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Synthesis of the A–B Subunit of Angelmicin B

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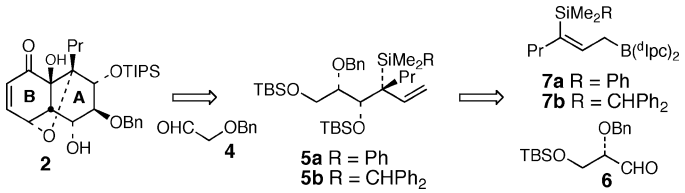
ABSTRACT



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 tetrahydrofuranyl core of 2, a strategy highlighted by the stereoselective [3 + 2] annulation of allylsilanes 5a/5b with aldehyde 4. The efficiency of the [3 + 2] annulation was greatly improved by using the allylic benzhydryldimethylsilane 5b compared to the allylic phenyldimethylsilane 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 *src* 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 differentitation.[3b] Hibarimicin B, which was isolated independently in 1995,[2b,4] is identical to angelmicin B.

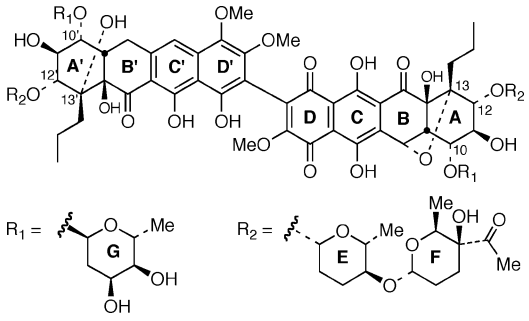


Figure 1. Angelmicin B (**1**).

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

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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. Antiobiot.* **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.

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(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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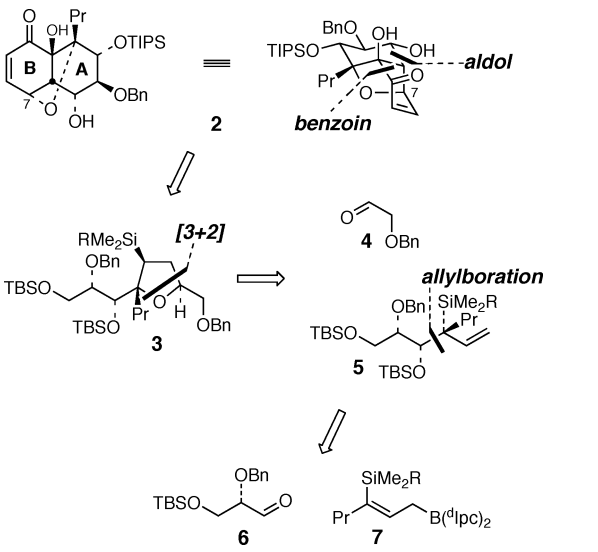
rings. Experimental evidence from a model system containing all four of the substituents ortho to the D−D′ biaryl linkage has suggested that a substantial barrier (>20 kcal/mol) exists to atropisomerism by rotation about this bond.[5d] However, Sulikowski has noted that atropisomerism is rapid about 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 confgurations 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 angelimicin B.

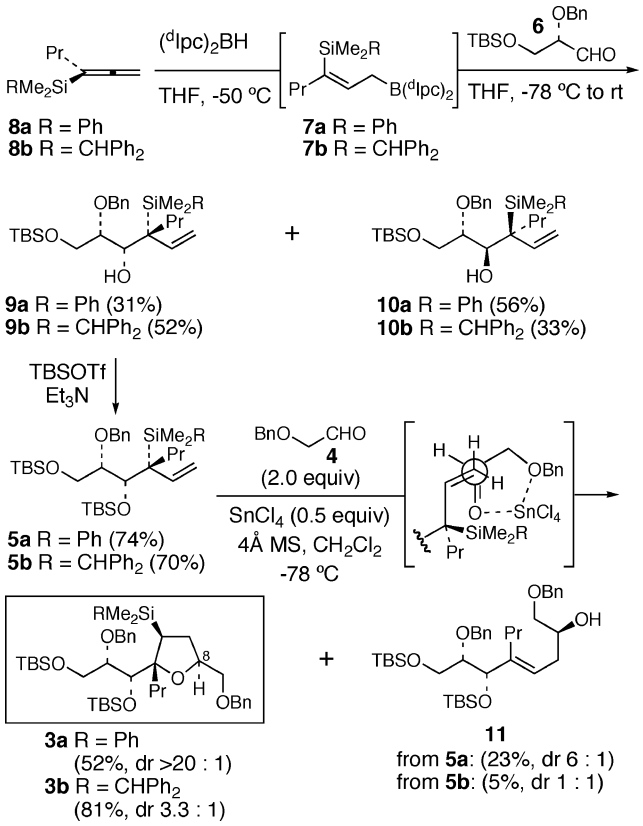
The formal three-component coupling of γ-silylallylboranes and two aldehydes developed in these laboratories constitutes a highly useful method for the stereoselective synthesis of substituted tetrahydrofurans.[6] We sought to apply this strategy in the construction of the bridging THF ring in **2** 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 tetrahydrofuranylsilane **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 $(^{d}Ipc)_2BH$[10] at −50 °C followed by addition of aldehyde **6** 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 Et_3N gave **5a**, which was subsequently treated with 2-benzyloxyacetaldehyde (**4**; 2.0 equiv) and

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



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



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(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.

