

NOVEL SYNTHESSES OF OPTICALLY ACTIVE CC-1065, U-73,975(ADOZELESIN), U-80,244(CARZELESIN), U-77,779(BIZELESIN), KW-2189, AND DU-86¹

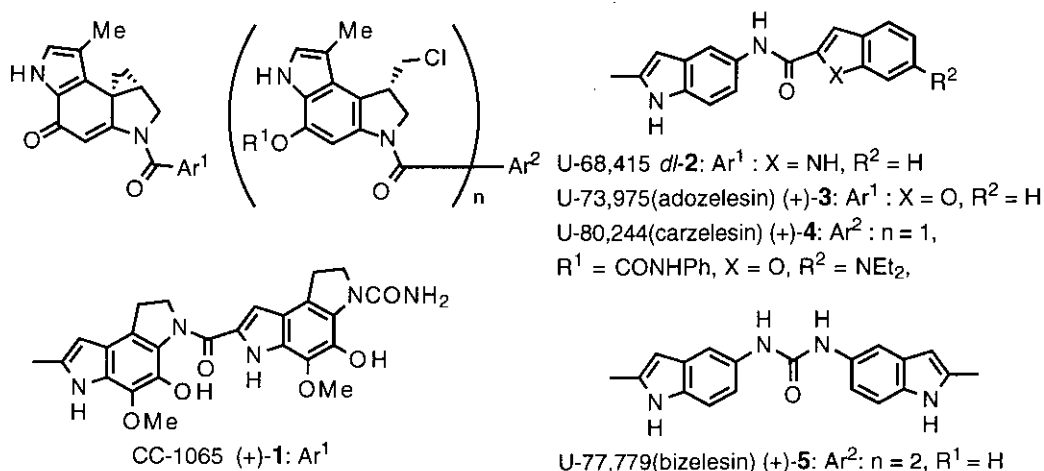
Yasumichi Fukuda,^{*a} Hirosuke Furuta,^a Futoshi Shiga,^a Yoshikazu Asahina,^{*a} and Shiro Terashima^{*b}

a. Central Research Laboratories, Kyorin Pharmaceutical Co. Ltd., Mitarai, Nogi, Tochigi 329-01, Japan b. Sagami Chemical Research Center, Nishi-Onnuma, Sagami-hara, Kanagawa 229, Japan

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.

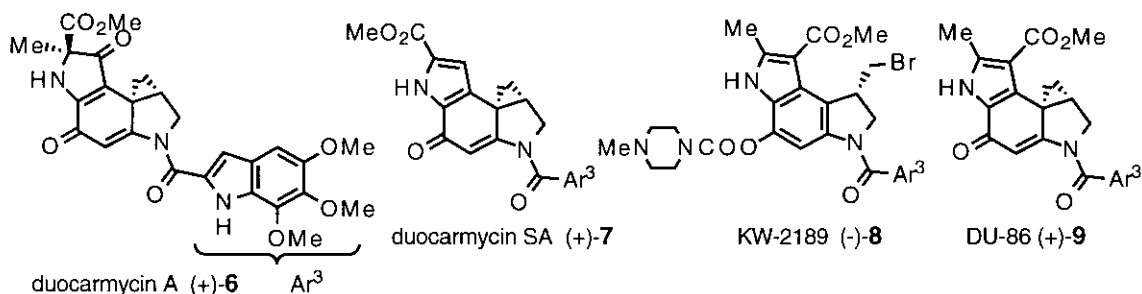
CC-1065 [(+)-**1**],² duocarmycin A [(+)-**6**],³ and duocarmycin SA [(+)-**7**]⁴ carrying a cyclopropapyrroloindole (CPI) moiety as the common pharmacophore are well known as potent antitumor antibiotics isolated from *Streptomyces* sp. The CPI system has been recognized to be responsible for their 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



