NOVEL SYNTHESES OF OPTICALLY ACTIVE CC-1065, U-73,975(ADOZELESIN), U-80,244(CARZELESIN), U-77,779(BIZELESIN), KW-2189, AND DU-86[1]

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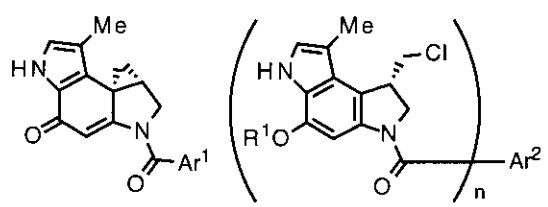
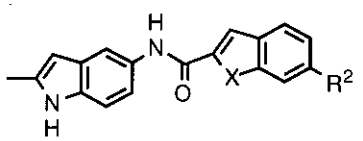
Abstract-The title syntheses were achieved by the method featuring oxidative cyclization of the enamino esters [(*S*)-**13** and (*S*)-**24**] derived from the 5-aminoindoline [(*S*)-**12**], acylation with various structural types of indole-2-carboxylic acids, and formation of cyclopropapyrroloindole moieties.

CC-1065 [(+)-**1**],[2] duocarmycin A [(+)-**6**],[3] and duocarmycin SA [(+)-**7**][4] carrying a cyclopropapyrroloindole (CPI) moiety as the common pharmacophore are well known as potent antitumor antibiotics isolated from *Streptomyces* sp. The CPI system has been recognized to be responsible for their prominent cytotoxicity through sequence selective alkylation of double strand DNA.[5] Since unusual delayed lethality was observed for (+)-**1**,[6] various types of congeners have been synthesized and evaluated to explore less toxic analogues of (+)-**1**, resulting in the development of U-68,415 (*dl*-**2**),[5c] U-73,975 (adozelesin) [(+)-**3**],[7] and U-80,244 (carzelesin) [(+)-**4**][8] as novel antitumor agents showing no delayed toxicity. In addition to these derivatives, bisalkylator, U-77,779 (bizelesin) [(+)-**5**][9] showing more prominent cytotoxicity was also reported (**Figure 1**).

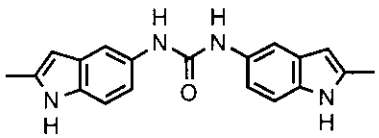
Figure 1



CC-1065 (+)-**1**: Ar^1



U-68,415 *dl*-**2**: Ar^1 : X = NH, R^2 = H
U-73,975(adozelesin) (+)-**3**: Ar^1 : X = O, R^2 = H
U-80,244(carzelesin) (+)-**4**: Ar^2 : n = 1,
R^1 = CONHPh, X = O, R^2 = NEt_2,

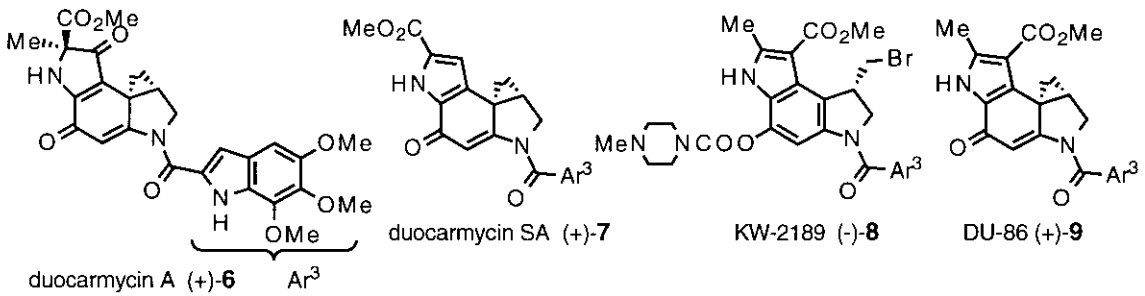


U-77,779(bizelesin) (+)-**5**: Ar^2: n = 2, R^1 = H

This paper is dedicated to 25th Anniversary of HETEROCYCLES.

