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Total Synthesis of (+)-Yatakemycin

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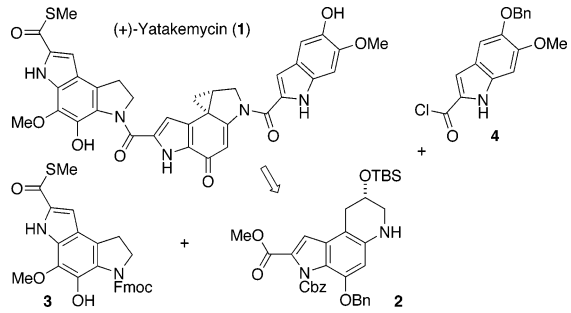
(+)-Yatakemycin (**1**), which was isolated from a culture broth of *Streptomyces* sp. TP-A0356 by Igarashi in 2003,[1] is an antitumor antibiotic that has a characteristic dienone cyclopropane ring found in duocarmycin SA,[2] duocarmycin A,[3] and CC-1065.[4] These compounds possess remarkable antitumor activity through a sequence-selective DNA alkylation at the activated cyclopropane. Among these compounds, yatakemycin has been found to exhibit the most potent activity and, therefore, has attracted a great deal of attention regarding the nature of its interaction with DNA.[5a] The first total synthesis of this compound has recently been reported by Boger and co-workers, who also revised its structure and determined the absolute configuration.[5b]

As outlined in the retrosynthetic analysis (Scheme 1), we planned to form the highly reactive spirocyclopropane by ring contraction of the hydroxytetrahydroquinoline at a later stage in the synthesis. Disconnections at the two amide bonds should then lead to three segments **2**−**4**. Key synthetic issues here would be the effective preparation of these highly functionalized nitrogen-containing heterocycles and the order in which these segments are assembled without affecting the sensitive thiol ester functionality. For the synthesis of these segments, we intended to use the exceptionally mild copper-mediated aryl amination reaction developed in our laboratories.[6] We describe herein a highly convergent and efficient total synthesis of **1** featuring the construction of all of the aryl−nitrogen bonds by means of our variant of a copper-mediated aryl amination reaction.

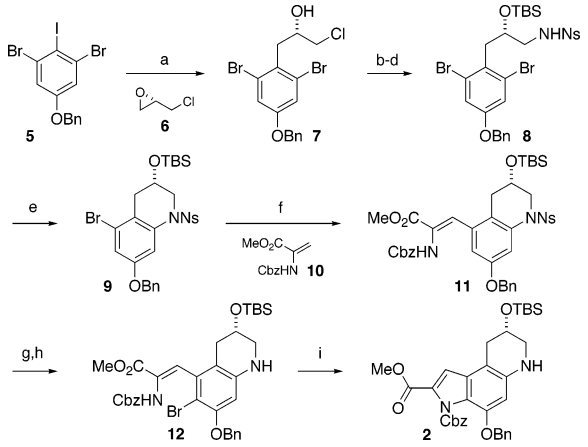
Synthesis of the middle segment **2** commenced with the regioselective ring opening of (*S*)-epichlorohydrin (**6**) with 2,6-dibromophenyllithium species, which was prepared by iodoselective lithiation of 2,6-dibromoiodobenzene derivative **5** (Scheme 2).[7] Cleavage of the epoxide in **6** proceeded smoothly in the presence of $BF_3{\cdot}OEt_2$ to provide exclusively the desired chlorohydrin **7**.[8] We then converted **7** to the amination precursor **8** in a three-step sequence involving the introduction of an azide group, the Staudinger reaction,[9] and finally in situ treatment of the resultant primary amine with NsCl.[10] The crucial intramolecular amination proceeded uneventfully to give the desired tetrahydroquinoline **9** with complete retention of the other bromo group.[11] Heck reaction[12] of this hindered bromide with a dehydroalanine derivative **10**[13] was performed successfully using a combination of $Pd_2(dba)_3$ and 2-di-(*t*-Bu)phosphino-1,1′-biphenyl. After removal of the nosyl group, a bromo substituent was regioselectively introduced and the second amination reaction at the highly sterically hindered position was examined. A high-yielding process could be realized by using a stoichiometric amount of CuI at ambient temperature to furnish the middle segment **2**.[11]

The copper-mediated aryl amination proved to be highly effective for the facile construction of the left-hand segment **3** (Scheme 3).

