

Synthesis of the A–B Subunit of Angelmicin B

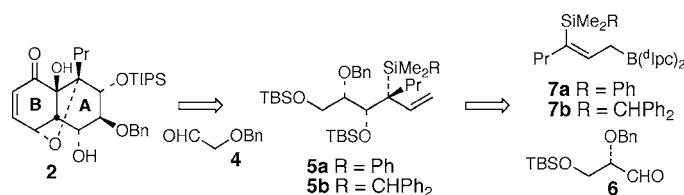
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ABSTRACT



An efficient synthesis of the tricyclic A–B subunit **2** of angelmicin B is described. A formal three-component coupling of aldehydes **4** and **6** with γ -silylallylborane **7** was employed to assemble the tetrahydrofuran core of **2**, a strategy highlighted by the stereoselective [3 + 2] annulation of allylsilanes **5a/b** with aldehyde **4**. The efficiency of the [3 + 2] annulation was greatly improved by using the allylic benzhydryldimethylsilane **5b** compared to the allyldimethylsilane **5a**.

Angelmicin B (**1**, Figure 1) is an oncogenic signal transduction inhibitor first isolated in 1993 from the culture broth of the rare actinomycete *Microbiospora*.^{1,2} Angelmicin B selectively inhibits protein tyrosine kinase with negligible inhibition of protein serine/threonine kinases A and C.¹ Additionally, **1** was found to inhibit the growth of tumor cells and to induce differentiation of human myeloid leukemia cells.³ It is unclear at present if these effects are related, however, as the concentration of angelmicin B required for *src* kinase inactivation is 100-fold higher than that required for inhibition of cell proliferation and induction of cell differentiation.^{3a} Although the aglycon of angelmicin B displayed more potent kinase inhibitory activity than angelmicin B itself, it was less selective than its glycosylated congeners and did not induce cell differentiation.^{3b} Hiba-

rimicin B, which was isolated independently in 1995,^{2b,4} is identical to angelmicin B.

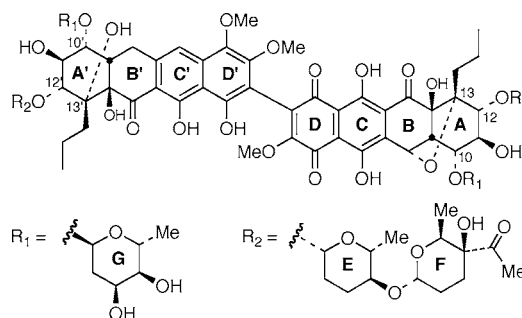


Figure 1. Angelmicin B (**1**).

Angelmicin B is pseudodimeric, with the two halves differing in the oxidation states of the B/B', C/C', and D/D'

(4) (a) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 394. (b) Cho, S. I.; Fukazawa, H.; Honma, Y.; Kajiura, T.; Hori, H.; Igarashi, Y.; Furumai, T.; Oki, T.; Uehara, Y. *J. Antibiot.* **2002**, *55*, 270.

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(1) 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.

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

(3) (a) Yokoyama, A.; Okabe-Kado, J.; Uehara, Y.; Oki, T.; Tomoyasu, S.; Tsuruoka, N.; Honma, Y. *Leukemia Res.* **1996**, *20*, 491. (b) Showlater, H. D. H.; Kraker, A. J. *Pharmacol. Ther.* **1997**, *76*, 55.

