ORGANIC LETTERS

2005
Vol. 7, No. 17
3617−3620

Synthesis of the Aglycones of Altromycins and Kidamycin from a Common Intermediate

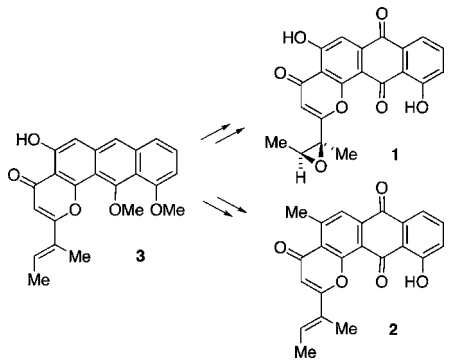
ZhongBo Fei and Frank E. McDonald*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

fmcdona@emory.edu

Received April 29, 2005

ABSTRACT



The aglycone structures 1 and 2, respectively corresponding to the antitumor antibiotic natural products altromycin and kidamycin, have been efficiently synthesized from a common advanced intermediate 3. A series of Claisen condensations and aromatizations affords the anthracene section of 3, followed by annulation of the pyrone ring. The functional groups of 3 can be manipulated for enantioselective introduction of the epoxide side-chain of altromycin aglycone 1, as well as synthesis of the kidamycin aglycone 2.

The altromycins (**4** and **5**, Figure 1) and kidamycin (**6**) are secondary metabolites of soil *Streptomyces*. The altromycins were first reported in the early 1990s as antibiotics with selective activity against Gram-positive bacteria (Staphylococci and Streptococci)[1] and were later shown to have anticancer activity, including in vivo activity in P388 leukemia, as well as colon, lung, and ovarian tumors. Kidamycin (**6**) also exhibits cytotoxicity against leukemia L-1210 and Ehrlich ascites tumors.[2]

Hurley has shown that altromycin B (**4**, $R_1 = R_2 = Me$; $X = Y = OH$) preferentially inhibits RNA and DNA synthesis relative to protein synthesis by covalent modification of guanine by alkylation of the epoxide at C16.[3] Although some stereochemical elements of the altromycins **4** and **5** remain undetermined, the kidamycin structure (**6**) has been fully elucidated by a combination of NMR and crystallographic studies.[4] Previous synthetic work to date in this general area has been limited to the synthesis of the branched *C*-glycoside substructure of altromycin B[5,6] and preparation of the kidamycin aglycone as the *O*-methyl ether.[7] In this communication, we describe an efficient

(1) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Swanson, S. J.; Barlow, G. J.; Tillis, P. M.; McAlpine, J. B. *J. Antibiot.* **1990**, *43*, 223. (b) Brill, G. M.; McAlpine, J. B.; Whittern, D. N.; Buko, A. M. *J. Antibiot.* **1990**, *43*, 229. (c) Brill, G. M.; Jackson, M.; Whittern, D. N.; Buko, A. M.; Hill, P.; Chen, R. H.; McAlpine, J. B. *J. Antibiot.* **1994**, *47*, 1160.

(2) (a) Kanda, N. *J. Antibiot.* **1971**, *24*, 599. (b) Kanda, N. *J. Antibiot.* **1972**, *25*, 557. (c) Kanda, N.; Kono, M.; Asano, K. *J. Antibiot.* **1972**, *25*, 553. (d) Berdy, J. *Adv. Appl. Microbiol.* **1974**, *18*, 309.

(3) (a) Sun, D.; Hansen, M.; Clement, J.; Hurley, L. H. *Biochemistry* **1993**, *32*, 8068. (b) Hansen, M.; Hurley, L. *J. Am. Chem. Soc.* **1995**, *117*, 2421. (c) Sun, D.; Hansen, M.; Hurley, L. *J. Am. Chem. Soc.* **1995**, *117*, 2430.

(4) (a) Furukawa, M.; Hayakawa, I.; Ohta, G.; Iitaka, Y. *Tetrahedron* **1975**, *31*, 2989. (b) Furukawa, M.; Iitaka, Y. *Tetrahedron Lett.* **1974**, *15*, 3287.

(5) Pasetto, P.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 8042.

(6) For another synthesis of the altromycin branched *C*-glycoside substructure, see the following communication: Koo, B.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3621.

(7) (a) Hauser, F. M.; Rhee, P. R. *J. Am. Chem. Soc.* **1979**, *101*, 1628. (b) Hauser, F. M.; Rhee, P. R. *J. Org. Chem.* **1980**, *45*, 3061.

