Letter

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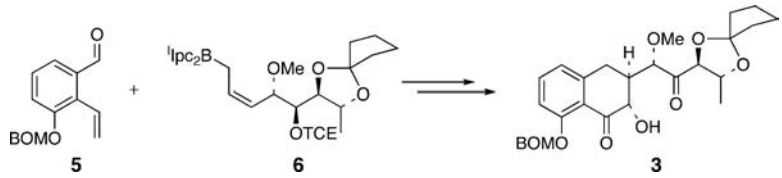
Org. Lett., **2008**, 10 (20), 4613-4616• DOI: 10.1021/ol8018727 • Publication Date (Web): 23 September 2008



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ORGANIC LETTERS

2008
Vol. 10, No. 20
4613−4616

Studies on the Synthesis of Durhamycin A: Stereoselective Synthesis of a Model Aglycone

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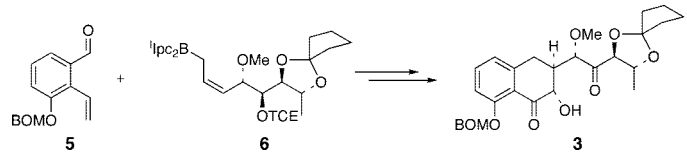
Received August 12, 2008

ABSTRACT



A stereoselective synthesis of the model aglycone corresponding to the anti-HIV aureolic acids durhamycins A (1) and B (2) is described.

The aureolic acids are a family of structually related antitumor antibiotics that include olivomycin A, chromomycin A_3, mithramycin, and UCH9.[1−7] Several members of this family have been used clinically.[1−3] The aglycone of the different family members differs only by the nature of the C(7) substituent. However, considerable structural diversity occurs in the 2,6-dideoxy di-, tri-, and tetrasaccharide units that are appended to the C(2)-hydroxyl and C(6)-phenol of the aglycone. The anticancer properties of the aureolic acids originate from their ability to bind to the minor groove of DNA as 2:1 complexes with Mg^{2+}.[8−12] Structural activity relationship data derive primarily from studies of the family of metabolites isolated along with the parent antibiotics, as well as from analogues generated biosynthetically.[13−17] Recent efforts especially from the Rohr laboratory have highlighted the importance of the oligosaccharide chains[13,14] as well as the C(3)[15−17] and C(7)[12,14] substituents on the biological properties of individual aureolic acids.

The newest members of the aureolic acid family are durhamycins A (**1**) and B (**2**),[18,19] which were isolated from *Actinoplanes durhamensis* (Figure 1). In contrast to all other well-studied aureolic acids, which are known for their antitumor properties (vide supra), durhamycins A and B have

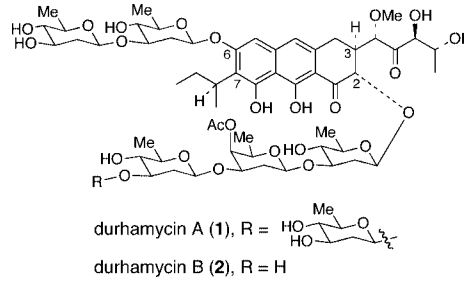


Figure 1. Durhamycins A and B.

(1) Remers, W. A. In *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; pp 133−175.
(2) Skarbek, J. D.; Speedie, M. K. In *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; Aszalos, A., Ed.; CRC Press: Boca Raton, FL, 1981; Vol. 1, pp 191−235.
(3) Remers, W. A.; Iyengar, B. S. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995; pp 577−679.
(4) Wohlert, S. E.; Künzel, E.; Machinek, R.; Méndez, C.; Salas, J. A.; Rohr, J. *J. Nat. Prod.* **1999**, *62*, 119.
(5) Ogawa, H.; Yamashita, Y.; Katahira, R.; Chiba, S.; Iwasaki, T.; Ashizawa, T.; Nakano, H. *J. Antibiot.* **1998**, *51*, 261.
(6) Katahira, R.; Uosaki, Y.; Ogawa, H.; Yamashita, Y.; Nakano, H.; Yoshida, M. *J. Antibiot.* **1998**, *51*, 267.
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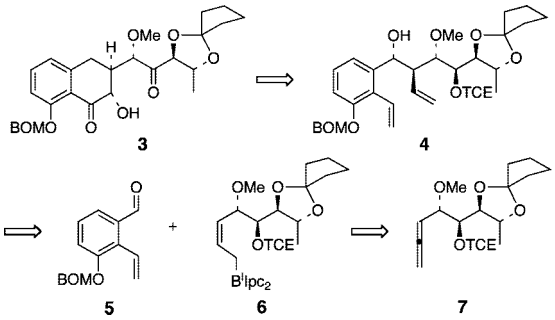
10.1021/ol8018727 CCC: $40.75
Published on Web 09/23/2008