Scheme 1. Retrosynthetic Analysis of (+)-Yatakemycin



Scheme 2. Synthesis of the Middle Segment[a]



[a] Reagents and conditions: (a) *n*-BuLi (1.0 equiv), toluene, −78 °C, 10 min; $BF_3{\cdot}OEt_2$, **6**, −78 °C, 5 min, 93%; (b) NaN_3, DMF, 90 °C, 9 h; (c) TBSCl, imidazole, DMAP, DMF, 50 °C, 6 h, 99% (2 steps); (d) $P(n\text{-}Bu)_3$, THF, rt, 30 min; H_2O, rt, 2 h; NsCl, $NaHCO_3$ aq., rt, 24 h, 89%; (e) CuI (0.5 equiv), CsOAc (5.0 equiv), DMSO, 60 °C, 24 h, 83%; (f) **10**, $Pd_2(dba)_3$ (5 mol %), 2-di(*t*-Bu)phosphino-1,1′-biphenyl (20 mol %), Et_3N, LiCl, DMF, 90 °C, 1 h, 89%; (g) PhSH, Cs_2CO_3, MeCN, rt, 30 min, 99%; (h) NBS, CH_2Cl_2, 0 °C, 20 min, 90%; (i) CuI (1.0 equiv), CsOAc (2.5 equiv), DMSO, rt, 12 h, quant.

Dibromination of **13**[14] in the presence of $FeCl_3$,[15] removal of the trifluoroacetyl group, and subsequent oxidation provided dihydroisoquinoline **14**, which was readily converted to hemiaminal **15** by treatment with NsCl and then with water. The cyclization precursor **16**, obtained by reductive opening of hemiaminal **15**, was subjected to the first amination reaction using 10 mol % of CuI to give the desired indoline **17** with retention of the other bromo group.

After conversion of **17** to the dehydroalanine derivative **19** by oxidation and Horner−Wadsworth−Emmons reaction,[16] the second amination was performed to provide dihydropyrroloindole **20** in good yield.[11] The Ns group and benzyl ester in **20** were then converted to a Fmoc group and a methanethiol ester, respectively. Finally, an Fmoc-directed, regioselective demethylation was performed with BCl_3 to furnish the left segment **3**.[17] The right-hand

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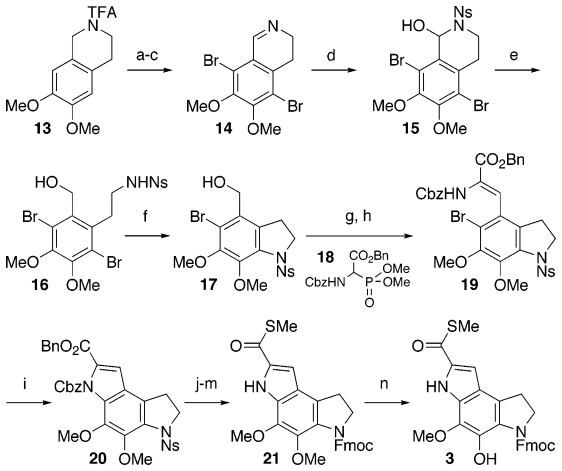
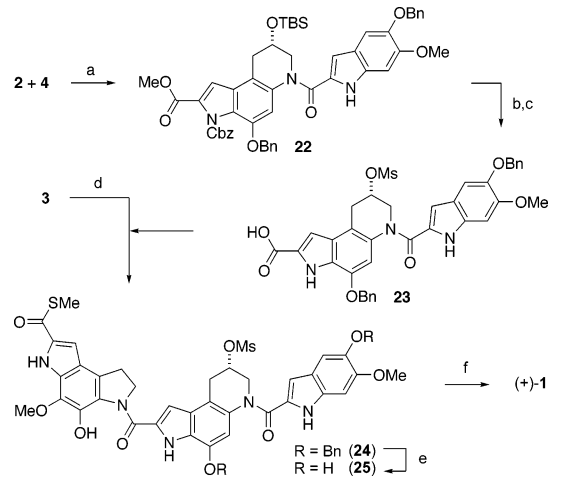
Scheme 3. Synthesis of the Left Segment[a]