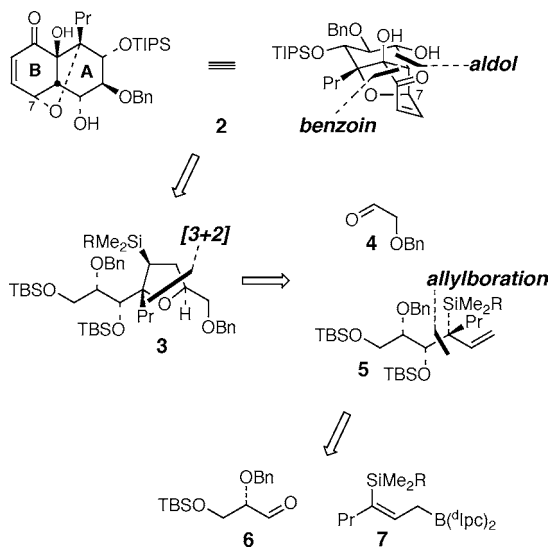
rings. Experimental evidence from a model system containing all four of the substituents ortho to the D–D' biaryl linkage has suggested that a substantial barrier (>20 kcal/mol) exists to atropisomerism by rotation about this bond.^{5d} However, Sulikowski has noted that atropisomerism is rapid about the D–D' bond in a model system containing three of the four flanking ortho substituents, owing to the accessibility of a quinone methide tautomer in this system.^{5c} Thus, it remains unknown if angelmicin B is a configurationally stable atropisomer and, if so, what the stereochemistry about the D–D' linkage might be. The absolute configurations of the E, F, and G sugar subunits, the stereochemistry at C13', and the relative configurations of the A–B/A'–B' rings also remain unassigned. However, it is presumed that the relative configurations at C13' and of the A–B and A'–B' ring systems are as shown in Figure 1 based on the assumption that both halves of angelmicin B derive from a common biosynthetic precursor.^{3b}

The compelling biological activity of angelmicin B, coupled with the stereochemical uncertainties noted above, make **1** an important synthetic target.⁵ We were attracted to the challenge of the synthesis of the stereochemically complex A–B ring system, which features seven contiguous asymmetric centers adorning an intriguing tricyclic scaffold. In this paper, we report a stereoselective synthesis of **2**, the A–B subunit of angelmicin B.

The formal three-component coupling of γ -silylallylboranes and two aldehydes developed in these laboratories constitutes a highly useful method for the stereoselective synthesis of substituted tetrahydrofurans.⁶ We sought to apply this strategy in the construction of the bridging THF ring in **2** as an initial goal in the synthesis of the A–B subunit (Scheme 1). Accordingly, A–B enone **2** was identified as a key synthetic target, with the expectation that **2** would also serve as a precursor to the related A'–B' unit via reductive fragmentation of the C(7)–O bond at an appropriate stage of the total synthesis. Antithetic disconnection of the two carbocyclic rings in **2** leads to the tetrahydrofuransilane **3**, the expected product of a [3 + 2] annulation reaction of aldehyde **4** and the tertiary allylic silane **5**.⁷ In turn, allylsilane **5** would be assembled in stereoselective fashion by the reaction of the known L-glyceraldehyde derivative **6**⁸ with the chiral (*Z*)- γ -silyl-allylborane **7**.⁹ Thus, **3** may be formally viewed as the three-component coupling product of **4**, **6**, and **7**.

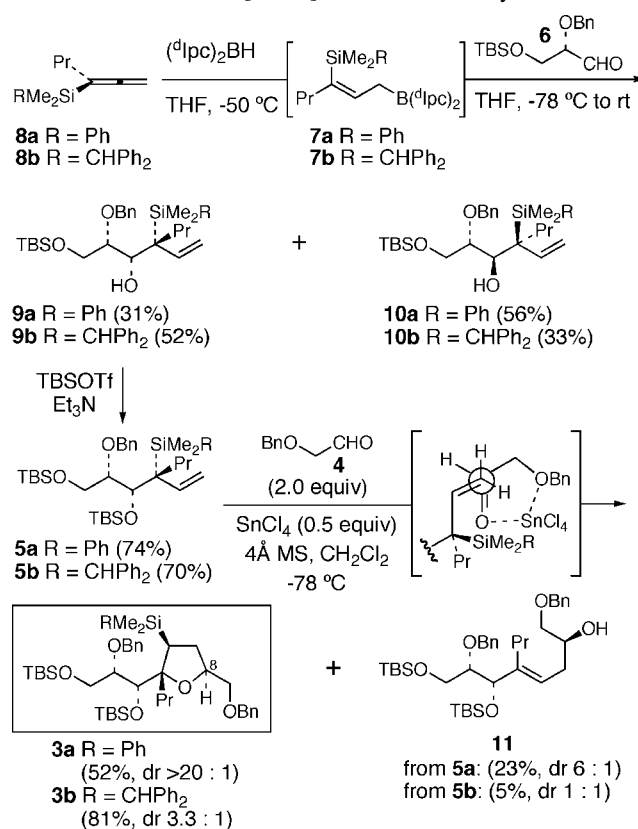
The synthesis of the A–B tetrahydrofuran core unit is depicted in Scheme 2. Hydroboration of allene **8a**⁹ with (*d*Ipc)₂BH¹⁰ at –50 °C followed by addition of aldehyde **6**

