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A Novel Synthesis of (+)-Duocarmycin SA

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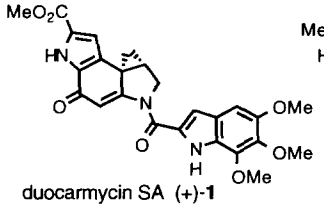
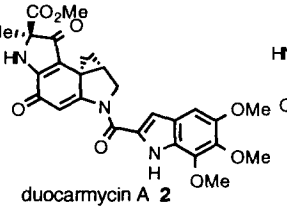
Abstract: The title synthesis was achieved in eight steps from (*S*)-5-aminoindoline (*S*)-**4** by a method featuring sequential dehydrogenation, double bond isomerization, and oxidative cyclization of (*S*)-5-[(1-methoxycarbonylethyl)amino]indoline **5** as the key steps. The sequential reaction was effected by using MnO_2-$Pd(OAc)_2$ as the oxidizing agent in the presence of an acid catalyst.

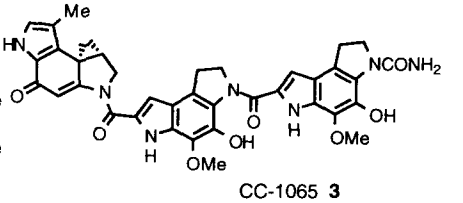
Duocarmycin SA [(+)-**1**] isolated from *Streptomyces sp.*[1] is a potent antitumor antibiotic structurally related to duocarmycin A (**2**)[2] and CC-1065 (**3**).[3] The cyclopropapyrroloindole(CPI) moieties involved in (+)-**1**, **2**, and **3** have been recognized as the common pharmacophore responsible for their cytotoxicity through sequence selective alkylation of double strand DNA[4]. It is also reported that (+)-**1** shows the most excellent cytotoxicity and stability in buffer among these CPI congeners and that the cytotoxicity of (+)-**1** is 10 times stronger than that of *ent*-(-)-**1**.[5]



duocarmycin SA (+)-**1**



duocarmycin A **2**

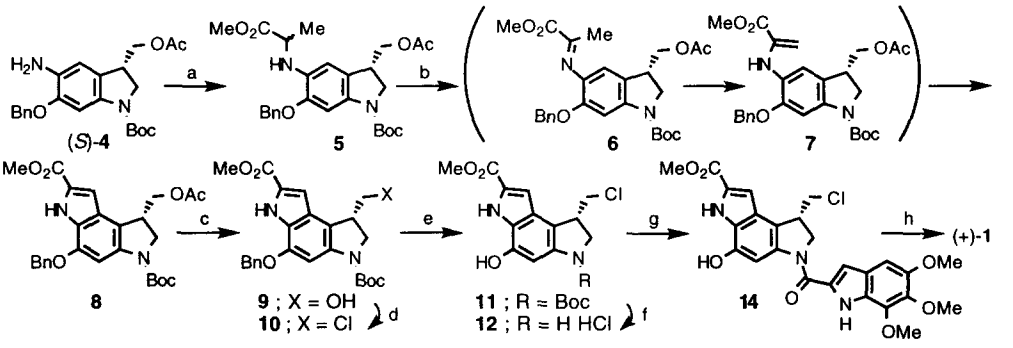


CC-1065 **3**

Although four total syntheses of (+)-**1** have already been reported,[6,7] a more efficient synthetic route to (+)-**1** was sought which can afford large quantities of (+)-**1** and its congeners required for developing novel antitumor agents. Herein, we wish to report a novel synthesis of (+)-**1** in eight steps from (*S*)-5-aminoindoline (*S*)-**4** which is obviously more efficient than methods so far reported[6,7] in light of its capability to provide large quantities of (+)-**1** and its congeners and the operational simplicity. The explored synthetic scheme features sequential dehydrogenation, double bond isomerization, and oxidative cyclization of (*S*)-5-[(1-methoxycarbonylethyl)amino]indoline **5** as the key steps. The sequential reaction is effected by using MnO_2-$Pd(OAc)_2$ as the oxidizing agent in the presence of an acid catalyst. The reaction substrate **5** is readily prepared from the optically pure (*S*)-5-aminoindoline (*S*)-**4** produced by the optical resolution and subsequent manipulation.[8]

