistry, Hunter College, 695 Park Avenue, New York, New York 10065 and The Graduate Center, CUNY, 365 5th Avenue, New York, New York 10016

## **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 $_{50}$ :  $0.10 \pm 0.02~\mu g/mL$ ). 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.  $^4$ 

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 bond. The A

<sup>© 2008</sup> American Chemical Society

<sup>\*</sup>E-mail: dmootoo@hunter.cuny.edu.

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. 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)- $\gamma$ -silylallylborane. S

We envisaged an approach to 2 that centered on the elaboration of a complex decalin 3, which could be obtained from the IMDA<sup>7</sup> reaction on triene 4 (Scheme 1). Triene 4 was expected from enyne 5 through a RCEYM strategy.<sup>8,9</sup> 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 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. <sup>12</sup> 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  $\bf 5$  was effected under Mori's conditions, using 10% Grubb's second generation catalyst under an ethylene atmosphere at room temperature in CH<sub>2</sub>-Cl<sub>2</sub> (Scheme 3). <sup>13</sup> Diene  $\bf 9$  was obtained in 50% isolated yield or 85% based on recovered  $\bf 5$ . 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  $\bf 9$  with acroyl chloride provided  $\bf 4$ , the triene substrate for the key IMDA reaction. The reaction of  $\bf 4$  in xylene at reflux afforded the exo adduct  $\bf 3$  with the desired configuration at the ring junction (C9), as the sole DA product. The structure of  $\bf 3$  was confirmed by 2D COSY, NOESY, and HSQC experiments (Supporting Information). High exo selectivity in IMDA reactions of related substrates has been previously noted. <sup>14</sup>

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).

In preparation for the introduction of the THF ring in the final product, lactol **11** was treated with diiodosobenzene diacetate/I<sub>2</sub> following the conditions developed by Suárez (Scheme 4).

<sup>15</sup> 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<sub>2</sub>CO<sub>3</sub> in MeOH/CH<sub>2</sub>Cl<sub>2</sub>. 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. <sup>15</sup> Notwithstanding the mechanistic underpinings, this reaction provides simultaenous 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. <sup>16</sup> 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 <sup>17</sup> that was applied to a similar intermediate in the Roush synthesis, <sup>5b</sup> **16** was converted to **2** in 66% isolated yield (80% brsm). The <sup>1</sup>H and <sup>13</sup>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.

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.

## **Acknowledgment**

This investigation was supported by grant R01 GM57865 from the National Institute of General Medical Sciences of the National Institutes of Health (NIH). "Research Centers in Minority Institutions" award RR-03037 from the National Center for Research Resources of the NIH, which supports the infrastructure and instrumentation of the Chemistry Department at Hunter College, is also acknowledged.

## References

- (1). Uehara Y, Li PM, Fukazawa H, Mizuno S, Nihei U, Nishio M, Hanada M, Yamamoto C, Furumai T, Oki T. J. Antibiot 1993;46:1306. [PubMed: 8407594]
- (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. [PubMed: 9630861]
- (3)(a). Cho SI, Fukazawa H, Honma Y, Kajiura T, Hori H, Igarashi Y, Furumai T, Oki Y, Uehara Y. J. Antibiot 2002;55:270. [PubMed: 12014442] (b) Igarashi Y, Kajiura T, Furumai T, Hori H, Higashi K, Ishiyama T, Uramoto M, Uehara Y, Oki T. J. Antibiot 2002;55:61. [PubMed: 11918068] (c)