Scheme 1. Retrosynthetic Analysis AB Subunit **2** of Angelmicin B



to the resultant (*Z*)- γ -silylallylborane **7a** at –78 °C provided a 1:1.8 mixture of the β -hydroxysilanes **9a** and **10a**,⁹ with the undesired diastereomer **10a** predominating. Silylation of **9a** with TBSOTf and Et₃N gave **5a**, which was subsequently treated with 2-benzyloxyacetaldehyde (**4**; 2.0 equiv) and

Scheme 2. Synthesis of the THF Core of the Angelimicin B A–B Subunit via [3 + 2] Annulation of Allylsilane **5**



(5) For synthetic efforts targeting angelmicin B, see: (a) Lee, C.-S.; Audelo, M. Q.; Reibenpies, J.; Sulikowski, G. A. *Tetrahedron* **2002**, *58*, 4403. (b) Kim, K.; Maharoo, U. S. M.; Raushel, J.; Sulikowski, G. A. *Org. Lett.* **2003**, *5*, 2777. (c) Maharoo, U. S. M.; Sulikowski, G. A. *Tetrahedron Lett.* **2003**, *44*, 9021. (d) Narayan, S.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3789.

(6) (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461. (b) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.

(7) For a review on [3 + 2] annulation chemistry, see: Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

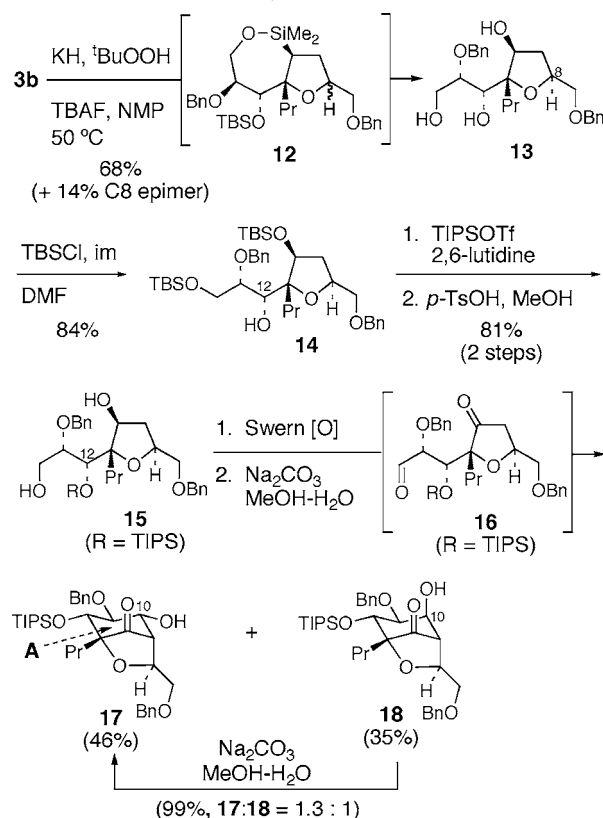
(8) Mukaiyama, T.; Shiina, I.; Sakata, K.; Emura, T.; Seto, K.; Saitoh, M. *Chem. Lett.* **1995**, 179.

(9) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693.