10.1021/ol0509742 CCC: $30.25
Published on Web 07/20/2005

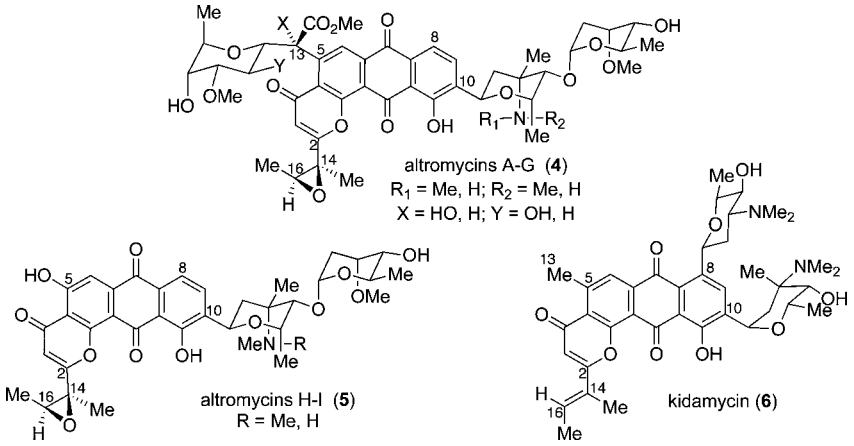
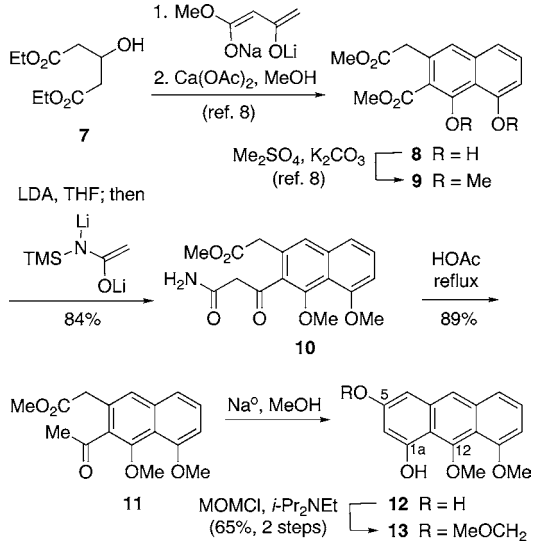


Figure 1. Structures of altromycin and kidamycin antitumor antibiotics.

synthesis of the altromycin and kidamycin aglycones **1** and **2** as the initial stage for projected total syntheses of both families of natural products **4**−**6**.

Our synthesis began with the preparation of the known naphthalene diester **8** (Scheme 1) by applying biomimetic

Scheme 1. Synthesis of **12**



Claisen condensation methodology, as pioneered by the laboratories of Harris and Yamaguchi.[8] We found that freshly drying the calcium acetate monohydrate[8c] was crucial for this procedure to reliably provide the naphthyl diester product. After methylation of **8** to afford the protected naphthalene diester **9**,[8c] the enolizable ester was temporarily masked as an enolate and the dianion of *N*-(trimethylsilyl)-acetamide selectively added to the aryl ester,[8a] generating naphthalene amide **10**. Although Dieckmann condensations of **10** to form the third aromatic ring were unsuccessful, we unexpectedly obtained the methyl ketone **11** upon refluxing **10** in acetic acid, and ketone **11** then underwent Dieckmann condensation to provide anthracene **12**. As it is unlikely that the amide could be hydrolyzed under these nonaqueous conditions, a decarboxylation process is presumably not involved, but rather an analogous acid-promoted deamidation process (loss of HN═C═O) might be occurring. To the best of our knowledge, this is the first reported example of a decarbamidation. Selective monoprotection[9] of the C5 hydroxyl of crude anthracene **12** with MOMCl afforded anthracene **13**.

The plan for annulation of the pyrone ring was to first form the carbon−oxygen bond by addition−elimination[10] followed by an intramolecular Friedel−Crafts acylation, as established by Bycroft in a simpler system.[9] Thus, deprotonation of anthracene **13** and addition of 3-chloro-2,4-dienoate **14**[11] provided the desired product **15** but mixed with (*E*)- and (*Z*)-isomers of **16** (ratio **15**:**16***E*:**16***Z* = 2:1:1, Scheme 2). However, saponification provided acid **17**, which was easily separated from isomers **18**-*E* and **18**-*Z* by column chromatography. Initial attempts to close the C4−C4a bond by generating the acid chloride from **17** with oxalyl chloride resulted in Friedel−Crafts oxalylation at C7, but activation of acid **17** with 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine[12] resulted in spontaneous cyclization to **3** in 86% yield. Interestingly, treatment of the mixture of isomers **18**-*E* and **18**-*Z* under the same conditions also provided pyrone **3**, although in low yield (23%).[13] In both cases, the methoxy-

(8) (a) Gilbreath, S. G.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6172. (b) Harris, T. M.; Harris, C. M.; Kuzma, P. C.; Lee, J. Y. C.; Mahalingam, S.; Gilbreath, S. G. *J. Am. Chem. Soc.* **1988**, *110*, 6186. (c) Yamaguchi, M.; Hasebe, K.; Higashi, H.; Uchida, M.; Irie, A.; Minami, T. *J. Org. Chem.* **1990**, *55*, 1611.