shown potent inhibition of HIV Tat transactivation (IC_{50} = 4.8 and 48 nM, respectively) and appear to be relatively noncytotoxic.[5,13,18] The unique biological activity of the durhamycins has prompted us to explore new synthetic routes to the aglycone core that is more amenable to analogue synthesis than the routes to the aglycone employed[20,21] in our total synthesis of olivomycin A.[22] Accordingly, we report herein our initial studies on the development of a third-generation synthesis of the aureolic acid aglycones.

We describe herein a highly diastereoselective synthesis of model aglycone **3** which contains the naturally occurring aureolic acid C(3) polyoxygenated side chain (Scheme 1).

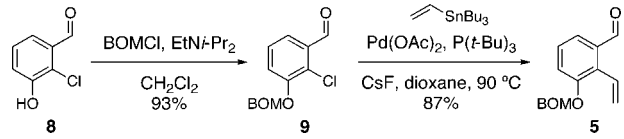
Scheme 1. Retrosynthetic Analysis of Acyloin **3**



We envisioned the acyloin unit of **3** would be installed from diene **4** via a ring-closing metathesis (RCM) and oxidation sequence. A highly diastereoselective allylation of aldehyde **5** with the chiral allylborane **6**, to be derived by hydroboration of allene **7**, would afford diene **4**.

Aldehyde **5** was generated in a straightforward manner from commercially available 2-chloro-3-hydroxybenzaldehyde **8** (Scheme 2). Protection of the phenol unit of **8** as a

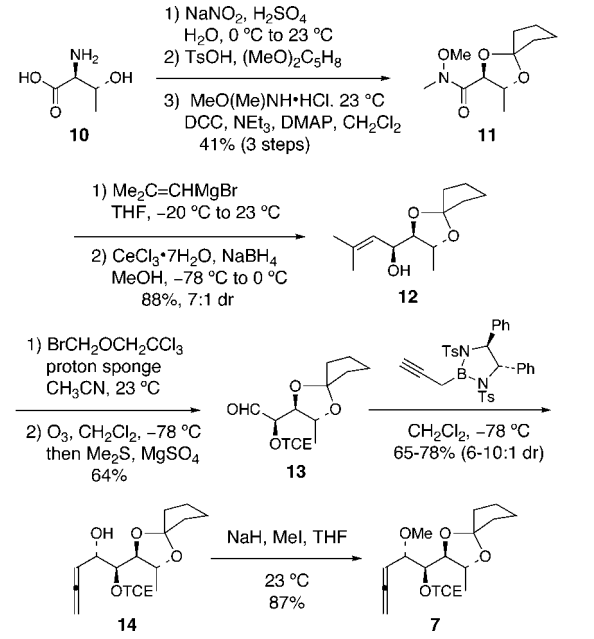
Scheme 2. Synthesis of Aldehyde **5**



BOM ether provided **9** in 93% yield. Stille coupling of **9** with vinyl(tributyl)stannane using conditions described by Fu[23] then provided aldehyde **5** in 87% yield.