SnCl₄ (0.5 equiv)¹¹ to afford the [3 + 2] adduct **3a** (dr > 20:1) along with homoallylic alcohol **11** (dr 6:1) in a ratio of 2.3:1. The stereochemistry of **3a** is consistent with the involvement of the *syn*-synclinal¹² transition state **A** illustrated in Scheme 2. The competition of an allylation reaction pathway leading to **11** prompted an evaluation of the effect that a different trialkylsilyl group would exert on the partition between the two competing pathways. Encouraged by reports from Meyers¹³ and Woerpel¹⁴ detailing the [3 + 2] annulation reactivity of allylic trityldimethyl- and benzhydryldimethylsilanes, respectively, we sought to modify our synthesis by substituting the benzhydryldimethylsilyl-substituted allene **8b** for **8a** in the sequence outlined in Scheme 2. Thus, hydroboration of **8b** followed by addition of **6** gave the desired β -hydroxysilane diastereomer (**9b**) as the major product, in this case favored by a ratio of 1.6:1 over **10b**. Although this reversal in diastereoselectivity from the phenyldimethylsilyl series is fortuitous, its origins are not yet clear.¹⁵ Silylation of **9b** gave **5b**, which was subjected to the SnCl₄-promoted reaction with **4** using the previously described conditions to give **3b** (dr 3.3:1) and **11** (dr 1:1) in a much-improved ratio of 16:1. The reason for the diminished [3 + 2] annulation diastereoselectivity (relative to **5a** \rightarrow **3a**) in this case is unclear; however, the desired diastereomer of **3b** is obtained in 62% overall yield from **5b**, with minimal interference from the allylation pathway leading to **11**. Reports of efficient, stereoselective syntheses of 2,2,5-trisubstituted tetrahydrofurans via [3 + 2] annulation reactions of tertiary allylsilanes (e.g., **5** \rightarrow **3**) are scarce;⁹ this synthesis of **3b** from **5b** thus represents a valuable extension of this methodology.

We next turned our attention to the elaboration of **3b** (an inseparable 3.3:1 mixture of diastereomers) via the first of two carbocyclizations required by our synthetic plan. Subjection of **3b** to Woerpel's modification (KH, *t*-BuOOH, TBAF in *N*-methyl pyrrolidinone (NMP))¹⁶ of the Tamao–Fleming oxidation¹⁷ proceeded via siloxane intermediate **12**¹⁸ and gave triol **13** in 68% yield along with 14% of its C(8) epimer (Scheme 3). Regioselective silylation of **13** with TBS-Cl and imidazole in DMF then provided the di-TBS ether **14** in 91% yield. After masking the remaining C(12) hydroxyl group

Scheme 3. A-Ring Assembly via Intramolecular Aldol Cyclization



as a TIPS ether, the TBS ethers were cleaved with *p*-TsOH·H₂O in MeOH to provide diol **15** in 81% yield over two steps. Swern oxidation¹⁹ of **15** gave the keto aldehyde **16** which, without purification, was treated with Na₂CO₃ in MeOH–H₂O²⁰ to effect aldol cyclization. This provided the desired aldol product **17** in 46% yield, along with 35% of its C(10) epimer **18**. Gratifyingly, these compounds were separable by silica gel chromatography, and resubjection of **18** to the original aldol conditions (Na₂CO₃ in MeOH–H₂O) returned the identical 1.3:1 equilibrium ratio (¹H NMR analysis) of **17** and **18** in 99% yield. Consequently, aldol **17** was obtained in 71% overall yield from **15** after two recycles of **18**.

Installation of the B ring of **2** was initiated by the homologation of the carbon chain at C(7) of **17**. Accordingly, treatment of **17** with TES-Cl and imidazole followed by hydrogenolysis of the primary benzyl ether gave alcohol **19** in 96% yield (Scheme 4). Swern oxidation of **19** followed by in situ treatment of the resulting aldehyde with (triphenylphosphoranylidene)acetaldehyde at room temperature gave the expected (*E*)-enal, which was hydrogenated over Pd/C to afford keto aldehyde **20** in 71% yield over three steps. Initial attempts to achieve cyclization of **20** in the

(10) (a) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945. (b) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059.

