Pergamon

Bioorganic & Medicinal Chemistry, Vol. 3, No. 1, pp. 67–77, 1995

0968-0896/95 $9.50 + .00

0968-0896(94)00147-2

Diastereoselective Dieckmann Condensation Suitable for Introduction of the Duocarmycin A C6 Center: Development of a Divergent Strategy for the Total Synthesis of Duocarmycins A and SA

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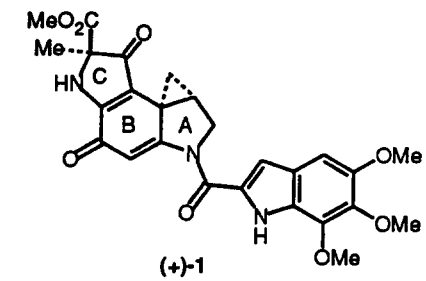
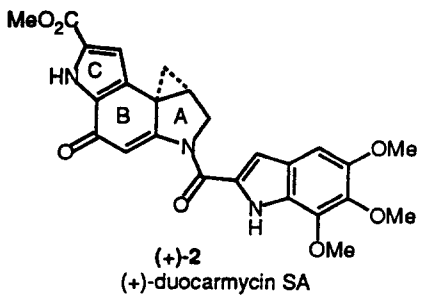
Abstract—The development of a divergent approach to the introduction of the C-ring of the duocarmycin A and SA alkylation subunits is detailed and includes the development of a diastereoselective Dieckmann condensation suitable for introduction of the duocarmycin A C6 center with control of its relative and natural *R* absolute configuration.

Two recent efforts have described the isolation and structure determination of the initial members of a new class of exceptionally potent antitumor anti-biotics including duocarmycin A (**1**),[1,2] duocarmycin SA (**2**),[3] B_1–B_2,[4] and C_1–C_2.[2,4,5] Since the disclosure of **1** and **2** in 1988 and 1990, respectively, a number of efforts have been conducted to define and exploit their properties.[6–8] In these studies, the agents have been shown to participate in a reversible, sequence selective adenine N3 alkylation of DNA,[9–14] and the use of synthetic analogs[15–20] bearing deep-seated changes in their structure and synthetic samples[21] of the scarce natural products have proven valuable in the definition and examination of such properties.



(+)-1
(+)-duocarmycin A

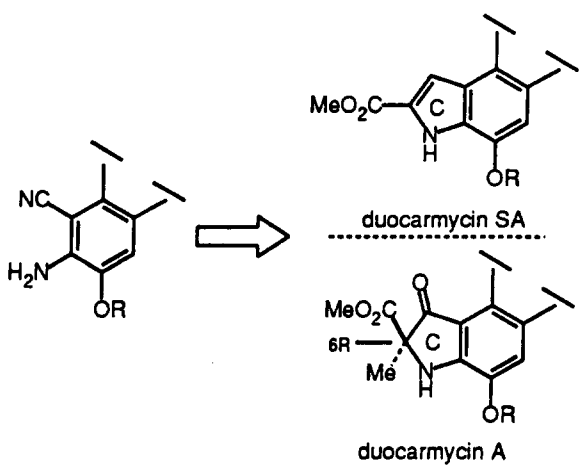


(+)-2
(+)-duocarmycin SA

To date, no synthetic approach to **1** and **2**[20–22] or related agents including CC-1065[23–25] and its analogs[26] has been successfully adopted to provide a useful asymmetric synthesis.[27] For duocarmycin A, this would not only require control of the cyclopropane stereochemistry but also the absolute stereochemistry at C6. Even the control of the relative cyclopropane/C6 stereochemistry is not easily addressed and the initial synthesis of **1** described by Terashima and coworkers[20] provided a 1:1 mixture of racemic **1** and its C6 epimer, 6-*epi*-duocarmycin A. Although these studies provided samples of both enantiomers of **1** and 6-*epi*-**1** upon diastereomeric derivatization and chromatographic resolution which were important in establishing the role of the relative and absolute stereochemistry on the agent properties,[12] studies to date have not yet successfully addressed the enantioselective or diastereoselective preparation of the natural product, the most potent of the four possible stereoisomers. Herein we detail studies on the development of a divergent approach to **1** and **2** including the development of a diastereoselective Dieckmann condensation for the introduction of the duocarmycin A C6 center suitable for control of its relative and natural *R* absolute configuration.

