Communication

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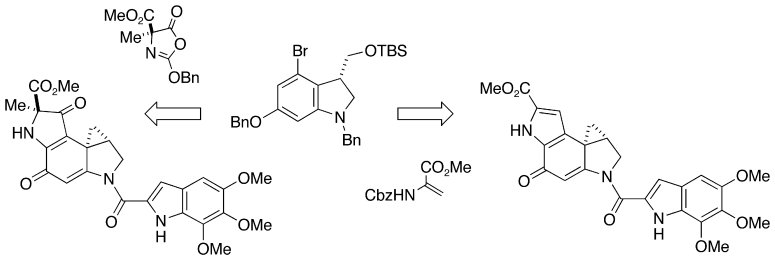

1: (+)-Duocarmycin A

2: (+)-Duocarmycin SA

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Total Synthesis of the Duocarmycins

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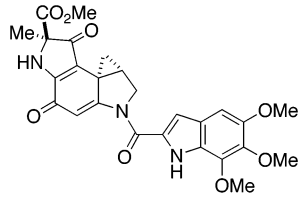
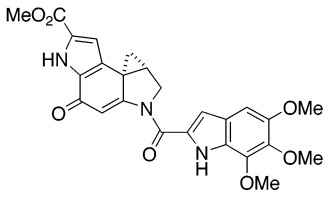
(+)-Duocarmycins A and SA are prominent members of the potent antitumor antibiotics isolated from *Streptomyces* species.[1] Coupled with the unique mode of action that derives from sequence-selective alkylation of DNA,[2] their novel structures make them attractive synthetic targets. Among several syntheses of the duocarmycins that have been reported to date,[3] there is only one report on the synthesis of duocarmycin A with complete stereocontrol.[4] Herein, we report a convergent synthesis of (+)-duocarmycin A, whose strategy was readily amenable to the synthesis of its congener, (+)-duocarmycin SA.



1: (+)-Duocarmycin A



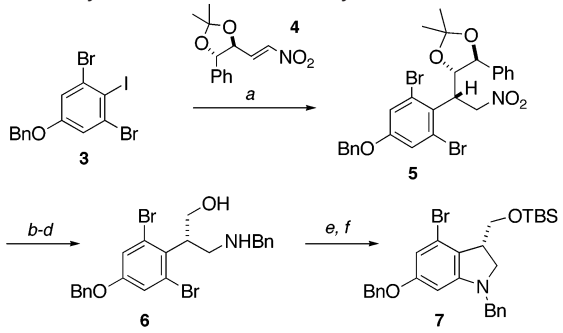
2: (+)-Duocarmycin SA

We began our synthesis of duocarmycin A (**1**) with the preparation of chiral indoline **7** (Scheme 1), whose absolute stereochemistry was controlled by diastereoselective addition[5] of the aryllithium reagent to nitroalkene **4**[6] bearing a chiral auxiliary. The unprecedented selective lithium−iodine exchange of 2,6-dibromoiodobenzene derivative **3**[7] was achieved by treatment with *n*-butyllithium at −78 °C, using toluene as the solvent.[8] Subsequent addition of **4** to the solution at −78 °C resulted in a smooth conjugate addition to give **5** with high diastereoselectivity (dr = 10:1). Acidic hydrolysis of the acetonide of the major adduct, cleavage of the resultant diol with periodic acid, and the subsequent one-pot reduction of the aldehyde afforded the corresponding nitro alcohol in high enantiomeric purity. Selective reduction of the aliphatic nitro group with Fe−$FeCl_2$ gave an amino-alcohol, which was subsequently converted to **6** via the *o*-nosylamide.[9]

The key transformation in our synthesis was the amination of aryl dibromide **6**, the challenge posed by the presence of an additional bromide, whose retention was required for the ensuing transformations. Thus, when **6** was treated under the conditions of the typical palladium-catalyzed amination reactions,[10] the desired product was obtained only in low yields, presumably due to the complications arising from the unwanted oxidative addition to the remaining bromide by the palladium catalyst.[11] Eventually, we overcame this problem by the discovery of a novel copper-mediated aryl amination reaction,[12] which cleanly gave the desired indoline under exceptionally mild conditions. Upon protection of the primary alcohol as the TBS ether, the stage was set for further elaboration into the tricyclic skeleton by the use of the remaining bromide as a synthetic handle.

