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FIRST TOTAL SYNTHESIS OF *dl*-DUOCARMYCIN A

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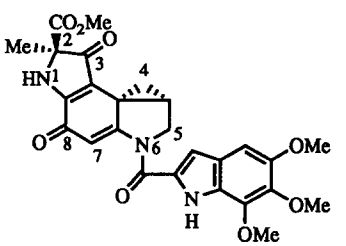
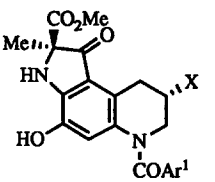
Summary : The title synthesis could be achieved by featuring introduction of a methoxycarbonyl group into the C-4 position of a 5-aminoindoline nucleus by way of an isatin derivative and subsequent ring closure to a methyl 2-methylindoxyl-2-carboxylate system by the Dieckmann cyclization.

Duocarmycins, A (**1**), C_1 (**2**), C_2 (**3**), B_1 (**4**) and B_2 (**5**) isolated from *Streptomyces sp.* by a research group at Kyowa Hakko are novel antitumor antibiotics which are effective against various strains of experimental murine cancers.[2] Almost at the same time, workers at Meiji Seika also reported isolation of two new antitumor antibiotics, pyrindamycin A and B, from the culture broth of *Streptomyces sp.*,[3] and these antibiotics were found to be identical with **3** and **2**, respectively.[2c] It was further disclosed that treatment of **1** with hydrochloric acid or potassium bromide affords a mixture of **2** and **3** or **4** and **5** and that **1** can be reproduced from **5** by treating under basic conditions.[2b,d]

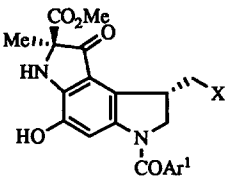
The structural feature of **1** holding a central position of the duocarmycin family is obviously its close resemblance to the potent antitumor antibiotic CC-1065 (**6**).[4] Especially, the upper half of **1** may exhibit the biochemical properties similar to the left hand segment of **6** [cyclopropapyrroloindole (CPI) system], which is essential for its pronounced biological activities.[5] Since **6** showed unusual delayed lethality,[6] numerous



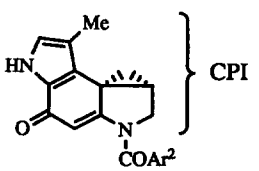
duocarmycin A **1**



duocarmycin C_1 **2** : X = Cl
(pyrindamycin B)
duocarmycin B_1 **4** : X = Br

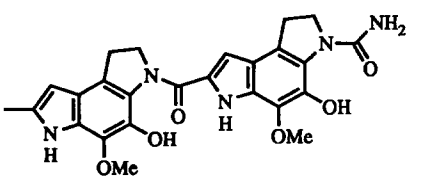


duocarmycin C_2 **3** : X = Cl
(pyrindamycin A)
duocarmycin B_2 **5** : X = Br

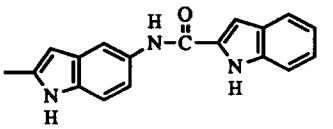


CPI

CC-1065 **6** Ar^2 =



U-71,184 **7** Ar^2 =



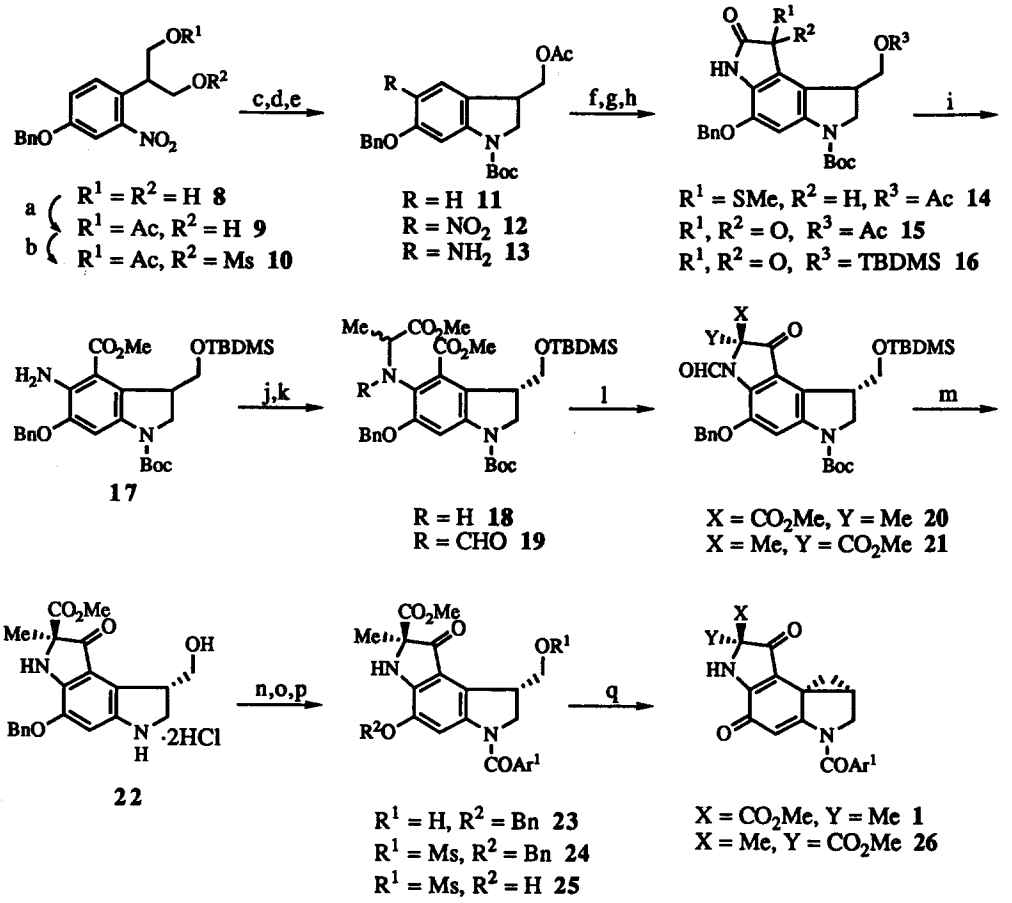
synthetic efforts have been devoted to explore less toxic analogues of **6**,[5,7] culminating in the development of U-71,184 (**7**) lacking delayed toxicity.[5,7a] With these notable aspects in mind, we embarked on the synthetic studies on **1** and its analogues to explore prominent anticancer agents. Herein, we wish to record first total synthesis of *dl*-**1** and its 2-epimer, *dl*-2-epiduocarmycin A (**26**).