[a] Reagents and conditions: (a) Br_2, $FeCl_3$, 0 °C, 30 min, 88%; (b) K_2CO_3, MeOH, rt, 6 h; (c) MnO_2, CH_2Cl_2, rt, 18 h, 90% (2 steps); (d) NsCl, THF, 0 °C, 5 min; rt, 1 h; $NaHCO_3$ aq., rt, 30 min; (e) $NaBH_4$, MeOH, 0 °C, 1 h, 78% (2 steps); (f) CuI (10 mol %), CsOAc (2.5 equiv), DMSO, 80 °C, 24 h; (g) TPAP (2 mol %), NMO, MS 4 Å, CH_2Cl_2, rt, 1 h, 85% (2 steps); (h) **18**, 1,1,3,3-tetramethylguanidine, CH_2Cl_2, rt, 6 h, 84%; (i) CuI (1.0 equiv), CsOAc (5.0 equiv), DMSO, rt, 12 h, 77%; (j) PhSH, Cs_2CO_3, MeCN, rt, 3 h, 95%; (k) FmocCl, $NaHCO_3$, THF−H_2O (3:1), rt, 10 min, 91%; (l) Pd/C, H_2, THF−EtOH (1:1), rt, 3 h; (m) MeSH, WSCD·HCl, DMAP, DMF, 0 °C, 3 h, 76% (2 steps); (n) BCl_3, CH_2Cl_2, 0 °C, 20 min, 97%.

Scheme 4. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) pyridine, CH_2Cl_2, 0 °C, 5 min, quant; (b) TBAF, THF, rt, 30 min; evaporation; MsCl, pyridine, CH_2Cl_2, rt, 4 h, 97%; (c) LiOH·H_2O, THF−H_2O (3:1), rt, 18 h, 92%; (d) TBAF, THF, rt, 30 min; WSCD·HCl; **23**, HOBt, THF, rt, 2 h, 96%; (e) BCl_3 (4.0 equiv), pentamethylbenzene (10 equiv), CH_2Cl_2, −78 °C, 15 min, 83%; (f) $NaHCO_3$, DMF−H_2O (2:1), rt, 2 h, 94%.

segment **4** was also prepared in a straightforward manner by using the aryl amination strategy.[18]

Having synthesized the requisite three segments, we then turned to the facile assembly of these compounds (Scheme 4). After coupling of the middle segment **2** with the right-hand segment **4** by acylation, the TBS ether was converted into a mesylate. Subsequent hydrolysis of the methyl ester and concomitant removal of the Cbz group then provided **23**. Initially, the crucial coupling with the left-hand segment met with limited success due to the instability of the amine derived from **3**. After extensive optimization, we were able to overcome this problem by carrying out the deprotection of the Fmoc group and subsequent condensation with **23** in one pot. The benzyl groups were then removed by BCl_3 in the presence of pentamethylbenzene, which served as a scavenger of benzyl cation.[19] Finally, spirocyclopropanation was effected by treatment with $NaHCO_3$ in aqueous DMF[5b] to furnish (+)-yatakemycin (**1**), which is identical in all respects to the natural product.

In conclusion, we have accomplished a highly efficient total synthesis of (+)-yatakemycin (**1**) based on the novel coupling of (*S*)-epichlorohydrin (**6**) with 2,6-dibromophenyllithium species and the copper-mediated construction of all five aryl−nitrogen bonds in **1**. The present strategy consisting of these two technologies allowed us to conduct a sub-gram-scale preparation of **1** in 13% overall yield over 20 steps (longest linear steps) and should be generally applicable to the synthesis of this class of compounds.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For the preparation, see Supporting Information.
(19) In the absence of pentamethylbenzene, **25** was obtained in low yield.

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