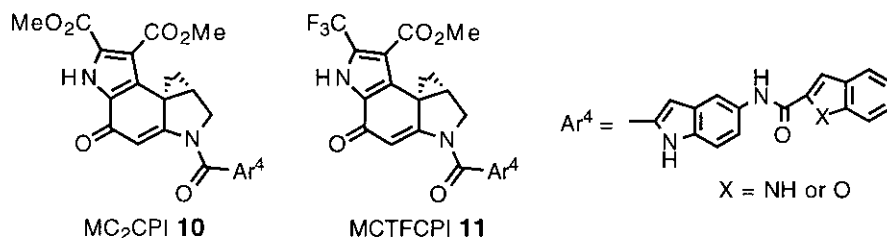
As for (+)-**6**, synthetic efforts have been devoted to the preparation of its congeners, culminating in the exploration of KW-2189 [(-)-**8**]¹⁰ and DU-86[(+)-**9**]¹⁰ as semi-synthetic antitumor agents (**Figure 2**). Some of these novel antitumor agents [(+)-**3**, (+)-**4**, and (-)-**8**] are presently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

Figure 2



Recently, we reported the synthesis and antitumor activity of novel CPI derivatives, bis(methoxycarbonyl)-cyclopropapyrroloindole (MC₂CPI)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.

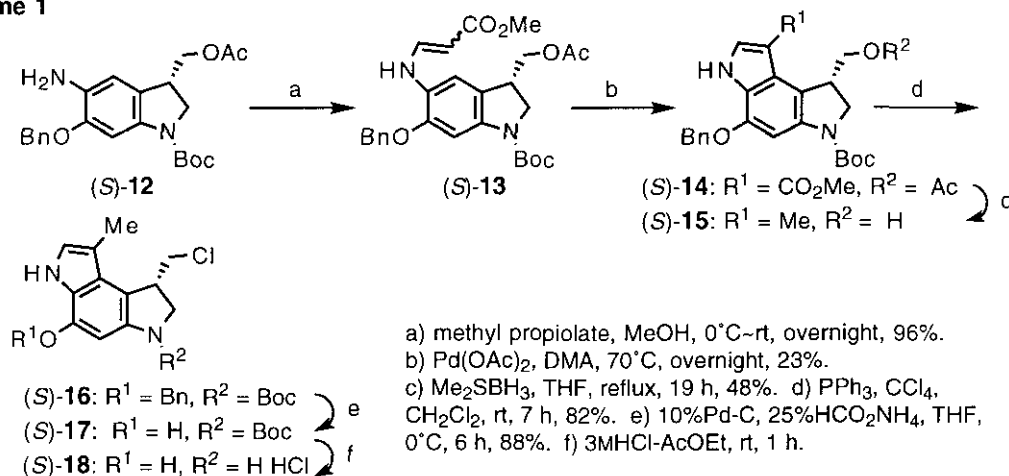
Synthesis of CC-1065 [(+)-**1**], U-73,975 (adozelesin) [(+)-**3**], U-80,244 (carzelesin) [(+)-**4**], and U-77,779 (bizelesin) [(+)-**5**]

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**.