The asymmetric synthesis of quaternary carbons has been reviewed recently[28] and few of the existing technologies are generally applicable to introduction of the quaternary C6 center of duocarmycin A. Of the two most direct approaches requiring either the asymmetric acylation or alkylation of an immediate precursor to the duocarmycin A alkylation subunit, the asymmetric alkylation has been the most thoroughly investigated. Past efforts to address such an asymmetric alkylation include the alkylations of β-keto esters using optically active phase transfer catalysts (low *e.e.*),[29] the palladium-catalyzed allylations of β-keto esters in the

presence of optically active ligands (low *e.e.*, limited electrophile),[30] the alkylation of chiral enamines of β-keto esters,[31] and the alkylation of optically active β-keto ester enolates bearing chiral ester auxiliaries[32–35] or the acylation of optically active hydrazones.[36] Of these, the latter two approaches have proven most useful and were briefly explored in our studies along with the alternative and relatively unexplored intramolecular acylation reaction of optically active ester enolates bearing a chiral auxiliary: an asymmetric Dieckmann condensation.[35,37]



Scheme 1.

Duocarmycin SA C-ring introduction

In the continued development of our synthetic approach to the duocarmycins based on nucleophilic additions to a *p*-quinonediimide,[38] the most accessible potential precursor in our studies consisted of an *o*-amino-benzonitrile. Consequently, we elected to examine the divergent introduction of both the duocarmycin A and SA alkylation subunit C-ring with **3**. For duocarmycin SA, two complementary approaches to the conversion of **3–10** were explored (Scheme 2). Alkylation of the sodium salt of **4a**, derived from mono BOC protection of **3** (54%), with methyl bromoacetate proceeded cleanly to provide **5** in quantitative conversion and attempts to directly alkylate **3** (1.2 eq. $CsCO_3$, 1.2 eq. $BrCH_2CO_2CH_3$ DMF, 70 °C) provided predominantly the dialkylated material in low conversion.[39] Dieckmann condensation of **5** cleanly effected by treatment with LDA provided **6** (89%) which was found to exist exclusively as the indole tautomer ($CHCl_3$) and which proved surprisingly stable to hydrolysis. Although the attempted hydrolysis of **6** in pH 4–6 phosphate buffer provided only recovered starting material, treatment of **6** with Dowex 50 in aqueous methanol at 25 °C provided clean albeit slow conversion to **7** (80%, 3 d) without competitive *N*–BOC deprotection or ester hydrolysis. Shorter reaction times as well as efforts to accelerate this conversion by use of elevated reaction temperatures led to lower conversions.[40] In contrast to **6**, **7** was found to existexclusively in the keto tautomer form in $CHCl_3$. Without any effort to optimize the following sequence, reduction of **7** with $NaBH_4$ provided **8** as a single diastereomer [*cis*, $J(2,3)$ = 8.8 Hz] in near quantitative conversion. Subsequent elimination of water upon Mitsunobu activation of the alcohol cleanly provided **9** and acid-catalyzed deprotection of **9** provided **10** (100%).

Alternatively, reduction of **3** directly to aldehyde **11** (2.5 eq. Dibal-H, CH_2Cl_2, 0–25 °C, 4 h) followed by protection of the free amine as its formamide provided **12**. Without any attempt at optimization, alkylation of the sodium salt of **12** with methyl bromoacetate in the presence of excess NaH (3–5 eq., DMF, 25 °C) provided **10** (73%) directly without isolation or detection of intermediates **13–15**. Conducting this reaction under more controlled conditions (1.2 eq. NaH, 1.2 eq. $BrCH_2CO_2CH_3$, DMF, 0 °C, 4 h) did permit the intermediate isolation and characterization of **13**[41] (48%, without optimization) thus insuring a second straightforward approach to introduction of the C-ring of the duocarmycin SA alkylation subunit. Notably, although this latter approach proved more direct, the former approach employs intermediates including **7** that are also applicable to introduction of the duocarmycin A C-ring system.