The synthesis of allene **7** began with the diazotization of L-threonine in water **(10**, Scheme 3).[24] Protection of the crude

Scheme 3. Synthesis of Allene **7**



diol as the cyclopentylidene ketal followed by DCC-mediated coupling of the carboxylic acid with *N*-methoxy-*N*-methylamine afforded Weinreb amide **11** in 41% yield over the three steps. Amide **11** was then treated with 2-methyl-1-propenylmagnesium bromide.[25] Luche reduction[26] of the derived enone with $NaBH_4$ and $CeCl_3$ then provided alcohol **12** in 88% yield as an inseparable 7:1 mixture of diastereomers. Fortunately, the two isomers could be separated following protection of the hydroxyl group as a 2,2,2-trichloroethoxymethyl (TCE) ether.[27] The olefin of the major TCE ether diastereomer (73% isolated yield) was cleaved by ozonolysis at −78 °C followed by treatment with Me_2S and $MgSO_4$ to reduce the ozonide intermediate.[28] In this way,

(13) Remsing, L. L.; González, A. M.; Nur-e-Alam, M.; Fernández-Lozano, M. J.; Braña, A. F.; Rix, U.; Oliveira, M. A.; Méndez, C.; Salas, J. A.; Rohr, J. *J. Am. Chem. Soc.* **2003**, *125*, 5745.

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(20) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984.

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(24) Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.

(25) Treatment of **11** with vinylmagnesium bromide afforded an enone which was susceptible to Michael adddition by MeNH(OMe) under the reaction conditions.

(26) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

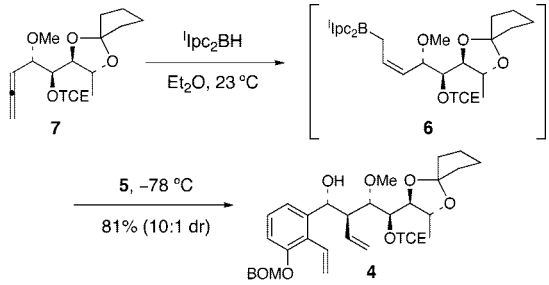
(27) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(28) Without $MgSO_4$ addition at −78 °C prior to warming the reaction mixture to 23 °C, large amounts of the hydrated form of aldehyde **13** were isolated.

aldehyde **13** was obtained in 87% yield (64% from **12**). Diastereoselective allenylation of aldehyde **13** was then performed under Corey conditions[29] to afford allenol **14** in 65−78% yield with up to 10:1 selectivity.[30] *O*-Methylation of **14** uncontaminated with its epimer then provided allene **7** as a single isomer in 87% yield.

The key allylation step was executed as summarized in Scheme 4. Allene **7** was treated with $^{l}Ipc_2BH$ in Et_2O[31] for

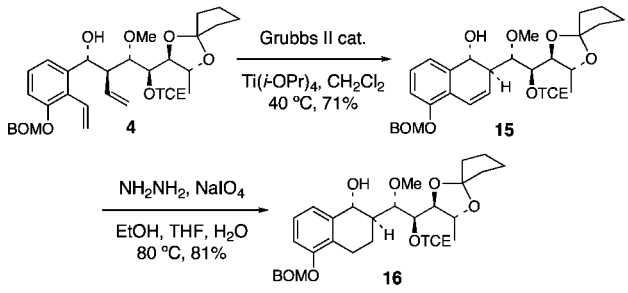
Scheme 4. Synthesis of Diene **4**



10 min[32] to provide a solution of (*Z*)-allylborane **6**, which was cooled to −78 °C and treated with aldehyde **5**. This reaction provided diene **4** in 81% yield and with 10:1 diastereoselectivity. The assignment of (*Z*)-olefin geometry to allylborane **6** derives from the stereochemistry of **4**, together with the expectation that the reaction of **5** and **6** proceeds via a chairlike transition state.[33]

The stereochemistry of **4** was assigned following conversion to **16** (Scheme 5). Initial attempts to effect the ring-