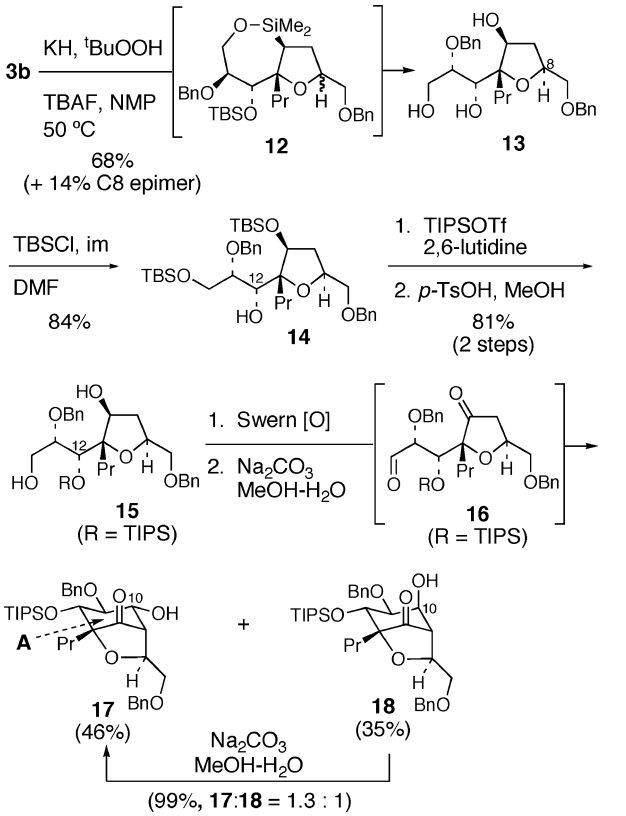
(8) Mukaiyama, T.; Shiina, I.; Sakata, K.; Emura, T.; Seto, K.; Saitoh, M. *Chem. Lett.* **1995**, 179.

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

$SnCl_4$ (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*-synclinal[12] 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 Meyers[13] and Woerpel[14] 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 $SnCl_4$-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** → **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** → **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 oxidation[17] 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·H_2O in MeOH to provide diol **15** in 81% yield over two steps. Swern oxidation[19] of **15** gave the keto aldehyde **16** which, without purification, was treated with Na_2CO_3 in MeOH−H_2O[20] 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 (Na_2CO_3 in MeOH−H_2O) returned the identical 1.3:1 equilibrium ratio (^{1}H 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

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(11) Use of stoichiometric quantities of $SnCl_4$ gave inferior ratios of **3**:**11**; for example, 21% **3a** and 45% **11** were isolated from **5a** using 1.1 equiv of $SnCl_4$.

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

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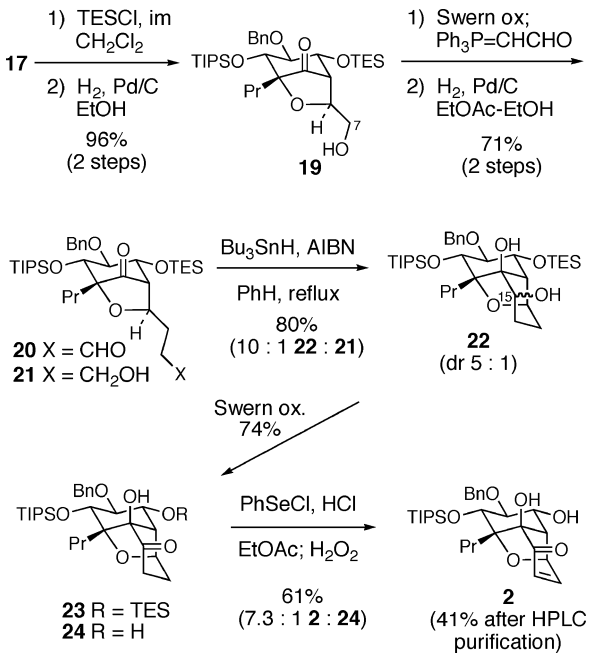
(20) For related intramolecular aldol cyclizations to form bicyclo[3.2.1]-octanes, see: (a) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765. (b) Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009.

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



intramolecular benzoin manifold[21] to give the α-hydroxy ketone **23** were unfruitful; however, pinacol cyclization using the method reported by Fu[22] fortunately proved to be a viable alternative. Thus, treatment of **20** with Bu_3SnH and AIBN in refluxing PhH gave diol **22** (dr 5:1 at C(15); contaminated 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 elimination[24] 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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(22) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283.

(23) Interestingly, treatment of **20** with $TiCl_4$, Zn, and pyridine in THF at room temperature gave a 1:1.7 mixture of **22** (dr 1.7:1)/**21** in 48% yield.

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