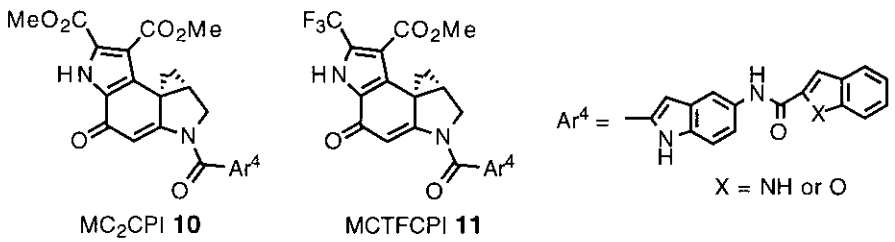
As for (+)-**6**, synthetic efforts have been devoted to the preparation of its congeners, culminating in the exploration of KW-2189 [(-)-**8**][10] and DU-86[(+)-**9**][10] as semi-synthetic antitumor agents (**Figure 2**). Some of these novel antitumor agents [(+)-**3**, (+)-**4**, and (-)-**8**] are presently under clinical trials.

Figure 2



Recently, we reported the synthesis and antitumor activity of novel CPI derivatives, bis(methoxycarbonyl)-cyclopropapyrroloindole (MC_2CPI)[11] and 3-methoxycarbonyl-2-trifluoromethylcyclopropapyrroloindole (MCTFCPI)[12] derivatives (**10** and **11**), showing prominent antitumor activity against murine leukemia and

Figure 3



solid tumors (**Figure 3**).[11,12] These novel CPI derivatives (**10** and **11**) were prepared by employing oxidative cyclization of the enamino esters derived from the 5-aminoindoline [(*S*)-**12**]. Moreover, we also explored a highly efficient method for preparing (*S*)-**12** by the combination of optical resolution and subsequent manipulation, making it possible to obtain optically pure (*S*)-**12** in a kilogram scale.[13] With an aim to progress our project directed at developing novel antitumor agents, it became necessary for us to compare antitumor activity of **10** and **11** with that of the known CPI derivatives, [(+)-**1**~(+)-**9**]. Furthermore, (+)-**1** was also required to disclose whether or not **10** and **11** show delayed toxicity. Since the total syntheses of (+)-**6** and (+)-**7** had been achieved by our hands[13,14] and *dl*-**2** was readily obtainable according to the reported procedure,[5c] we embarked on the total syntheses of (+)-**1**, (+)-**3**~(+)-**5**, (-)-**8**, and (+)-**9** required as the standard compounds for our screening systems similarly to *dl*-**2**, (+)-**6**, and (+)-**7**. Herein, we wish to report on the novel total syntheses of (+)-**1**, (+)-**3**~(+)-**5**, (-)-**8**, and (+)-**9** achieved by employing oxidative cyclization of the enamino esters [(*S*)-**13** and (*S*)-**24**] derived from (*S*)-**12** as the key steps.

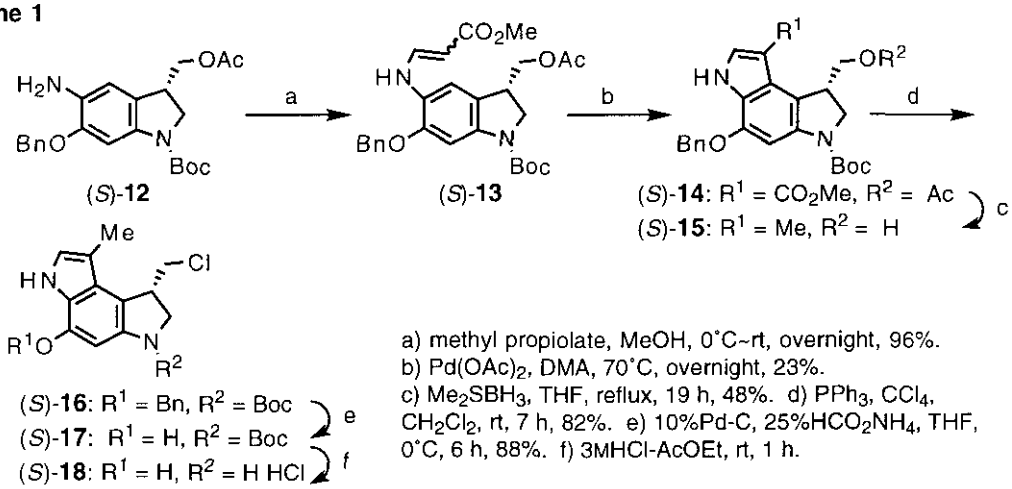
Synthesis of CC-1065 [(+)-1], U-73,975 (adozelesin) [(+)-3], U-80,244 (carzelesin) [(+)-4], and U-77,779 (bizelesin) [(+)-5]