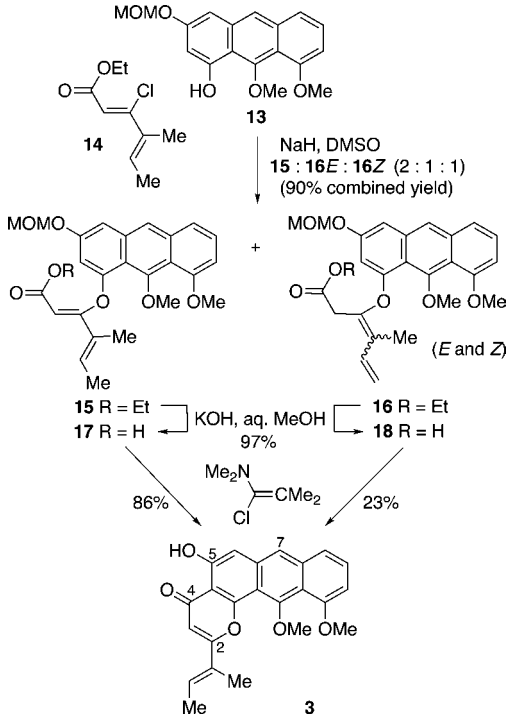
(9) Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc.* **1963**, 4868.

(10) For similar examples of this addition−elimination reaction, see: (a) Hormi, O. E. O. *J. Org. Chem.* **1988**, *53*, 880. (b) Hormi, O. E. O.; Hirvela, L. *Tetrahedron Lett.* **1993**, *40*, 6463. For mechanistic discussion, see: Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474.

(11) Chloro-2,4-dienoate **14** was prepared by the reaction of ethyl (*E*)-4-methyl-3-oxohex-4-enoate with $POCl_3$ and tributylamine (see Supporting Information). (a) Andrews, J. F. P.; Regan, A. C. *Tetrahedron Lett.* **1991**, *32*, 7731. (b) Hormi, O. E. O. *Synth. Commun.* **1986**, *16*, 997.

(12) Devos, A.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180.

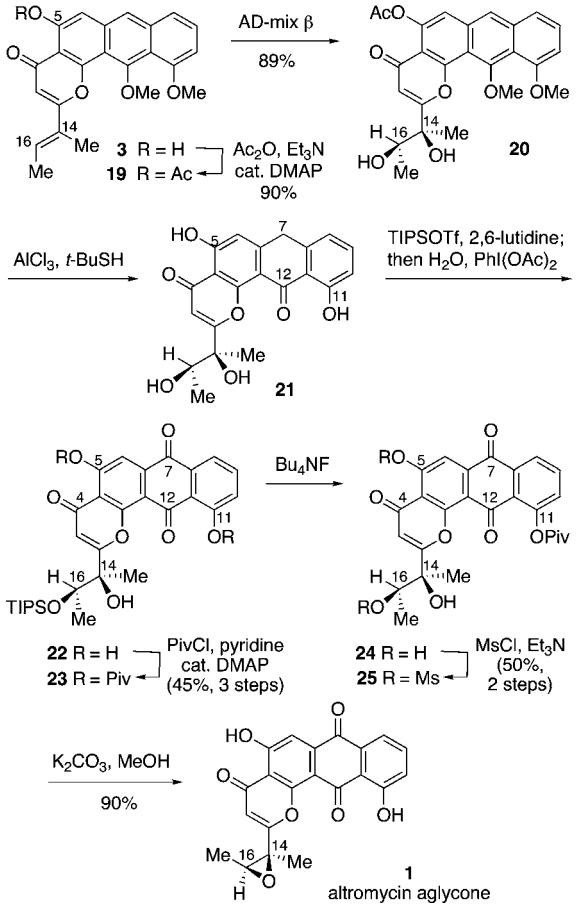
Scheme 2. Annulation of Pyrone Ring



methyl (MOM) O-protective group was lost under the pyrone closure conditions.