Duocarmycin A: Dieckmann condensation

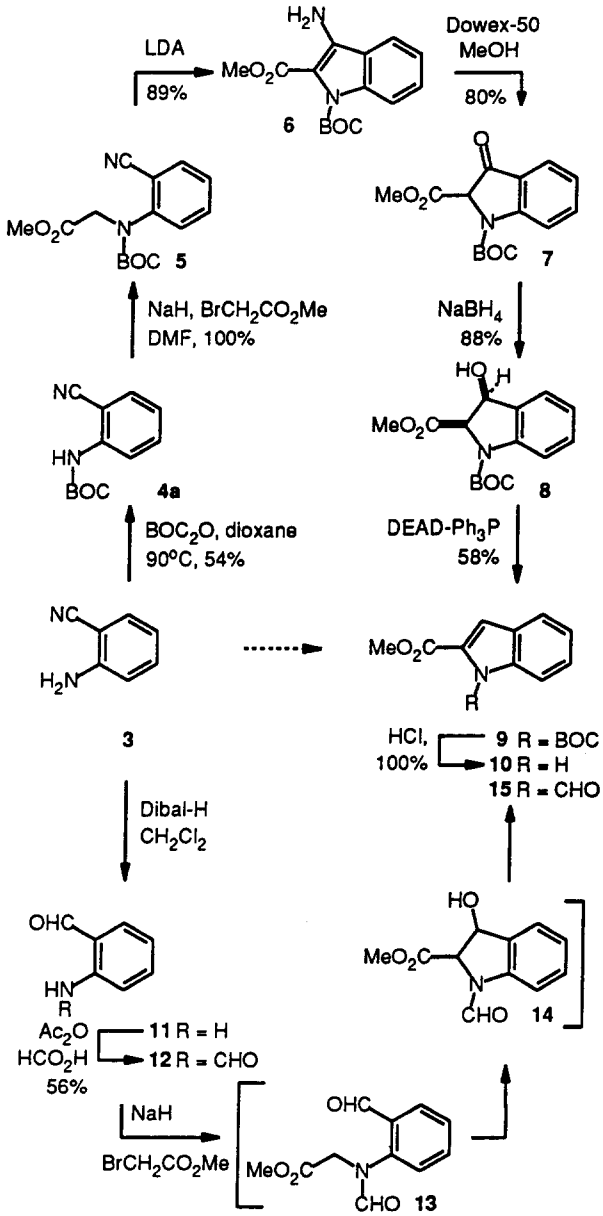
As a prelude to the study of the asymmetric introduction of the duocarmycin A C-ring, the achiral Dieckmann condensation was examined with **16** (Scheme 3). Alkylation of the sodium salt of **4a** with methyl 2–bromopropionate (3 eq. NaH, 1.2 eq. $BrCH(CH_3)CO_2CH_3$, DMF, 25 °C, 12 h, 76%) proceeded to provide **17a** directly without the viable isolation of **16a**. The subsequent Dieckmann condensation of **16a** was found to occur so readily that even attempts to convert **4a** to **16a** using 1.2 eq. NaH provided predominantly **17a**. Imine hydrolysis of **17a** effected by treatment with Dowex 50 (CH_3OH–H_2O, 25 °C, 3 h, 82%)[42] followed by deprotection of the amine **18a** (4 N HCl–EtOAc, 25 °C, 4 h, 91%) cleanly provided **19**.

In contrast, alkylation of the sodium salt of **4b** with methyl 2-bromopropionate (1.2 eq. NaH, 1.2 eq. $BrCH(CH_3)CO_2CH_3$, DMF, 25 °C, 16 h, 77%) permitted the intermediate isolation of the simple alkylation product **16b**.[43] The Dieckmann condensation of **16b** effected by treatment with LDA (1.2 eq., THF, –78 °C, 2 h, 94%) cleanly and effectively provided **17b**[43] which was isolated as the free imine. Subsequent imine hydrolysis (Dowex 50, CH_3OH–H_2O, 25 °C, 2 h, 84%) provided **18b**.[42,43]