(11) Use of stoichiometric quantities of SnCl₄ gave inferior ratios of **3**:**11**; for example, 21% **3a** and 45% **11** were isolated from **5a** using 1.1 equiv of SnCl₄.

(12) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.

(13) (a) Brengel, G. P.; Rithner, C.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 5144. (b) Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3230. (c) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517.

(14) (a) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379. (b) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675.

(15) The allylboration of **6** with γ -silylallylboranes **7a** and **7b** are stereochemically mismatched in the pathway leading to **9a** and **9b**.

(16) (a) Smirnovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044. (b) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945.

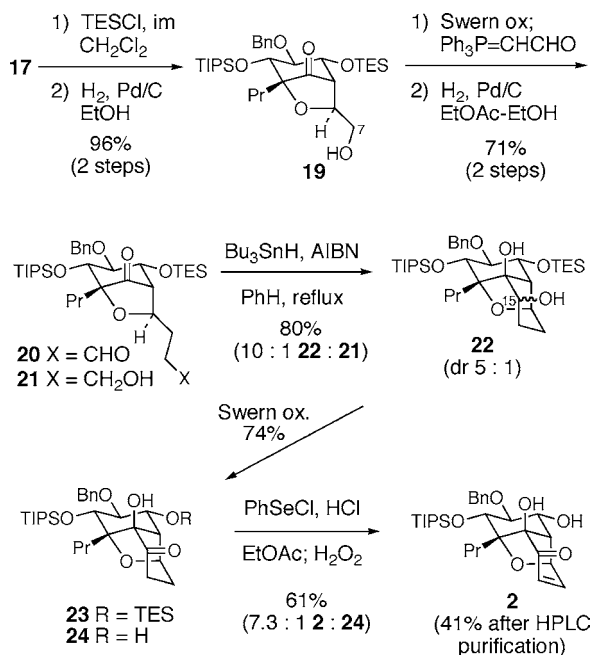
(17) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (c) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

(18) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405.

(19) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(20) For related intramolecular aldol cyclizations to form bicyclo[3.2.1]-octanes, see: (a) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765. (b) Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009.

Scheme 4. B-Ring Closure via Pinacol Cyclization: Synthesis of the A–B Subunit **2**



intramolecular benzoin manifold²¹ to give the α -hydroxy ketone **23** were unfruitful; however, pinacol cyclization using the method reported by Fu²² fortunately proved to be a viable alternative. Thus, treatment of **20** with Bu₃SnH and AIBN in refluxing PhH gave diol **22** (dr 5:1 at C(15)); contaminated

(21) (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, 346, 1097. (b) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111.

(22) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, 117, 7283.

with ca. 10% of alcohol **21** in 80% yield.²³ Subsequent oxidation of **22** under Swern conditions then afforded the desired ketone **23** in 74% yield, along with 5% of recovered **20**. Finally, dehydrogenation of the cyclohexanone moiety in **23** via α -selenylation/selenoxide elimination²⁴ was accompanied by cleavage of the C(10) TES ether, and a 7.3:1 mixture of the desired A–B enone **2** and ketone **24** was isolated in 61% yield. Further purification of this mixture by HPLC provided **2** (>95% purity) in 41% yield from **23**.

In conclusion, we have achieved the synthesis of the A–B subunit **2** of angelmicin B. The [3 + 2] annulation reaction of **5b** and **4** effected the construction of the tetrahydrofuran fragment **3b**. Intramolecular aldol and pinacol reactions were then employed to close the A and B rings, respectively. Overall, the synthesis of **2** from allene **8b** required 16 steps and proceeded in 2% overall yield. Further progress toward the total synthesis of angelmicin B will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(23) Interestingly, treatment of **20** with TiCl₄, Zn, and pyridine in THF at room temperature gave a 1:1.7 mixture of **22** (dr 1.7:1)/**21** in 48% yield.

(24) (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, 95, 6137. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, 97, 5434. (b) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, 103, 4136.