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TOTAL SYNTHESIS OF NATURAL (+)-DUOCARMYCIN SA

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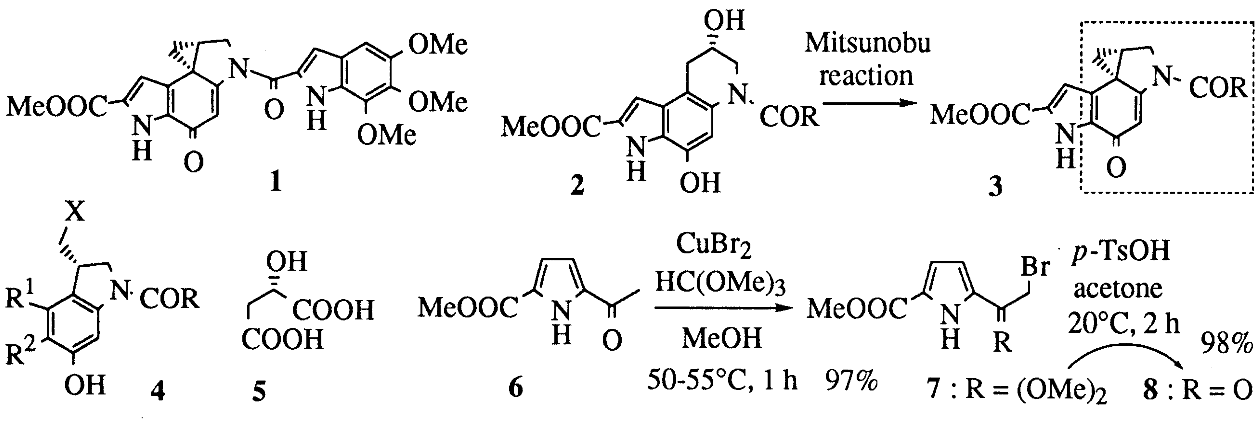
A total synthesis of natural (+)-duocarmycin SA (**1**) was achieved as shown in Chart 1, starting from L-malic acid (**5**) by using a Lewis acid-mediated indole formation reaction of a pyrrole precursor **14** to form the key compound **15**.

KEY WORDS duocarmycin SA; antitumor antibiotic; total synthesis; indole formation reaction

Last year, we reported a 12-step total synthesis of duocarmycin SA (**1**),[1] a potent antitumor antibiotic isolated from a culture broth of the *Streptomyces* species,[2] in the racemic form by employing a new strategy (**2** → **3**) for construction of the *N*-acylcyclopropanoindolinone unit (dashed line in **3**), which plays a pivotal role in exerting extremely potent biological activities.[3] In contrast to the previous syntheses of **1**,[4] duocarmycin A[5] and CC-1065[6] using **4** as a synthetic intermediate, our adoption of **2** made it easy to design an enantioselective access to **2**, and here we report a total synthesis of natural (+)-duocarmycin SA (**1**).

Our synthetic plan was to select L-malic acid (**5**) for the starting material, and this was converted into an indole formation precursor **14**. Our procedure[7] was applied to **14** for the synthesis of a hydroxyindole to finally identify appropriate reaction conditions affording **15**. Succeeding operations, *i.e.*, transformation of the carboxylic acid into a nitrogen function (**17** → **18**) and subsequent construction of the piperidine ring (**19** → **20**), would provide **2** having the hydroxyl group of the requisite absolute configuration.

The synthesis was started with diol **9**, prepared from **5** according to the literature.[8] Its dibenzyl ether **10** was reduced with diisobutylaluminum hydride (DIBAL),[9] and the resulting aldehyde **11** was condensed with an anion derived from benzyl acetate to form **12**,[10] which was oxidized to the β-keto ester **13**. Coupling of **13** with the pyrrole part **8**, prepared from **6**[11] by way of **7**, afforded a cyclization precursor **14**. Indole formation was accomplished by treatment of **14** with 2-ethyl-2-methyl-1,3-dioxane (50 mol eq) in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (6 mol eq) at room temperature for 44 h, and **15** was produced in 54% yield, along with a furan



