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

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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 structurally related antitumor antibiotics that include olivomycin A, chromomycin A₃, 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 Mg²⁺.^{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 analogs 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 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 shown potent inhibition of HIV Tat transactivation (IC₅₀ = 4.8 nM and 48 nM, respectively) and appear to be relatively non-cytotoxic.^{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 analog 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 sidechain (Scheme 1). 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 an allene **7**, would afford diene **4**.

Aldehyde **5** was generated in a straightforward manner from commercially available 2-chloro-3-hydroxy-benzaldehyde **8** (Scheme 2). Protection of the phenol unit of **8** as a BOM ether provided **9** in 93% yield. Stille coupling of **9** with vinyl(tributyl)stannane using conditions described by Fu²³ 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 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 reduction²⁶ of the derived enone with NaBH₄ and CeCl₃ 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 Me₂S and MgSO₄ to reduce the ozonide intermediate.²⁸ In this way, aldehyde **13** was obtained in 87% yield (64% from **12**). Diastereoselective allenylation of aldehyde **13** was then performed under Corey conditions²⁹ 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 ¹Ipc₂BH in Et₂O³¹ for 10 min³² 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 chair-like t.s.³³

The stereochemistry of **4** was assigned following conversion to **16** (Scheme 5). Initial attempts to effect the ring-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 Supporting Information).³⁶ Further manipulation of **15** via diimide reduction³⁷ to tetrahydronaphthalene **16** (81% yield) allowed assignment of the trans C(3)-C(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 chair-like 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 **18**), 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 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 the methallyl tautomer **x**, 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 Bu₃SnH reduction of

21 was accomplished by using Et₃B as the initiator.^{40,41} The reduction product was then subjected to RCM cyclization using the 2nd generation Grubbs catalyst⁴² 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 reagent⁴⁴ provided ketone **23**, thereby setting the stage for the oxidation of the dihydronaphthalene unit to the acyloin unit of **3**.

Osmium⁴⁵ and ruthenium⁴⁶ 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 KMnO₄ and CuSO₄•5H₂O under phase transfer conditions⁴⁷ 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 KMnO₄⁴⁹ 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 CDCl₃.^{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 Bu₃SnH reduction of xanthate **21**, the RCM cyclization of the diene derived from **4**, and the keto-hydroxylation of the highly functionalized dihydronaphthalene **23**. Further progress toward the total synthesis of durhamycin A and aureolic acid analogs will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Remers, WA. The Chemistry of Antitumor Antibiotics. Wiley-Interscience; New York: 1979. p. 133-175.
2. Skarbek, JD.; Speedie, MK. Antitumor Compounds of Natural Origin: Chemistry and Biochemistry. Aszalos, A., editor. 1. CRC Press; Boca Raton, FL: 1981. p. 191-235.
3. Remers, WA.; Iyengar, BS. Cancer Chemotherapeutic Agents. Foye, WO., editor. American Chemical Society; Washington, DC: 1995. p. 577-679.
4. Wohler SE, Künzel E, Machinek R, Méndez C, Salas JA, Rohr J. J Nat Prod 1999;62:119. [PubMed: 9917296]
5. Ogawa H, Yamashita Y, Katahira R, Chiba S, Iwasaki T, Ashizawa T, Nakano H. J Antibiot 1998;51:261. [PubMed: 9589060]
6. Katahira R, Uosaki Y, Ogawa H, Yamashita Y, Nakano H, Yoshida M. J Antibiot 1998;51:267. [PubMed: 9589061]
7. Lombó F, Menéndez N, Salas JA, Méndez C. Appl Microbiol Biotechnol 2006;73:1. [PubMed: 17013601]
8. Gao X, Mirau P, Patel DJ. J Mol Biol 1992;223:259. [PubMed: 1731073]
9. Sastry M, Patel DJ. Biochemistry 1993;32:6588. [PubMed: 8329387]
10. Liu C, Chen F-M. Biochemistry 1994;33:1419. [PubMed: 8312261]