Total synthesis of (+)-**1** and (+)-**3**~(+)-**5**[5c,9a,15] had already been accomplished by acylation of the 4-chloromethyl-3-methylpyrroloindole [(*S*)-**18**] with various structural types of indole-2-carboxylic acids,

(**19**,[15,16] **21a,b**,[5c] and **23**[9a]), followed by formation of the cyclopropapyrroloindole moieties. Accordingly, we selected (*S*)-**18** as a target molecule and studied the preparation of (*S*)-**18** from (*S*)-**12** by *employing oxidative cyclization of* (*S*)-**13**.

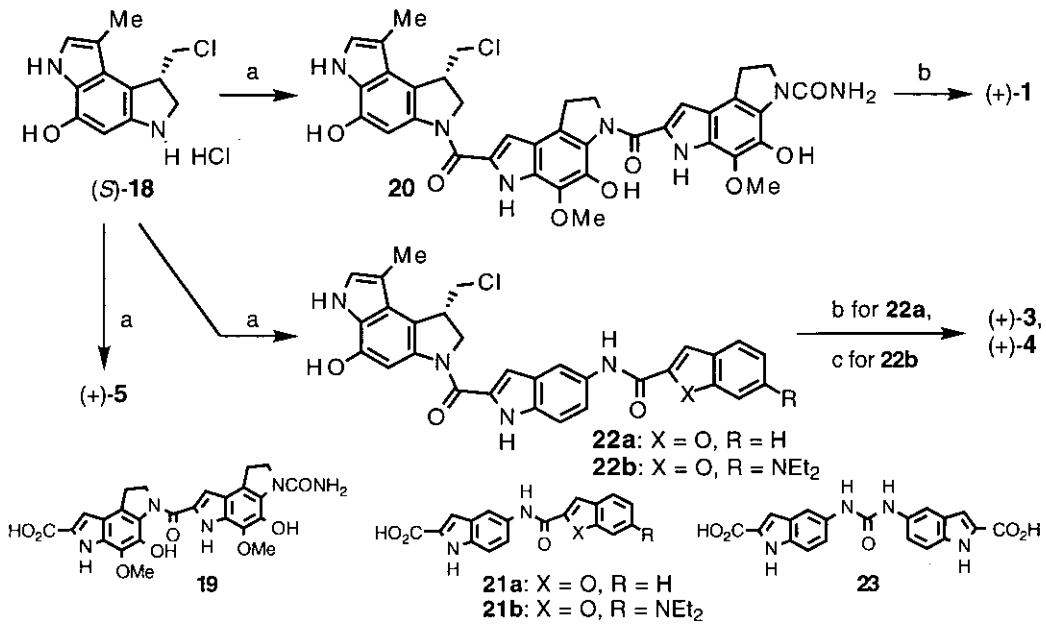
Thus, Michael addition of (*S*)-**12**, $[\alpha]_D^{25}$ = +28° (c = 0.29, CH_2Cl_2), with methyl propiolate in methanol cleanly provided (*S*)-**13**.[19] Oxidative cyclization of (*S*)-**13** was effected with $Pd(OAc)_2$ in *N*,*N*-dimethylacetamide (DMA) to afford the 3-methoxycarbonylpyrroloindole [(*S*)-**14**] as a sole product. Treatment of (*S*)-**14** with borane-dimethyl sulfide complex underwent simultaneous reductions of both the methyl ester and the acetate, giving rise to alcohol [(*S*)-**15**]. This was converted to phenol [(*S*)-**17**] by way of chloride [(*S*)-**16**] by sequential chlorination and removal of the benzyl group by transfer hydrogenolysis. Treatment of (*S*)-**17** with 3MHCl-AcOEt furnished (*S*)-**18** as its hydrochloride (**Scheme 1**). Taking into account the number of steps, the novel synthetic route to (*S*)-**18** from (*S*)-**12** seems to be more practical than those reported.[5c,15]