Asymmetric synthesis of the duocarmycin A C-ring

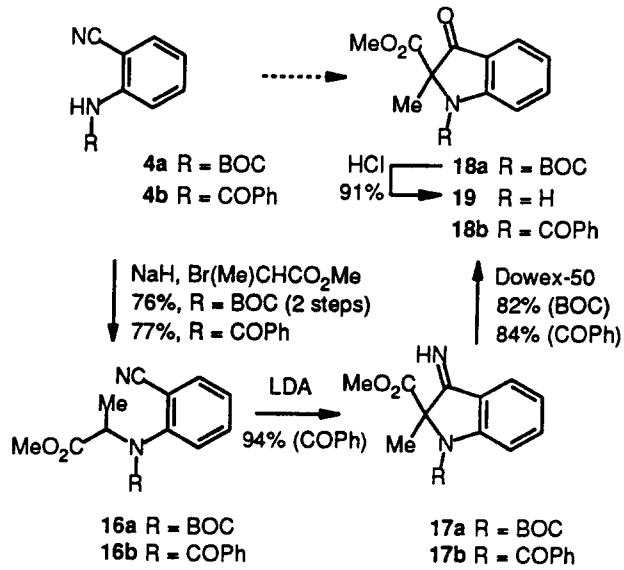
Initial attempts to use Koga's alkylation[31] of the L-valine imines of β-keto esters which generally proceed with dependably high *e.e.*'s were not productive with **20** since we were unable to prepare the requisite imines in

a satisfactory manner (equation 1). Although this was not investigated in detail, attempts to convert **7** to **20** under a variety of prescribed reaction conditions[44] failed to provide the imine or its enamine tautomer.

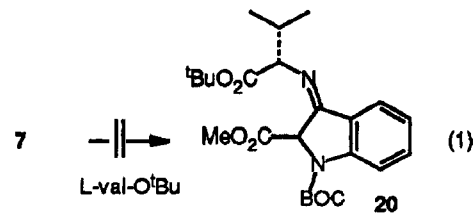


Scheme 2.

In conjunction with these studies, we examined the potential diastereoselective alkylations of **21–22** and the Dieckmann condensations of **23–27** employing a range of ester chiral auxiliaries.[32–35] We were predisposed to the latter even though there was little precedent[37] for their use since it would constitute the most convergent of the two approaches (Scheme 4). In the conduct of the studies, the *N*-BOC, *N*-benzoyl, and *N*-formyl derivatives were initially and briefly examined. Although this was not exhaustively examined, the *N*-BOC derivatives proved more stable to the conditions of alkylation or Dieckmann condensation than the *N*-formyl derivatives and more readily deprotected than the *N*-benzoyl series. Consequently, our detailed studies were conducted with the *N*-BOC series **21–27a.**



Scheme 3.



Of these two approaches, the diastereoselective Dieckmann condensation proved most successful. Representative results are summarized in Table 1. Moreover, only the Evans' optically active oxazolidinones[45] provided useful levels of diastereoselection among the series of chiral auxiliaries examined. In addition, they proved to be the only chiral auxiliaries in the series in which the major and minor diastereomers were chromatographically separable. Thus, the useful albeit not superb level of diastereoselection (7:1) coupled with chromatographic resolution of the major and minor diastereomers ultimately provided the desired product (2*R*)-**39** in high chemical yield (86%) and in pure enantiomeric form (> 99% *e.e.*).

These successful studies and the most pertinent related efforts are summarized in Scheme 5. Initial efforts to implement the asymmetric alkylation reaction with **21–22** proved problematic. Although the alkylation of **4a** with **28**[45] (69%) or **29**[45] (63%) proceeded satisfactorily to provide the required precursors (1.5 eq. NaH, DMF, 0–25 °C, 16 h) and Dieckmann condensations of **30**[46] and **33**[47] proceeded rather uneventfully to provide **31**[46] (65%) and **34**[47] (64%), respectively, their subsequent