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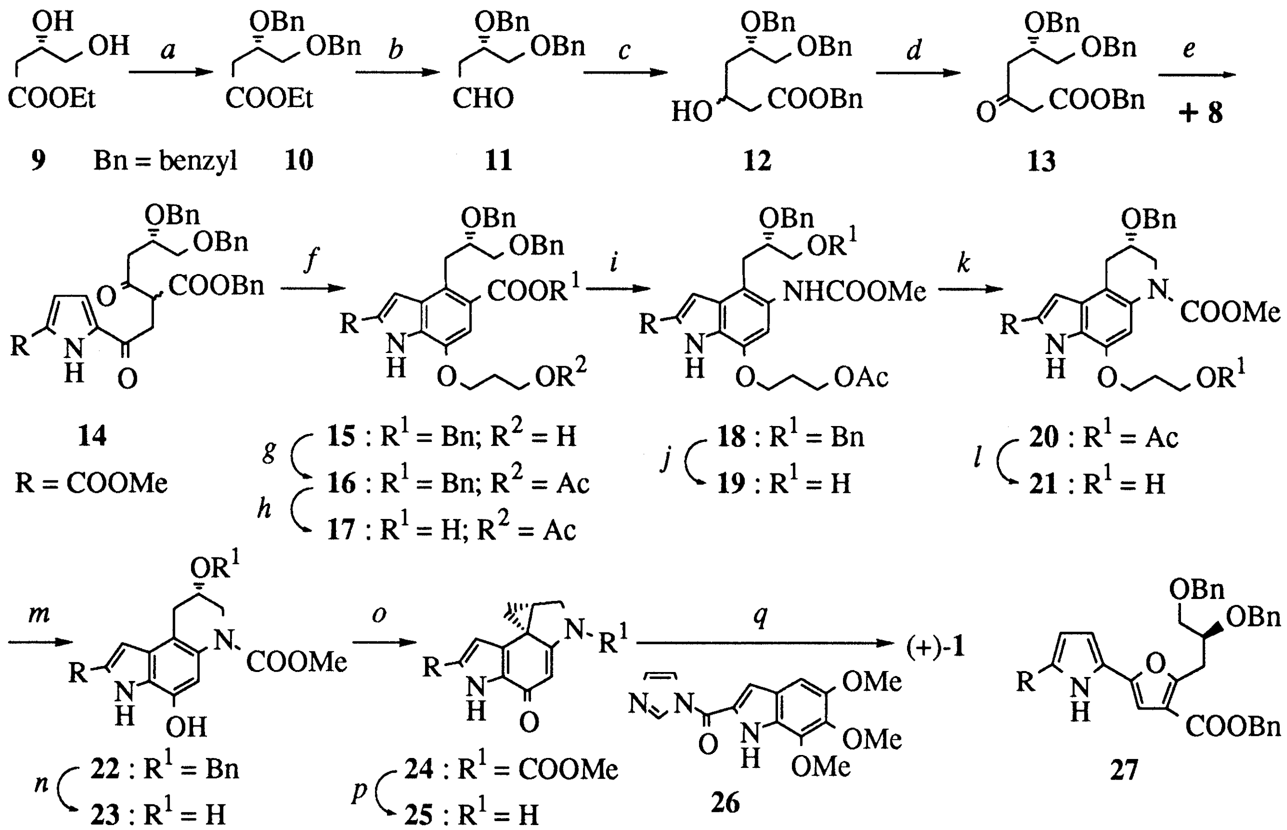
derivative **27** (10% yield) as an inevitable by-product. The hydroxypropyl function in **15** was conveniently used as a protecting group of the phenol function. The acetate **16**, prepared from **15**, was partially hydrogenated with Pd-C in EtOAc in particular to give mostly a mono-debenzylated acid **17** for the Curtius rearrangement. This reaction with diphenylphosphoryl azide (DPPA)[12] had to be carried out with some caution, and a modified procedure[13] for the reaction of **17** with DPPA and iso-Pr_2NEt in benzene, followed by treatment with MeOH, afforded **18** in a good yield.

The benzyl group at the primary alcohol in **18** was predominantly eliminated with BBr_3, and the resulting **19** was treated under Mitsunobu conditions.[14] Clean cyclization to the piperidine ring was accomplished in a very good yield to afford **20**. The phenol protecting group was removed by i) methanolysis of the acetate, ii) Dess-Martin oxidation and iii) β-elimination with Et_3N to produce **22**, whose benzyl group was taken off by hydrogenation over Pearlman's catalyst in MeOH. Formation of the cyclopropanoindolinone **24** from **23** was



a: $Cl_3CC(=NH)OBn$, CF_3SO_3H, cyclohexane-CH_2Cl_2, 0-26°C, 52%. *b*: DIBAL, PhMe, -76 – -63°C, 87%. *c*: LDA + CH_3COOBn in THF, -71 – -66°C, 78%. *d*: Dess-Martin periodinane, CH_2Cl_2, reflux, 86%. *e*: *tert*-BuOK, THF, 0 – 23°C, 86%. *f*: 2-ethyl-2-methyl-1,3-dioxane, $BF_3 \cdot OEt_2$, CH_2Cl_2, 20°C, 54%. *g*: Ac_2O, pyridine, CH_2Cl_2, 16°C, 97%. *h*: H_2, 10% Pd-C, EtOAc, 13°C, 75%. *i*: i) DPPA, iso-Pr_2NEt, benzene, reflux; ii) MeOH, reflux, 69%. *j*: BBr_3, CH_2Cl_2, -80 – -55°C, 61%. *k*: DEAD, Ph_3P, THF, 21°C, 90%. *l*: K_2CO_3, MeOH, 21°C, 98%. *m*: i) Dess-Martin periodinane, CH_2Cl_2, reflux; ii) Et_3N, CH_2Cl_2, reflux, 86%. *n*: H_2 (5 atm), 20% $Pd(OH)_2$-C, MeOH, 25°C, 96%. *o*: *N*-piperidyl-CO-N=N-CO-*N*-piperidyl, *n*-Bu_3P, THF, 20°C, 88%. *p*: K_2CO_3, MeOH, 18°C, 96%. *q*: i) NaH, DMF-THF; ii) **26**, 0°C, 74%.

Chart 1

effected with 1,1'-(azodicarbonyl)dipiperidine[15] as in the case of the racemic series.[1] Methanolysis of **24**, followed by condensation of **25** with 1-(5,6,7-trimethoxyindole-2-carbonyl)imidazole (**26**), completed a total synthesis of natural (+)-duocarmycin SA (**1**), {$[\alpha]_D^{21}$ +192° (c = 0.352, MeOH); lit.[2a]: $[\alpha]_D^{24}$ +180° (c = 0.1, MeOH)}.

In summary, a novel indole formation reaction was applied to **14** for construction of the important intermediate **15** carrying in its side chain the requisite chiral center derived from L-malic acid. Mitsunobu reaction was successfully applied not only to the cyclopropanoindolinone formation (**23** → **24**) but also to dehydrative bond connection between the methyl carbamate group and the primary alcohol to give the *N*-methoxycarbonylpiperidine ring system (**19** → **20**). Using these reactions in key steps, a total synthesis of natural (+)-duocarmycin SA (**1**) was achieved starting from L-malic acid (**5**) and a pyrrole derivative **6**.

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