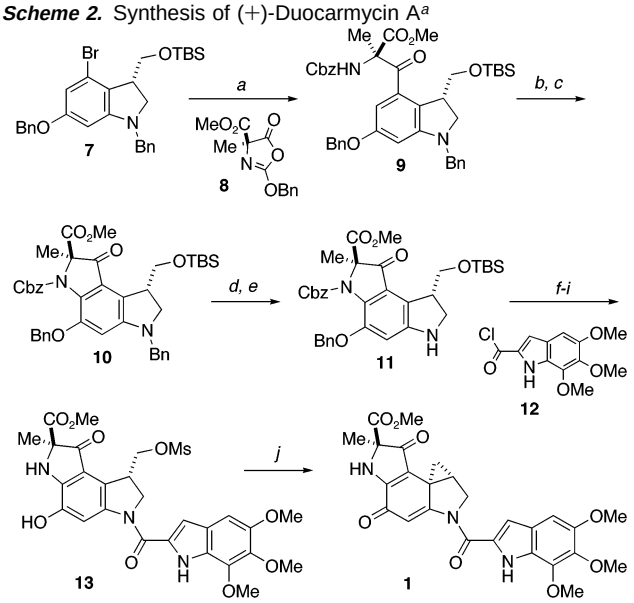
We selected azlactone **8**[13] as the electrophile for the reaction with the aryllithium derived from indoline **7** (Scheme 2). While additions of nitrogen and oxygen nucleophiles to azlactones are prevalent, their reactions with carbon nucleophiles have been scarcely documented.[14] Nonetheless, the regioselective addition took place in high yield, providing the adduct that bears all of the requisite functional groups with the correct stereochemistry in a single step. Next, *para*-selective bromination of indoline **9** was effected with NBS in DMF.[15] Gratifyingly, application of the aforementioned aryl amination reaction with 2 equiv of copper iodide at room temperature quantitatively provided the indolinone

Scheme 1. Synthesis of the Indoline Key Intermediate[a]



[a] Reagents and conditions: (a) *n*-BuLi, toluene, −78 °C; then **4** in toluene, 20 min, 58%; (b) AcOH−H_2O (1:4), reflux, 3 h, quant.; (c) H_5IO_6, THF, 0 °C, 5 min; $NaBH_4$, MeOH, −78 to 0 °C, 90% (>98% ee); (d) (i) Fe, $FeCl_2$, 1 N HCl, EtOH, reflux, 2 h; (ii) *o*-NsCl, $NaHCO_3$, CH_2Cl_2−H_2O, 23 °C, 5 min; (iii) BnBr, K_2CO_3, DMF, 23 °C, 1 h; then PhSH, 23 °C, 1 h, 74% (three steps); (e) CuI (10 mol %), CsOAc (1.4 equiv), DMSO, 23 °C, 24 h, 67%; (f) TBSCl, imid, DMF, 23 °C, 10 min, quant.

Scheme 2. Synthesis of (+)-Duocarmycin A[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; then **8** in toluene, −78 °C, 50 min, 75%; (b) NBS, DMF, 23 °C, 5 min, 82%; (c) CuI (2 equiv), CsOAc (5 equiv), DMSO, 23 °C, 3 h, quant.; (d) TrocCl, $NaHCO_3$, CH_3CN, 70 °C, 2 h, 70%; (e) Zn, KH_2PO_4, THF−H_2O (5:1), 23 °C, 1 h, 69%; (f) **12**, pyr, CH_2Cl_2, 0 °C, 10 min, 90%; (g) TBAF, THF, 23 °C, 30 min, 76%; (h) MsCl, pyr, 0 °C, 10 min, 88%; (i) H_2, Pd−C, EtOAc−EtOH, 23 °C, 8 h, 87%; (j) Cs_2CO_3, CH_3CN, 23 °C, 30 min, 77%.

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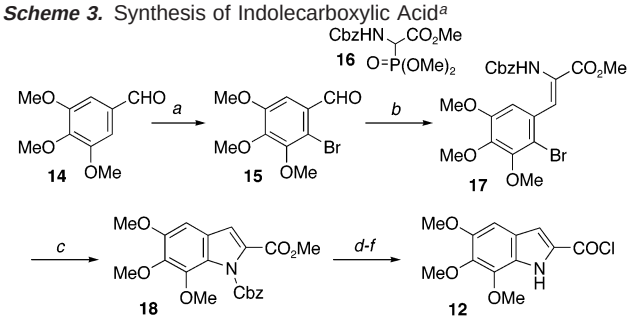
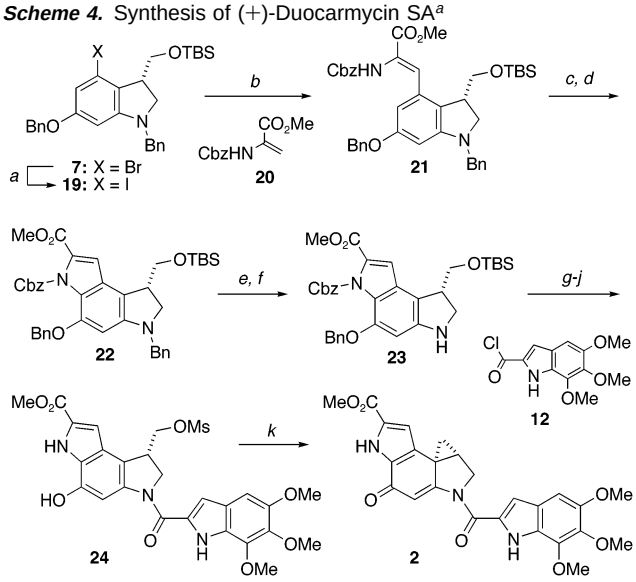
Scheme 3. Synthesis of Indolecarboxylic Acid[a]



[a] Reagents and conditions: (a) Br_2, AcOH, CH_2Cl_2, 0 °C, 45 min, 87%; (b) **16**, TMG, CH_2Cl_2, 23 °C, 3 days, 97%; (c) CuI (1.5 equiv), CsOAc (7 equiv), DMSO, 23 °C, 24 h, 98%; (d) H_2, Pd−C, EtOAc−EtOH, 23 °C, 3 h, 99%; (e) KOH, MeOH, reflux, 1 h, 89%; (f) $SOCl_2$, toluene, 60 °C, 20 min.