Thus, the reaction of (*S*)-**4** with methyl 2-bromopropionate in the presence of 1,8-bis(dimethylamino)-naphthalene (proton sponge) gave **5** in excellent yield.[9] After numerous experimentations,[10] it was finally found that the treatment of **5** with MnO_2-$Pd(OAc)_2$ in the presence of *p*-nitrobenzoic acid as an acid catalyst in *N,N*-dimethylacetamide (DMA), affords the pyrroloindole **8**. The successful preparation of **8** from **5** can be explained by sequential dehydrogenation of **5** to imine **6** with MnO_2, double bond isomerization of **6** to enamino ester **7** catalyzed by *p*-nitrobenzoic acid, and oxidative cyclization of **7** to **8** with $Pd(OAc)_2$.[11,12] The acetyl group of **8** was removed by methanolysis under basic conditions, giving rise to alcohol **9**. Conversion of **9** to chloride **10** followed by removal of the benzyl group by transfer hydrogenolysis gave the phenol **11**. Deprotection of **11** under acidic conditions provided the indoline **12** as its hydrochloride. This was immediately coupled with 5,6,7-trimethoxyindole-2-carboxylic acid **13**[9] in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) to give the seco-chloride **14**.[6] Finally, treatment of **14** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected spirocyclization, furnishing (+)-**1**,

$[\alpha]_D^{20}$ = +200° (c = 0.095, MeOH) {lit[1a]: $[\alpha]_D^{24}$ = +180° (c = 0.1, MeOH), lit[6]: $[\alpha]_D^{22}$ = +197° (c = 0.035, MeOH), lit[7]: $[\alpha]_D^{21}$ = +192° (c = 0.352, MeOH)}.



a) methyl 2-bromopropionate, proton sponge, benzene, 90°C, 50h, 97%. b) MnO_2 (1.5eq), $Pd(OAc)_2$ (2eq), 4-nitrobenzoic acid (1eq), DMA, 90°C, 18h, 23%. c) K_2CO_3, MeOH, r.t., 1h, 93%. d) PPh_3, CCl_4, CH_2Cl_2, r.t., 2h, 92%. e) 10%Pd-C, 25%HCO_2NH_4, THF, 0°C, 1h, 95%. f) 3MHCl-AcOEt. g) **13**, EDCI, DMF, r.t., overnight, 83%. h) DBU, MeCN, r.t., 3h, 91%.

As described above, we have completed a novel synthesis of (+)-**1** in eight steps from (*S*)-**4** by a method featuring sequential three-step reaction of **5** (**5**→**6**→**7**→**8**) as a key step. Since the explored synthetic scheme can be carried out in a multi-gram scale, it may hold promise for the synthesis and evaluation of various congeners of (+)-**1** as novel antitumor agents.

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10. For this three-step reaction, NiO_2 and $CuSO_4$ were found to be also usable as an oxidizing agent instead of MnO_2. However, the reaction did not work well either in the presence of AcOH, dichloroacetic acid, or succinic acid as an acid catalyst, or in MeCN, toluene, or AcOH as a reaction solvent.
11. Oxidative cyclization of an enamino ester to afford a pyrroloindole was first introduced by us for the synthesis of novel bis(methoxycarbonyl)-CPI and 3-methoxycarbonyl-2-trifluoromethyl-CPI derivatives. See, Fukuda, Y.; Oomori, Y.; Kusama, Y.; Terashima, S. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 749. and Fukuda, Y.; Furuta, H.; Shiga, F.; Oomori, Y.; Kusama, Y.; Ebisu, H.; Terashima, S. *ibid.*, **1997**, *13*, 1683.
12. In fact, oxidative cyclization of unstable **6** derived from (*S*)-**4** and methyl pyruvate was effected by using $Pd(OAc)_2$ to give **8** in 10% yield.

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