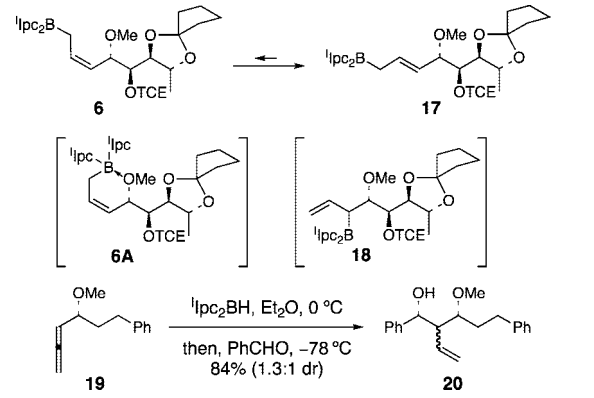
Scheme 5. Ring-Closing Metathesis of Diene **4**



closing metathesis reaction of **4** stalled at less than 10% conversion, owing presumably to formation of a chelate of a ruthenium carbene intermediate with one of the Lewis basic ether units in the substrate.[34] However, inclusion of Ti(*i*-OPr)$_4$ in the metathesis reaction allowed complete conversion of **4** to **15** at 40 °C.[35] The stereochemistry of the hydroxyl center [C(4)] in **15** was assigned by Mosher ester analysis (see the Supporting Information).[36] Further manipulation of **15** via diimide reduction[37] to tetrahydronaphthalene **16** (81% yield) allowed assignment of the trans H(3)−H(4) relationship ($^3J_{H3,H4} = 8.0$ Hz).[38] These data require the intermediacy of (*Z*)-allylborane **6** as the dominant intermediate in the allylboration of **5**, assuming that the reaction proceeds via the usual and highly conserved chairlike transition state.[33]

The conclusion that the allylboration reaction proceeds via (*Z*)-allylborane **6** was not expected, since crotyl(diisopinocampheyl)boranes (as well as other dialkylcrotylboranes) are known to undergo rapid olefin isomerization via reversible 1,3-migration of the dialkylboryl unit even at low temperatures.[39] We initially assumed that **6** might be stabilized by chelation with the δ-methoxy group (as in **6A**), shifting the equilibrium away from (*E*)-allylborane **17**. However, the stereocontrol was poor in the analogous hydroboration/allylboration of the simpler allenyl ether **19**, thus ruling out this hypothesis (Scheme 6). Therefore, the

Scheme 6. Expected Thermal Isomerization of **6**



synthetically useful stereoselectivity of the double diastereoselective allylboration reaction of **5** and **6** could be due to Curtin−Hammett control. However, it is also possible that the steric bulk of the oxygenated side chain in **6** destabilizes the transition state leading to methallyl isomer **18**, thereby slowing the rate of isomerization of **6** to **17**.

The synthesis of model acyloin **3** was completed as summarized in Scheme 7. Diene **4** was converted into xanthate **21** in 86% yield under standard conditions. The Bu_3SnH reduction of **21** was accomplished by using Et_3B as the initiator.[40,41] The reduction product was then subjected to RCM cyclization using the second-generation Grubbs

(29) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878.

(30) Reactions run on a 1.3 g scale (of **13**) gave slightly lower diastereoselectivity (6:1 dr).

(31) Hydroboration of allene **7** with $^{l}Ipc_2BH$ in CH_2Cl_2 or toluene led to elimination of the C(1′)-methoxy group, giving the corresponding diene, presumably by way of the allylic transposed allylborane isomer of **6**.

(32) Extending hydroboration reaction times beyond 10 min led to decreased diastereoselectivity (believed to originate from *E*/*Z* olefin 1,3-isomerization of **6** via the methallylic borane isomer) and lower yields.

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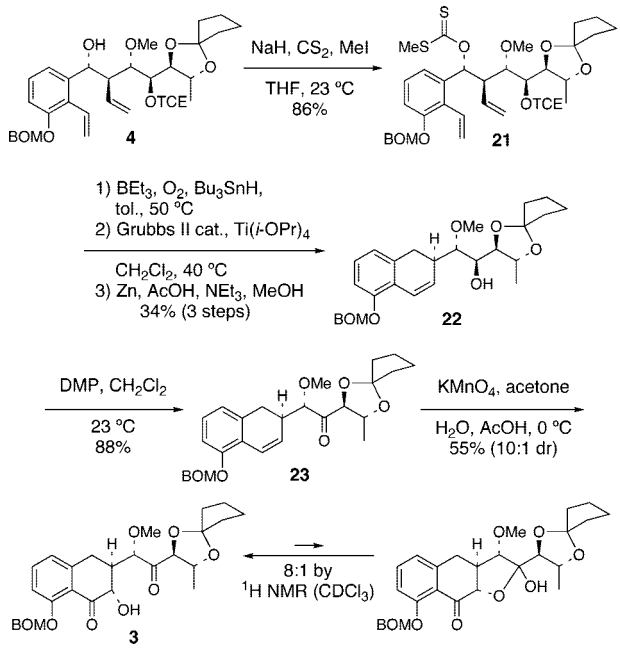
Scheme 7. Synthesis of Acyloin **3**