Scheme 1



With (*S*)-**18** in hand, the syntheses of (+)-**1** and (+)-**3**~(+)-**5** were next attempted according to the reported procedures (**Scheme 2**).[7~9,15,16] Thus, (*S*)-**18** was immediately coupled with-**19**[15,16] in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) to give the seco-chloride [(*S*)-**20**]. Subsequent treatment of (*S*)-**20** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected spiro-cyclization, affording (+)-**1**, $[\alpha]_D^{25}$ = +98° (c = 0.20, DMF) {lit.,[5b,15a]: $[\alpha]_D^{25}$ = +98° (c = 0.2, DMF)}. In a similar manner, couplings of (*S*)-**18** with **21a,b**[5c] and **23**[9a] gave the seco-chlorides (**22a,b**) and (+)-**5**, $[\alpha]_D^{26}$ = +37° (c = 0.20, DMF),[20] respectively. Treatment of **22a** with DBU underwent spiro-cyclization, yielding (+)-**3**, $[\alpha]_D^{31}$ = +141° (c = 0.20, THF).[20] Introduction of a phenylcarbamoyl group into **22b** as the prodrug moiety provided (+)-**4**, $[\alpha]_D^{31}$ = +41° (c = 0.20, THF).[20] With completion of the syntheses of (+)-**1** and (+)-**3**~(+)-**5**, we next attempted the preparation of (-)-**8** and (+)-**9**.

Scheme 2



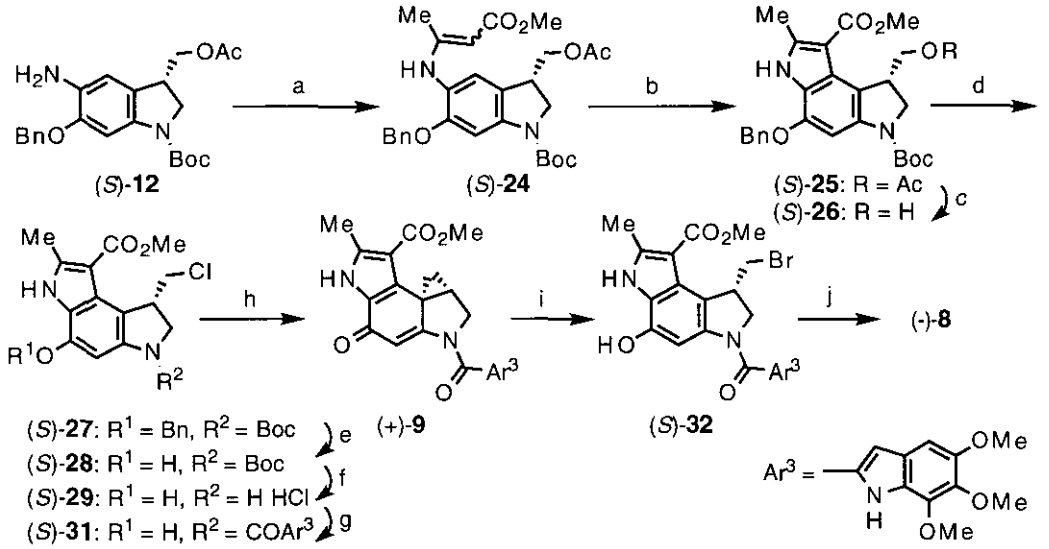
a) **19**, **21a,b** or **23**, EDCI, DMF, rt, overnight, **20**; 62% from (*S*)-**16**, **22a**; 50% from (*S*)-**17**, **22b**; 58% from (*S*)-**17**, (+)-**5**; 26% from (*S*)-**17**. b) DBU, MeCN, rt, 4 h, (+)-**1**; 45%, (+)-**3**; 49%. c) phenyl isocyanate, THF, Et_3N, rt, 18 h, 89%.

Synthesis of KW-2189 [(-)-8] and DU-86 [(+)-9]

The syntheses of (-)-**8** and (+)-**9** had been achieved by the transformation from (+)-**6** produced by *Streptomyces* sp.[10] We had also succeeded in the first total synthesis of (+)-**6**.[13] However, taking into account the number of synthetic steps and operational simplicity, the novel synthesis of (-)-**8** and (+)-**9** was examined by employing oxidative cyclization of (*S*)-**24**.