11. Aich P, Dasgupta D. *Biochemistry* 1995;34:1376. [PubMed: 7827085]
12. Katahira R, Katahira M, Yamashita Y, Ogawa H, Kyogoku Y, Yoshida M. *Nucleic Acids Res* 1998;26:744. [PubMed: 9443966]
13. Remsing LL, González AM, Nur-e-Alam M, Fernández-Lozano MJ, Braña AF, Rix U, Oliveira MA, Méndez C, Salas JA, Rohr J. *J Am Chem Soc* 2003;125:5745. [PubMed: 12733914]
14. Remsing LL, Bahadori HR, Carbone GM, McGuffie EM, Catapano CV, Rohr J. *Biochemistry* 2003;42:8313. [PubMed: 12846580]
15. Kumar V, Remers WA, Bradner WT. *J Med Chem* 1980;23:376. [PubMed: 7381837]
16. Silva DJ, Kahne DE. *J Am Chem Soc* 1993;115:7962.
17. Baig I, Perez M, Braña AF, Gomathinayagam R, Damodaran C, Salas JA, Méndez C, Rohr J. *J Nat Prod* 2008;71:199. [PubMed: 18197601]
18. Jayasuriya H, Lingham RB, Graham P, Quamina D, Herranz L, Genilloud O, Gagliardi M, Danzeisen R, Tomassini JE, Zink DL, Guan Z, Singh SB. *J Nat Prod* 2002;65:1091. [PubMed: 12193009]
19. We have published a synthesis of functionalized precursors for the oligosaccharides of durhamycins A (**1**) and B (**2**): Durham TB, Roush WR. *Org Lett* 2003;5:1875. [PubMed: 12762675]
20. Roush WR, Michaelides MR, Tai DF, Lesur BM, Chong WKM, Harris DJ. *J Am Chem Soc* 1989;111:2984.
21. Roush WR, Murphy M. *J Org Chem* 1992;57:6622.
22. Roush WR, Hartz RA, Gustin DJ. *J Am Chem Soc* 1999;121:1990.
23. Littke AF, Schwarz L, Fu GC. *J Am Chem Soc* 2002;124:6343. [PubMed: 12033863]
24. Servi S. *J Org Chem* 1985;50:5865.
25. Treatment of **11** with vinylmagnesium bromide afforded an enone which was susceptible to Michael addition by MeNH(OMe) under the reaction conditions.
26. Luche J-L. *J Am Chem Soc* 1978;100:2226.
27. Evans DA, Kaldor SW, Jones TK, Clardy J, Stout TJ. *J Am Chem Soc* 1990;112:7001.
28. Without MgSO₄ addition at -78 °C prior to warming the reaction mixture to 23 °C, large amounts of the hydrated form of aldehyde **13** were isolated.
29. Corey EJ, 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 ¹Ipc₂BH in CH₂Cl₂ 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.
33. Roush, WR. *Comprehensive Organic Synthesis*. Trost, BM., editor. 2. Pergamon Press; Oxford: 1991. p. 1Chemler, SR.; Roush, WR. *Modern Carbonyl Chemistry*. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 403
34. Harrity JP, Visser MS, Gleason JD, Hoveyda AH. *J Am Chem Soc* 1997;119:1488.
35. Fürstner A, Langemann K. *J Am Chem Soc* 1997;119:9130.
36. (a) Dale JA, Mosher HS. *J Am Chem Soc* 1973;95:512. (b) Ohtani I, Kusumi T, Kashman Y, Kakisawa H. *J Am Chem Soc* 1991;113:4092.
37. Lautens M, Hiebert S. *J Am Chem Soc* 2004;126:1437. [PubMed: 14759202]
38. Similar assignments by half-chair coupling constants: (a) Hobbs-Mallyon D, Li W, Whiting DA. *J Chem Soc, Perkin Trans 1* 1997:1511. (b) Thorey C, Bouquillon S, Helimi A, Hénin F, Muzart J. *Eur J Org Chem* 2002:2151.
39. For formation of (*E*)-allyl(diisopinocampheyl)boranes by room temperature allene hydroboration: (a) Naria G, Brown HC. *Tetrahedron Lett* 1997;38:219. For low temperature formation of (*Z*) and (*E*)-crotyl(diisopinocampheyl)boranes: (b) Brown HC, Bhat KS. *J Am Chem Soc* 1986;108:5919. For formation of a kinetic (*Z*)-silylallyl(diisopinocampheyl)borane by allene hydroboration and isomerization studies: (c) Heo J-N, Micalizio GC, Roush WR. *Org Lett* 2003;5:1693. [PubMed: 12762675]

- 12735754] For a discussion concerning the 1,3-migration of allylboron species: (d) Kramer GW, Brown HC. *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. For BEt_3 initiated Bu_3SnH xanthate reductions: (a) Nozaki K, Oshima K, Utimoto K. For a review on Bu_3SnH reductions: (b) Neumann WP. *Synthesis* 1987;665
42. Scholl M, Ding S, Lee CW, Grubbs RH. *Org Lett* 1999;1:953. [PubMed: 10823227]
43. Jacobson RM, Clader JW. *Synth Commun* 1979;9:57.
44. Dess PB, Martin JC. *J Am Chem Soc* 1978;100:300.
45. Fleming JJ, McReynolds MD, Dubois J. *J Am Chem Soc* 2007;129:9964. [PubMed: 17658800]
46. Plietker B. *Synthesis* 2005;15:2453.
47. Baskaran S, Das J, Chandrasekaran S. *J Org Chem* 1989;54:5182.
48. Ryoo ES, Shin DH, Han BH. *J Korean Chem Soc* 1987;31:359.
49. Srinivasan NS, Lee DG. *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 WR, Briner K, Kesler BS, Murphy M, Gustin DJ. *J Org Chem* 1996;61:6098. [PubMed: 11667440])

Figure 1.
Durhamycins A and B

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

Scheme 2.
Synthesis of Aldehyde **5**

Scheme 3.
 Synthesis of Allene **7**

Scheme 4.
Synthesis of Diene **4**

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

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

Scheme 7.
Synthesis of Acyloin **3**