Taking into account future possible applications of the explored synthetic route to the preparation of various analogues of **1**, the synthetic scheme was designed in which amide formation between the upper half of **1** with 5,6,7-trimethoxyindole-2-carboxylic acid (**27**) is examined after functionalizations for the crucial Ar_1-3-type Winstein cyclization have been completed.[8] Since construction of the indoline derivatives such as **12** and **13** had been well investigated in the previous synthetic studies on **6**,[9] our synthetic efforts were primarily focused on elaboration of the 2-methylindoxyl-2-carboxylic acid ester system characterizing the structure of **1**. After numerous model studies, an approach by the Dieckmann cyclization of diester (**19**) prepared through isatin and 5-amino-4-methoxycarbonylindoline derivatives (**16** and **17**) was found to be successful.

Thus, mono-acetylation of symmetrical diol (**8**)[10] and mesylation of the remaining alcohol provided mesylate (**10**). Reduction of the nitro group of **10** effected simultaneous indoline formation, affording 1-*t*-butoxycarbonylindoline (**11**) after *in situ* protection of the generated secondary amino group. Nitration of **11** with acetyl nitrate cleanly occurred at the C-5 position (indole numbering) to give nitro compound (**12**), which in turn was reduced to amino indoline derivative (**13**). The next task was the introduction of one carbon unit into the C-4 position of **13**. After experimentations, this could be realized by applying the Gassman's oxindole synthesis.[11] Thus, the reaction of **13** with chlorosulfonium salt of methyl (methylthio)acetate followed by base-promoted [2,3]sigmatropic rearrangement and acid-catalyzed ring closure cleanly afforded 3-methylthiooxindole (**14**).[5,7a] Oxidation of **14** to isatin derivative (**15**) was effectively achieved by treating with a combination of *cupric* chloride and cupric oxide. At this stage, the acetyl group of **15** was changed to a *t*-butyldimethylsilyl (TBDMS) group to afford TBDMS ether (**16**).

Our synthetic efforts were next focused on the ring opening of an isatin moiety and subsequent introduction of a propionic acid portion into the amino group of 5-aminoindoline derivative for the Dieckmann cyclization. Toward this end, **16** was oxidized with m-CPBA and the resulting isatoic anhydride was subjected to methanolysis under basic conditions, giving rise to anthranilic acid methyl ester (**17**). Alkylation of **17** with methyl 2-bromopropionate could be achieved in the presence of cesium carbonate to give dimethyl ester (**18**). The secondary amino group of **18** was then protected with a formyl group, producing formamide (**19**). Thus, the functionalizations were set up for the key cyclization. Treatment of **19** with LDA cleanly produced a diastereomeric mixture of tricyclic compounds (**20** and **21**) which could be separated by preparative TLC. Although the stereochemical assignment of **20** and **21** was not possible at this moment, successful elaboration of the less polar isomer (**20**) to *dl*-**1** definitely confirmed their stereochemistries as shown in the scheme.