catalyst[42] in the presence of Ti(*i*-OPr)$_4$ to give the dihydronaphthalene, and the TCE protecting group was removed by using activated zinc.[43] This three-step sequence furnished alcohol **22** in 34% yield. Oxidation of **22** by using the Dess−Martin reagent[44] provided ketone **23**, thereby setting the stage for the oxidation of the dihyrohaphthalene unit to the acyloin unit of **3**.

Osmium[45] and ruthenium[46] based keto-hydroxylation reactions were first examined as a means to convert **23** to **3**. These reactions yielded the 1,2-diol as the major product. In contrast, a protocol employing $KMnO_4$ and $CuSO_4{\cdot}5H_2O$ under phase transfer conditions[47] gave only acyloin **3**. However, this reaction required a large excess of oxidant and long reaction times, even with sonication.[48] It was ultimately found that treatment of ketone **23** in acidic acetone with $KMnO_4$[49] furnished a 9:1:1 mixture of **3**, the hemiketal isomer of **3** and the C(2) diastereomer of **3** (which appears to exist exclusively as a hemiketal). This mixture was separated by column chromatography to afford the major diastereomer, acyloin **3**, in 55% yield as an 8:1 mixture of the hydroxy ketone and hemiketal tautomers, respectively, in $CDCl_3$.[50,51] Coupling constant analysis of the hydroxy ketone tautomer of **3** ($^3J_{H2,H3}$ = 12.0 Hz) indicated that the newly formed C(2) carbinol proton is *anti* to the C(3) methine proton.

In summary, we have completed the synthesis of an advanced model system for the aglycone of durhamycin A. The highlights of this synthesis include the diastereoselective allylboration of aldehyde **5** and (*Z*)-*δ*-(alkoxyallyl)dialkylborane **6** to give **4**, the selective Bu_3SnH reduction of xanthate **21**, the RCM cyclization of the diene derived from **4**, and the keto-hydroxylation of the highly functionalized dihydronapththalene **23**. Further progress towards the total synthesis of durhamycin A and aureolic acid analogues will be reported in due course.

Acknowledgment. This work was supported by the National Institutes of Health (GM038436)

Supporting Information Available: Experimental procedures and tabulated 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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(37) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437.

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(39) (a) For formation of (*E*)-allyl(diisopinocampheyl)boranes by room temperature allene hydroboration: Naria, G.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 219. (b) For low-temperature formation of (*Z*)- and (*E*)-crotyl(diisopinocampheyl)boranes: Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (c) For formation of a kinetic (*Z*)-silylallyl(diisopinocampheyl)borane by allene hydroboration and isomerization studies: Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693. (d) For a discussion concerning the 1,3-migration of allylboron species: Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.

(40) Efforts to convert the benzylic alcohol to a halide, tosylate, or mesylate leaving group resulted in either elimination or cyclization of the TCE-protected alcohol to form a tetrahydrofuran.

(41) (a) For BEt_3-intiated Bu_3SnH xanthate reductions, see: Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6125. (b) For a review on Bu_3SnH reductions, see: Neumann, W. P. *Synthesis* **1987**, 665.

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(49) Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, *7*, 520.

(50) Keto-hydroxylation of substrates (not shown) lacking the C(2′) ketone (and therefore incapable of forming hemiketals) gave 8−10:1 mixtures of C(2) acyloin epimers.

(51) Hemiketal formation, analogous to that indicated here for **2**, is well documented in the olivin series (e.g., ref 22 and Roush, W. R.; Briner, K.; Kesler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098).