Thus, condensation of (*S*)-**12** and methyl acetoacetate in the presence of an acid catalyst cleanly provided (*S*)-**24**.[19] Oxidative cyclization of (*S*)-**24** was effected in a similar manner to that for (*S*)-**13**, giving rise to the 3-methoxycarbonyl-2-methylpyrroloindole [(*S*)-**25**] as a sole product. This was converted to phenol [(*S*)-**28**] by way of alcohol [(*S*)-**26**] and chloride [(*S*)-**27**] in the same manner as described for the preparation of (*S*)-**17**. Deprotection of (*S*)-**28** under acidic conditions gave the 4-chloromethyl-3-methoxycarbonyl-2-methylpyrroloindoline [(*S*)-**29**] as its hydrochloride. This was immediately coupled with the indole-2-carboxylic acid (**30**)[13] in the presence EDCI to give the seco-chloride [(*S*)-**31**]. Treatment of (*S*)-**31** with DBU underwent spiro-cyclization, providing (+)-**9**, $[\alpha]_D^{23}$ = +146° (c = 0.67, $CHCl_3$).[20] Reaction of (+)-**9** with 1MHBr gave the seco-bromide [(*S*)-**32**]. The phenolic hydroxyl group in (*S*)-**31** was masked with a *N*-methylpiperazinylcarbamoyl group, furnishing (-)-**8**, $[\alpha]_D^{24}$ = -8.8° (c = 1.2, $CHCl_3$)[20] (**Scheme 3**).

Scheme 3



a) methyl acetoacetate, TsOH, benzene, reflux, 5 h, 87%. b) $Pd(OAc)_2$, DMA, 70°C, 19 h, 36%. c) K_2CO_3, MeOH, rt, 5 h, 92%. d) PPh_3, CCl_4, CH_2Cl_2, rt, 19 h, 93%. e) 10%Pd-C, 25%HCO_2NH_4, THF, 0°C, 20.5 h. f) 3MHCl-AcOEt. g) Ar^3CO_2H (**30**), EDCI, DMF, rt, 85% from **27**. h) DBU, MeCN, rt, 97%. i) 1MHBr in MeCN, rt, 1.5 h, 90%. j) i) $ClCO_2PhNO_2$, Et_3N, 0°C, 1 h. ii) *N*-methylpiperazine, 0°C~rt, 7 h, 88% (2 steps).

As described above, we have succeeded in the novel syntheses of (+)-**1**, (+)-**3**~(+)-**5**, (-)-**8**, and (+)-**9** starting with (*S*)-**12**. Since we had already accomplished the total syntheses of (+)-**6** and (+)-**7** from (*S*)-**12**,[13,14] it became possible to obtain all the naturally occurring CPI derivatives [(+)-**1**, (+)-**6**, and (+)-**7**] and their derivatives [(+)-**3**~(+)-**5**, (-)-**8**], and (+)-**9** from the common starting material [(*S*)-**12**]. The CPI derivatives obtained here were useful as the standard compounds for our screening systems similarly to *dl*-**2**, (+)-**6**, and (+)-**7**. Our successful results definitely show potential of the oxidative cyclization of enamino esters to construct various structural types of CPI derivatives.

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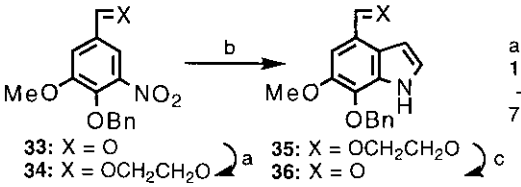
16. Synthesis of **19** was accomplished starting with **33**[18] with some improvements shown below. Thus, the indole derivative (**35**) was efficiently prepared by the reaction of the nitrobenzene (**34**) with vinylmagnesium bromide. See, also ref. 17.



a) ethylene glycol, TsOH, benzene, Dean Stark, 1 h, 100%. b) vinylmagnesium bromide, THF, -40°C, 1.5 h, 24%. c) 10%HCl, THF, rt, 0.5 h, 79%.

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19. Determination of the stereochemistries of the acrylate moieties for (*S*)-**13** and (*S*)-**24** was not attempted.
20. The optical rotation value of this compound has not been reported.

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