The remaining task to accomplish the projected synthesis was the coupling with **27** and formation of the cyclopropadienone system. Acid hydrolysis of **20** afforded diamino alcohol dihydrochloride (**22**) which was coupled with **27**.[12] As expected, the amide formation selectively occurred at the less hindered nitrogen, giving mono amide (**23**) as a sole product. Mesylation of the primary alcohol in **23** and subsequent hydrogenolysis of the benzyl ether of resulting mesylate (**24**) produced phenol (**25**), being structurally close to *dl*-**3** and **5**. Finally, formation of the cyclopropadienone system was achieved by treatment of **25** with NaH to furnish



a) Ac_2O, Et_3N, CH_2Cl_2, 0°C, 2.5h, 74% b) MsCl, Et_3N, CH_2Cl_2, 0°C, 0.5h, 100% c) 1. H_2 (3 atm), PtO_2, Et_3N, THF, rt, 20min 2. Boc_2O, CH_2Cl_2, rt, 12h, 95% d) HNO_3, Ac_2O, then **11**, CH_3NO_2, -20°C, 3h, 77% e) H_2 (3 atm), PtO_2, THF, rt, 15min f) 1. SO_2Cl_2, $CH_3SCH_2CO_2Me$, CH_2Cl_2, then **13**, 1,8-bis(dimethylamino)naphthalene, -78°C, 3.5h 2. Et_3N, -78°C, 2h, rt, 21h 3. AcOH, rt, 1h g) $CuCl_2$, CuO, acetone, rt, 1.5h, 77% from **13** h) 1. K_2CO_3, MeOH, rt, 2.5h 2. TBDMSCl, imidazole, DMF, rt, 8h, 78% i) 1. m-CPBA, $NaHCO_3$, CH_2Cl_2, -15°C, 2h 2. K_2CO_3, MeOH, 10°C, 1h, 94% j) $CH_3CHBrCO_2Me$, $CsCO_3$, CH_3CONMe_2, 70°C, 48h, 57% k) HCO_2H, Ac_2O, then **18**, rt, 9h, 93% l) LDA, THF, -78°C, 5.5h, less polar isomer **20** 28%, more polar isomer **21** 28% m) HCl in MeOH, rt, 11h, 100% n) **27**, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), $NaHCO_3$, DMF, rt, 20h, 57% o) MsCl, Et_3N, CH_2Cl_2, 10°C, 0.5h, 99% p) H_2 (1 atm), 10% Pd/C, THF, 85% q) NaH, THF, rt, 3.5h, 60%

dl-**1**.[14,15] The NMR spectra of *dl*-**1** was identical with that of authentic natural **1**. By employing the same reaction sequence, the more polar isomer of tricyclic compound (**21**) was also successfully transformed to *dl*-**26**.[15]

Thus, we have succeeded in first total synthesis of *dl*-**1** and *dl*-**26**. The synthetic scheme outlined here could provide not only optically active duocarmycins[10] but also a number of analogues which might exhibit prominent antitumor activities. Studies along this line are in progress.

Acknowledgement

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References and Notes

1. a) Visiting scientist from the Central Research Laboratories, Kyorin Pharmaceutical Co., Ltd. b) Present address: Department of Chemistry, Faculty of Sciences, Kyushu University, Fukuoka, 812, Japan.
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7. For example, a) Warpehoski, M. A. *Tetrahedron Lett.*, **1986**, *27*, 4103. b) Drost, K. J.; Jones, R. J.; Cava, M. P. *J. Org. Chem.*, **1989**, *54*, 5985. c) Boger, D. L.; Wysocki, R. J.; Ishizaki, T. *J. Am. Chem. Soc.*, **1990**, *112*, 5230.
8. a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.*, **1963**, *85*, 567. b) Wierenga, W. *ibid.* **1981**, *103*, 5621.
9. For studies directed toward the CPI segment; see Rawal, V. H.; Jones, R. L.; Cava, M. P. *Heterocycles*, **1987**, *25*, 701 and references cited therein. See also ref. 5, 7a and 8b.
10. The symmetrical diol (**8**) used as a starting material should be useful for future synthesis of optically active **1** and its analogues.
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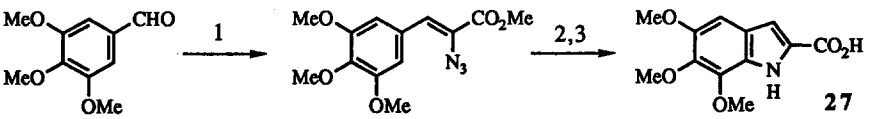
12. 5,6,7-Trimethoxyindole-2-carboxylic acid (**27**) could be prepared from 3,4,5-trimethoxybenzaldehyde according to the following procedure.[13]



27

1) $N_3CH_2CO_2Me$, NaOMe, MeOH, rt, 12h, 34% 2) xylene reflux, 1h, 94% 3) 40% KOH, MeOH, 50°C, 0.5h, 96%

13. Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 931.
14. Synthetic *dl*-**1** and natural **1** showed no clear melting point and gradually decomposed when heated up to ca. 230°C.
15. Samples of *dl*-**1**, *dl*-**26** and natural **1** showed the following IC_{50} values (ng/ml) when subjected to *in vitro* cytotoxicity assay against P388 murine leukemia. *dl*-**1**, 0.25; *dl*-**26**, 0.17; natural **1**, 0.079.

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