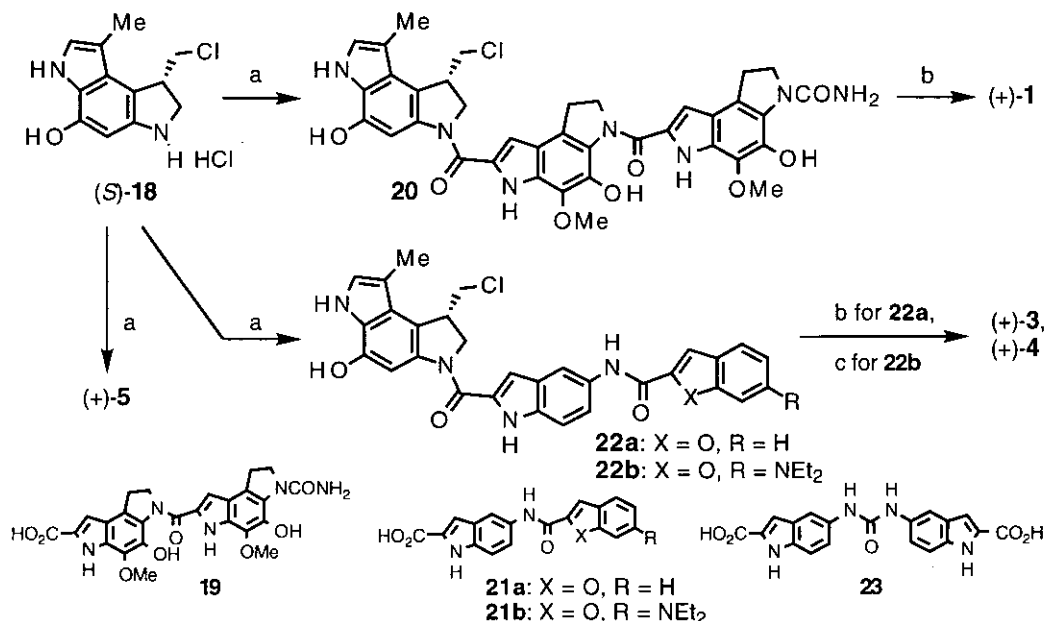
Thus, Michael addition of (*S*)-**12**, $[\alpha]_D^{25} = +28^\circ$ ($c = 0.29$, CH_2Cl_2), with methyl propiolate in methanol cleanly provided (*S*)-**13**.¹⁹ Oxidative cyclization of (*S*)-**13** was effected with $\text{Pd}(\text{OAc})_2$ in *N,N*-dimethylacetamide (DMA) to afford the 3-methoxycarbonylpyrroloindole [(*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 $3\text{MHCl}\cdot\text{AcOEt}$ 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**, $[\alpha]_D^{25} = +98^\circ$ ($c = 0.20$, DMF) {lit.,^{5b,15a}: $[\alpha]_D^{25} = +98^\circ$ ($c = 0.2$, DMF)}. In a similar manner, couplings of (*S*)-**18** with **21a,b**^{5c} and **23^{9a}** gave the seco-chlorides (**22a,b**) and (+)-**5**, $[\alpha]_D^{26} = +37^\circ$ ($c = 0.20$, DMF),²⁰ respectively. Treatment of **22a** with DBU underwent spiro-cyclization, yielding (+)-**3**, $[\alpha]_D^{31} = +141^\circ$ ($c = 0.20$, THF).²⁰ Introduction of a phenylcarbamoyl group into **22b** as the prodrug moiety provided (+)-**4**, $[\alpha]_D^{31} = +41^\circ$ ($c = 0.20$, THF).²⁰ With completion of the syntheses of (+)-**1** and (+)-**3**~(+)-**5**, we next attempted the preparation of (-)-**8** and (+)-**9**.

Scheme 2



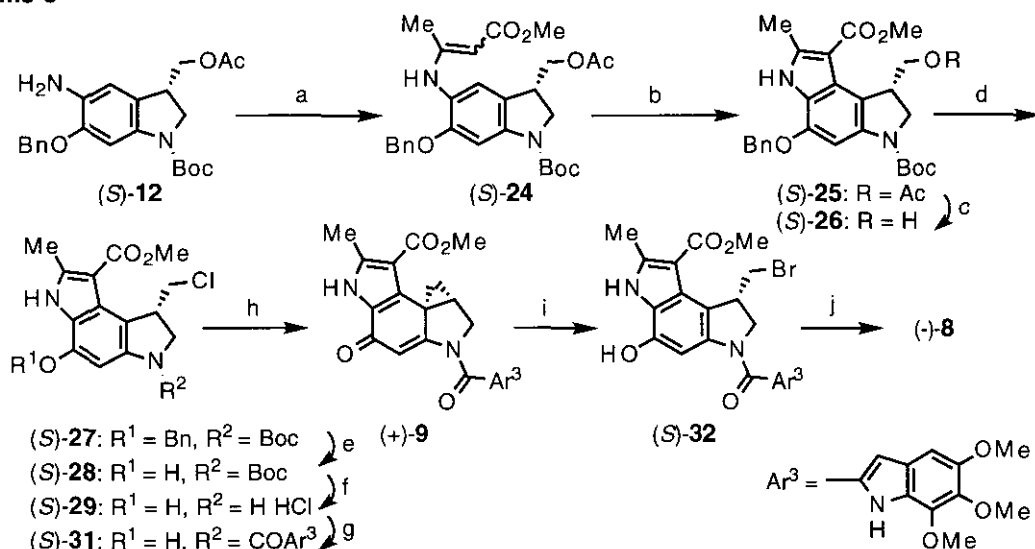
a) 19, 21a,b or 23, EDCI, DMF, rt, overnight, 20; 62% from (S)-16, 22a; 50% from (S)-17, 22b; 58% from (S)-17, (+)-5; 26% from (S)-17. b) DBU, MeCN, rt, 4 h, (+)-1; 45%, (+)-3; 49%. c) phenyl isocyanate, THF, Et₃N, rt, 18 h, 89%.