To prepare the altromycin aglycone from **3**, the 5-acetate derivative **19** (Scheme 3) was treated with AD-mix-β,[14] providing diol **20** with an enantiomeric ratio of 13:1, as determined by Mosher ester analysis.[15,16] Global O-deprotection was achieved by $AlCl_3$ and *tert*-butanethiol,[17] providing anthrone tetraol **21**, which in turn was transformed into the partially protected quinone **22** by a one-pot procedure, by initial reaction with excess TIPSOTf and 2,6-lutidine in THF to give a tris-TIPS ether,[18] followed by addition of water and $PhI(OAc)_2$.[19] The second stage of this one-pot reaction selectively removed both aryl TIPS ethers while retaining the alkyl C16 TIPS ether. This partially protected quinone **22** was not purified until after the two aryl hydroxyl groups were protected as the bispivaloate ester **23**, featuring two types of differentially protected hydroxyl groups. Although the protective group pattern of **23** was projected to avoid undesired mesylation of the phenols in the following epoxide

Scheme 3. Synthesis of Altromycin Aglycone (**1**) from **3**



formation steps, we observed that removal of the TIPS protective group was always accompanied by loss of the C5 pivaloate, to afford **24**.[20] Fortunately, the derived bismesylate compound **25** in the presence of potassium carbonate in methanol underwent epoxide formation by intramolecular S_N2 displacement as well as methanolysis of both mesylate and pivaloate ester phenolic protective groups to provide the crystalline altromycin aglycone **1**. The general lability of C5 O-protective groups may result from neighboring group participation of the C4 pyrone carbonyl oxygen. This work is the first synthesis of the altromycin aglycone **1**. Although **1** is not a known degradation product of altromycins, spectroscopic comparison of ^1H and ^{13}C NMR spectra as well as UV absorptions with altromycins B, H, and I are consistent with the structure of **1**.

The kidamycin aglycone could also be prepared from pyrone **3** via modified Kumada coupling[21] of the 5-triflate derivative **26** with dimethylzinc to provide **27** (Scheme 4).[22] Removal of O11 and O12 methyl ether protective groups afforded anthrone **28**, followed by oxidation[23] to the an-

(13) Attempted isomerization of **16** to the conjugated isomer **15** was unsuccessful under acidic or basic conditions.

(14) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(15) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732.

(16) As the absolute stereochemistry of the C14−C16 epoxide of altromycin has not been established, it is desirable to synthesize both epoxide enantiomers of **1**. Thus, treatment of **19** with AD-mix-α under the same conditions produced *ent*-**20** (12:1 er), which was converted into *ent*-**1**.

(17) (a) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275. (b) The use of ethanethiol (ref 17a) resulted in ethanethiol substitution at C12 as the sole product, but the more bulky *tert*-butanethiol was successfully applied to give only **21**.

(18) Tris-TIPS-protected intermediate was unstable and air oxidized to tris-TIPS-protected quinone during attempted product isolation.

(19) (a) Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273. (b) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327.

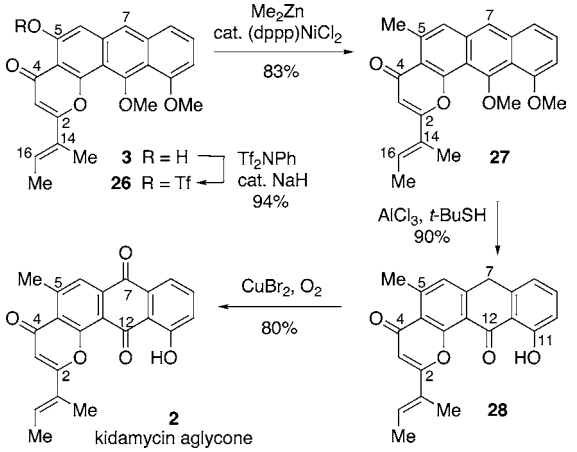
(20) Structure assignment was determined by NOE analysis of compound **25** (see Supporting Information).

(21) Kasak, P.; Putala, M. *Tetrahedron Lett.* **2004**, *45*, 5279.

(22) Use of methylmagnesium bromide occasionally resulted in significant amounts of a byproduct from conjugate addition of methyl Grignard to the C16−C14 alkene under extended reaction times.

(23) Krohn, K.; Vitz, J. *Eur. J. Org. Chem.* **2004**, 209.

Scheme 4. Synthesis of Kidamycin Aglycone (**2**) from **3**



thraquinone of kidamycin aglycone **2**. This constitutes the second synthesis of the kidamycin aglycone, and spectral data for **2** compare favorably with reported data for the synthetic *O*-11 methyl ether[7] as well as kidamycin natural product structure.

In conclusion, the efficient synthesis of tetracyclic pyrone **3** and formation of the aglycones of both altromycins and kidamycin from this common intermediate **3** provide an effective entry to projected total syntheses of various altromycin natural products **4** and **5**, as well as kidamycin **6**.

Acknowledgment. We thank the National Institutes of Health (CA 59703) for support of this research. We also acknowledge use of shared instrumentation provided by grants from the National Institutes of Health, National Science Foundation, and the Georgia Research Alliance (NMR spectroscopy, mass spectrometry), as well as the University Research Committee of Emory University (polarimeter). We thank Prof. Debra L. Mohler for the use of her laboratory's UV−visible spectrophotometer.

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

OL0509742