Scheme 4. Synthesis of (+)-Duocarmycin SA[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; then I_2, 97%; (b) **20**, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 90 °C, 4 h, 72%; (c) NBS, DMF, 23 °C, 5 min, 82%; (d) CuI (2 equiv), CsOAc (xs), DMSO, 23 °C, 10 min, quant.; (e) TrocCl, $NaHCO_3$, CH_3CN, 70 °C, 20 min, 77%; (f) Zn, KH_2PO_4, H_2O−THF (5:1), 23 °C, 1 h, 58%; (g) **12**, pyr, CH_2Cl_2, 0 °C, 10 min, 83%; (h) TBAF, THF, 23 °C, 30 min, 85%; (i) MsCl, pyr, 0 °C, 10 min, 88%; (j) H_2, Pd−C, EtOAc−EtOH, 23 °C, 10 min, 81%; (k) Cs_2CO_3, CH_3CN, 23 °C, 1 h, 92%.

10. Subsequent deprotection of the *N*-benzyl group afforded the free indoline **11**, which was acylated with acid chloride **12**. Conversion of the TBS ether to the mesylate and subsequent hydrogenolysis of the benzyl and Cbz groups furnished the substrate for the final spirocyclization. Upon treatment with excess cesium carbonate in acetonitrile, the mesylate **13** underwent smooth cyclization to afford (+)-duocarmycin A (**1**).

It is noteworthy that preparation of the indolecarboxylic acid moiety[16] involved once again a successful implementation of the copper-mediated aryl amination (Scheme 3). Thus, the Horner−Wadsworth−Emmons reaction of aldehyde **15** with phosphonate **16** furnished the requisite amination precursor **17** with excellent stereocontrol. When treated with excess copper iodide and cesium acetate at room temperature, the amination reaction proceeded smoothly to give the desired indole **18** in near-quantitative yield, which was then converted to the acid chloride **12** in three steps.

For the synthesis of duocarmycin SA (**2**), the common indoline intermediate **7** was first converted to the iodide **19** (Scheme 4). The subsequent Heck reaction with dehydroalanine **20**[17] gave indoline **21**, whose regioselective bromination was followed by the copper-mediated aryl amination to afford the tricyclic skeleton **22**. Finally, through application of a set of transformations essentially identical to those used for the synthesis of **1**, we were able to complete the total synthesis of **2**.

In conclusion, we have achieved a convergent synthesis of **1**, whose flexible strategy also enabled a straightforward synthesis of **2**. Furthermore, the novel copper-mediated aryl amination reaction has been used for forming all of the aryl−nitrogen bonds present in the duocarmycins, thereby providing a superior alternative to the existing palladium-catalyzed protocols.

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

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(6) Prepared from methyl cinnamate: (i) AD-mix-α, $MsNH_2$, *t*-BuOH−H_2O, 23 °C, 24 h, 66% (>99% ee after recrystallization); (ii) 2,2-dimethoxypropane, cat. *p*-TsOH, acetone, 23 °C, 3 h, 97%; (iii) DIBAL, toluene, −78 °C; MeOH, −78 to 23 °C; Et_3N, CH_3NO_2, 23 °C, 96%; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 88%.

(7) Prepared from *p*-nitrophenol: (i) MsCl, Et_3N, CH_2Cl_2, 0 to 23 °C, 3 h, 88%; (ii) H_2 (900 psi), Ra−Ni, EtOAc, 23 °C, 24 h, quant.; (iii) Br_2, MeOH−CH_2Cl_2 (1:1), 0 to 23 °C, 30 min, 87%; (iv) $NaNO_2$, H_2SO_4, CH_3CN−H_2O (1:1), 0 °C, 20 min; then KI, 0 to 23 °C, 96%; (v) KOH, CH_2Cl_2−MeOH (4:1), 23 °C, 5 min, quant.; (vi) BnBr, K_2CO_3, DMF, 23 °C, 1 h, 88%.

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(13) Prepared from dimethyl malonate: (i) $NaNO_2$, AcOH, 0 to 23 °C, 4 h; (ii) H_2 (1400 psi), Pd−C, EtOH, 23 °C, 12 h, 91% (two steps); (iii) CbzCl, pyr, CH_2Cl_2, 0 °C, 5 min, 96%; (iv) MeI, MeONa, MeOH, 50 °C, 2 h, 76%; (v) PLE, acetone−H_2O, pH 7.5−8.5, 23 °C, 3 days, quant. (94% ee, >98% ee after recrystallization); (vi) triphosgene, Et_3N, EtOAc, 23 °C, 5 min, quant.

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