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, [α]_D²³ = +146° (c = 0.67, CHCl₃).²⁰ Reaction of (+)-9 with 1MHBBr gave the seco-bromide [(S)-32]. The phenolic hydroxyl group in (S)-31 was masked with a *N*-methylpiperazinylcarbamoyl group, furnishing (-)-8, [α]_D²⁴ = -8.8° (c = 1.2, CHCl₃)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) K₂CO₃, MeOH, rt, 5 h, 92%. d) PPh₃, CCl₄, CH₂Cl₂, rt, 19 h, 93%. e) 10%Pd-C,
 25% HCO₂NH₄, THF, 0°C, 20.5 h. f) 3MHCl-AcOEt. g) Ar³CO₂H (**30**), EDCI, DMF, rt, 85% from
27. h) DBU, MeCN, rt, 97%. i) 1M HBr in MeCN, rt, 1.5 h, 90%. j) i) ClCO₂PhNO₂, Et₃N, 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.

ACKNOWLEDGEMENTS

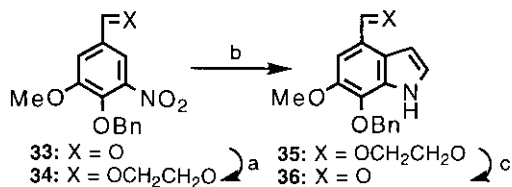
We are grateful to Dr. S. Suzue, Kyorin Pharmaceutical Co. Ltd., for many valuable suggestions and encouragement.

REFERENCES AND NOTES

Present address: Research Center, Kyorin Pharmaceutical Co. Ltd., Nogi, Tochigi 329-01, Japan.

1. This paper is submitted for publication by celebrating the 25th anniversary of Heterocycles.
2. D. G. Martin, C. G. Chidester, D. J. Duchamp, and S. A. Mizesak, *J. Antibiot.*, **1980**, *33*, 902.
3. a) M. Ichimura, K. Muroi, K. Asano, I. Kawamoto, F. Tomita, M. Morimoto, and H. Nakano, *J. Antibiot.*, **1988**, *41*, 1285. b) T. Yasuzawa, T. Iida, K. Muroi, M. Ichimura, K. Takahashi, and H. Sano, *Chem. Pharm. Bull.*, **1988**, *36*, 3728. c) I. Takahashi, K. Takahashi, M. Ichimura, M. Morimoto, K. Asano,