- Kajiura T, Furumai T, Igarashi Y, Hori H, Higashi K, Ishiyama T, Uramoto M, Uehara Y, Oki T. J. Antibiot 2002;55:53. [PubMed: 11918066] (d) Hori H, Kajiura T, Igarashi Y, Furumai T, Higashi K, Ishiyama T, Uramoto M, Uehara Y, Oki T. J. Antibiot 2002;55:46. [PubMed: 11918065]
- (4)(a). Yokoyama A, Okabekado J, uehara Y, Oki T, Tomoyasu S, Tsuruoka N, Honma Y. Leuk. Res 1996;20:491. [PubMed: 8709621] (b) Showalter HDH, Kraker A. J. Pharmacol. Ther 1997;76:55.
- (5)(a). Narayan S, Roush WR. Org. Let 2004;6:3789. [PubMed: 15469350] (b) Lambert WT, Roush WR. Org. Let 2005;7:5501. [PubMed: 16288541]
- (6)(a). Lee CS, Audelo MQ, Reibenpies J, Sulikowski GA. Tetrahedron 2002;58:4403. (b) Maharoof US, Sulikowski GA. Tetrahedron Lett 2003;44:9021. (c) Kim K, Maharoof US, Raushel J, Sulikowski GA. Org. Lett 2003;5:2777–2780. [PubMed: 12889872] (d) Lee W, Kim K, Sulikowski GA. Org. Lett 2005;7:1687. [PubMed: 15844881]
- (7)(a). For recent reviews on IMDA see: Bear BR, Sparks SM, Shea KJ. Angew. Chem., Int. Ed 2001;40:820–849.849(b)Nicolaou KC, Snyder SA, Montagnon T, Vassilikogiannakis G. Angew. Chem., Int. Ed 2002;41:1668–1698.1698(c)Takao K-I, Munakata R, Tadano K-I. Chem. Rev 2005;105:4779–4807.4807 [PubMed: 16351062]
- (8)(a). For recent reviews on RCEYM see: Diver ST, Giessert AJ. Chem. Rev 2004;104:1317–1382.1382 [PubMed: 15008625](b)Bruneau C, Dixneuf PH. Angew. Chem., Int. Ed 2006;45:2716–2203.2203
- (9)(a). For RCEYM on carbohydrate derivatives see: Poulsen CS, Madsen R. J. Org. Chem 2002;67:4441–4449.4449 [PubMed: 12076140](b)Dolhem F, Lièvre C, Demailly G. Eur. J. Org. Chem 2003:2336–2342.2342(c)Dolhem F, Lièvre C, Demailly G. J. Org. Chem 2004;69:3400–3407.3407 [PubMed: 15132548]
- (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- $\alpha$ -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- $\alpha$ -D-glucopyranoside (supporting information).
- (12)(a). Reetz MT. Angew. Chem., Int. Ed. Engl 1984;23:556–569. (b) Boyer F-D, Hanna I, Richard L. Org. Lett 2001;3:3095–3098. [PubMed: 11574003]
- (13). Mori M, Sakaibara N, Kinoshita A. J. Org. Chem 1998;63:6082–6083. [PubMed: 11672225]
- (14). Chu-Moyer MY, Danishefsky SJ. J. Am. Chem. Soc 1992;114:8333-8334.
- (15)(a). Freire R, Marrero JJ, Rodriguez MS, Suárez E. Tetrahedron Lett 1986;27:383–385. (b) Bentancor C, Freire R, Pérez-Martin I, Prangé T, Suárez E. Org. Lett 2002;4:1295–1297. [PubMed: 11950346] (c) Bentancor C, Freire R, Pérez-Martin I, Prangé T, Suárez E. Tetrahedron 2005;61:2803–2814.
- (16)(a). Nicolaou KC, Zhong Y-L, Baran PS. J. Am. Chem. Soc 2000;122:7596–7597.
   (b) Nicolaou KC, Montagnon T, Baran PS, Zhong Y-L. J. Am. Chem. Soc 2002;124:2245–2258.
   [PubMed: 11878978]
   (c) Kaliappan KP, Ravikumar V. Org. Lett 2007;9:2417–2419.
   [PubMed: 17489601]
- (17)(a). Sharpless KB, Lauer RF, Teranishi AY. J. Am. Chem. Soc 1973;95:6137. (b) Reich HJ, Renga JM, Reich IL. J. Am. Chem. Soc 1975;97:5434. (c) Danishefsky S, Vaughan K, Gadwood R, Tsuzuki K. J. Am. Chem. Soc 1981;103:4136.

$$R_1 = \begin{cases} O & \text{i.Me} \\ O & \text{OH} \end{cases}$$
 $R_2 = \begin{cases} O & \text{i.Me} \\ O & \text{OH} \end{cases}$ 
 $R_3 = \begin{cases} O & \text{i.Me} \\ O & \text{OH} \end{cases}$ 

**Figure 1.** Angelmicin B (1).

**Scheme 1.** Retrosynthetic Analysis of the AB Subunit

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.