- I. Kawamoto, F. Tomita, and H. Nakano, *J. Antibiot.*, **1988**, *41*, 1915. d) T. Ogawa, M. Ichimura, S. Katsumata, M. Morimoto, and K. Takahashi, *ibid.*, **1989**, *42*, 1299.
4. a) M. Ichimura, T. Ogawa, K. Takahashi, E. Kobayashi, I. Kawamoto, T. Yasuzawa, I. Takahashi, and H. Nakano, *J. Antibiot.*, **1990**, *43*, 1037. b) T. Yasuzawa, Y. Saitoh, M. Ichimura, I. Takahashi, and H. Sano, *ibid.*, **1991**, *44*, 445.
5. a) D. L. Boger, R. S. Coleman, B. J. Invergo, S. M. Sakya, T. Ishizaki, S. A. Munk, H. Zarrinmayeh, P. A. Kitos, and S. C. Thompson, *J. Am. Chem. Soc.*, **1990**, *112*, 4623. b) L. H. Hurley, M. A. Warpehoski, C.-S. Lee, J. P. McGovren, T. A. Scahill, R. C. Kelly, M. A. Mitchell, N. A. Wicnienski, I. Gebhard, P. D. Johnson, and V. S. Bradford, *ibid.*, **1990**, *112*, 4633. c) M. A. Warpehoski, I. Gebhard, R. C. Kelly, W. C. Krueger, L. H. Li, J. P. McGovren, M. D. Prairie, N. Wicnienski, and W. Wierenga, *J. Med. Chem.*, **1988**, *31*, 590. d) H. L. Chin and J. P. Dinshaw, *J. Am. Chem. Soc.*, **1992**, *114*, 10658. e) D. L. Boger, T. Ishizaki, H. Zarrinmayeh, S. A. Munk, P. A. Kitos, and O. Suntornwat, *ibid.*, **1990**, *112*, 8961. f) D. L. Boger, *Chemtracts: Org. Chem.*, **1991**, *4*, 329. g) H. Sugiyama, M. Hosoda, I. Saito, A. Asai, and H. Saito, *Tetrahedron Lett.*, **1990**, *31*, 7197 and references therein.
6. J. P. McGovren, G. L. Clarke, E. A. Pratt, and T. F. DeKoning, *J. Antibiot.*, **1984**, *37*, 63.
7. B. K. Bhuyan, K. S. Smith, E. G. Adams, G. L. Petzold, and J. P. McGovren, *Cancer Res.*, **1992**, *52*, 5687 and references therein.
8. L. H. Li, T. F. DeKoning, R. C. Kelly, W. C. Krueger, J. P. McGovren, G. E. Padbury, G. L. Petzold, T. L. Wallace, R. J. Ouding, M. D. Prairie, and I. Gebhard, *Cancer Res.*, **1992**, *52*, 4904.
9. a) M. A. Mitchell, R. C. Kelly, N. A. Wicnienski, N. T. Hatzenbuehler, M. G. Williams, G. L. Petzold, J. L. Slightom, and D. R. Siemieniak, *J. Am. Chem. Soc.*, **1991**, *113*, 8994. b) S.-J. Lee, F. C. Seaman, D. Sun, H. Xiong, R. C. Kelly, and L. H. Hurley, *ibid.*, **1997**, *119*, 3434 and references therein.
10. a) A. Asai, S. Nagamura, and H. Saito, *J. Am. Chem. Soc.*, **1994**, *116*, 4171. b) S. Nagamura, A. Asai, Y. Kanda, E. Kobayashi, K. Gomi, and H. Saito, *Chem. Pharm. Bull.*, **1996**, *44*, 1723.
11. Y. Fukuda, Y. Oomori, and S. Terashima, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 749.
12. Y. Fukuda, H. Furuta, F. Shiga, Y. Oomori, Y. Kusama, and S. Terashima, *Bioorg. Med. Chem. Lett.*, **1997**, *13*, 1683.
13. a) Y. Fukuda, K. Nakatani, Y. Ito, and S. Terashima, *Tetrahedron Lett.*, **1990**, *31*, 6699. b) Y. Fukuda, K. Nakatani, and S. Terashima, *Bioorg. Med. Chem. Lett.*, **1992**, *2*, 755. c) D. L. Boger, W. Yun, S. Terashima, Y. Fukuda, K. Nakatani, P. A. Kitos, and Q. Jin, *ibid.*, **1992**, *2*, 759. d) Y. Fukuda, Y. Ito, K. Nakatani, and S. Terashima, *Tetrahedron*, **1994**, *50*, 2793. e) Y. Fukuda, K. Nakatani, and S. Terashima, *ibid.*, **1994**, *50*, 2809. f) K. Nakatani, Y. Fukuda, and S. Terashima, *Pure&Appl. Chem.*, **1994**, *66*, 2255.
14. Y. Fukuda and S. Terashima, *Tetrahedron Lett.*, in press.
15. a) R. C. Kelly, I. Gebhard, N. Wicnienski, P. A. Aristoff, P. D. Johnson, and D. G. Martin, *J. Am. Chem. Soc.*, **1987**, *109*, 6837. b) D. L. Boger and R. S. Coleman, *ibid.*, **1988**, *110*, 1321.
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%.

17. G. Bartoli, G. Palmieri, M. Bosco, and R. Dalpozzo, *Tetrahedron Lett.*, **1989**, *30*, 2129.
18. a) P. Martin, *Helv. Chim. Acta*, **1989**, *72*, 1554. b) D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.*, **1987**, *109*, 2717.
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.

Received, 11th July, 1997