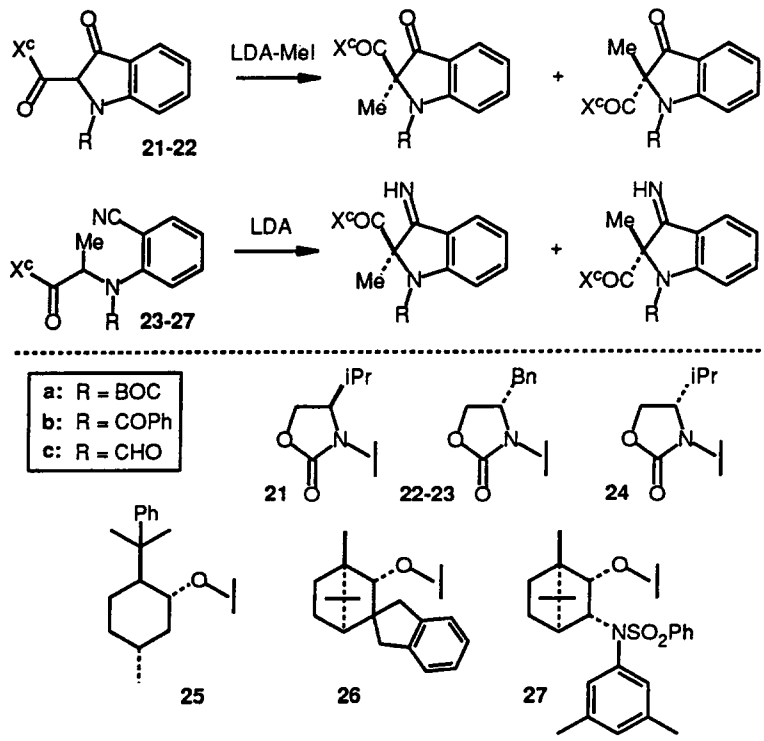
hydrolysis to provide **21a** and **22a** proved difficult. This may be attributed to the stability of **31** and **34** which preferentially exist in the indole tautomer. Mild hydrolysis conditions provided only recovered starting materials while more vigorous hydrolysis conditions[48] led to preferential *N*-BOC deprotection to provide **32** and **35** and, if forced, subsequent oxazolidinone hydrolysis. These observations on the problematic generations of **21a–22a** in conjunction with the more convergent nature of the preparation detailed below discouraged our further investigations of this approach.

Concurrent with these efforts, the direct Dieckmann condensations of **23** and **24** were examined.[49] Alkylation (1.2 eq. NaH, 1.5 eq. **36/37**, DMF, 0 °C, 3 h) of **4a** with **36**[50] or **37**[50] provided **24a** (88%) and **23a**[49] (75%), respectively. No evidence of a subsequent Dieckmann condensation product was detected in the reaction mixture. In addition, both diastereomers of **36** and **37** could be separated but were found to readily equilibrate to an approximately 2:1 mixture of the two diastereomers. Alkylation of **4a** with either diastereomer of **36** or **37** or with the 2:1 mixture of diastereomers provided a single diastereomer of **24a** and **23a**, respectively. Although the initial attempts at the Dieckmann condensation of **23-24a** were modest (Table 1), it was found that slow addition of the substrate **24a** to a solution of LDA (1.2 eq.) at –78 °C over a period of 30 min provided **39/40** in excellent yield (98%) with an acceptable level of diastereoselection (7:1). Moreover, the major and minor diastereomers proved to be easily separable by standard chromatography (α = 1.95, SiO_2, 50% EtOAc–hexane) and, consequently, the desired 2*R* diastereomer **39** was isolated in 86% yield. Thus, although the diastereoselection was modest, the high yields and acceptable selectivity coupled with the simple chromatographic resolution of the major diastereomers provided **39** in optically pure form (> 99.9% *e.e.*) in excellent yield (86%). If the substrate **24a** was added to the solution of LDA at –78 °C more

Table 1

Substrate	Conditions	Results % yield, 2*R*:2*S* ratio
23a	LDA, THF, –78 °C, 0.5 h	86%, 1.6:1
24a	LDA, THF, –78 °C, 1 h[a]	98%, 7:1
24a	LDA, THF–HMPA, –78 °C, 1 h	45%, 6:1
24a	LHMDS, THF, –78 °C , 4 h	21%, 2.8:1
25a	NaH, DMF, 0–25 °C[b]	53%,[c] 1.4:1
26a	NaH, DMF, 0–25 °C[b]	55%,[c] 1.3:1

[a]Slow addition of substrate over 30 min. [b]Cyclized upon alkylation of **4a** with Br(Me)CHCOX[c] (NaH, DMF, 25 °C). [c]Based on recovered starting material **4a** and the stereochemistry of products not determined.

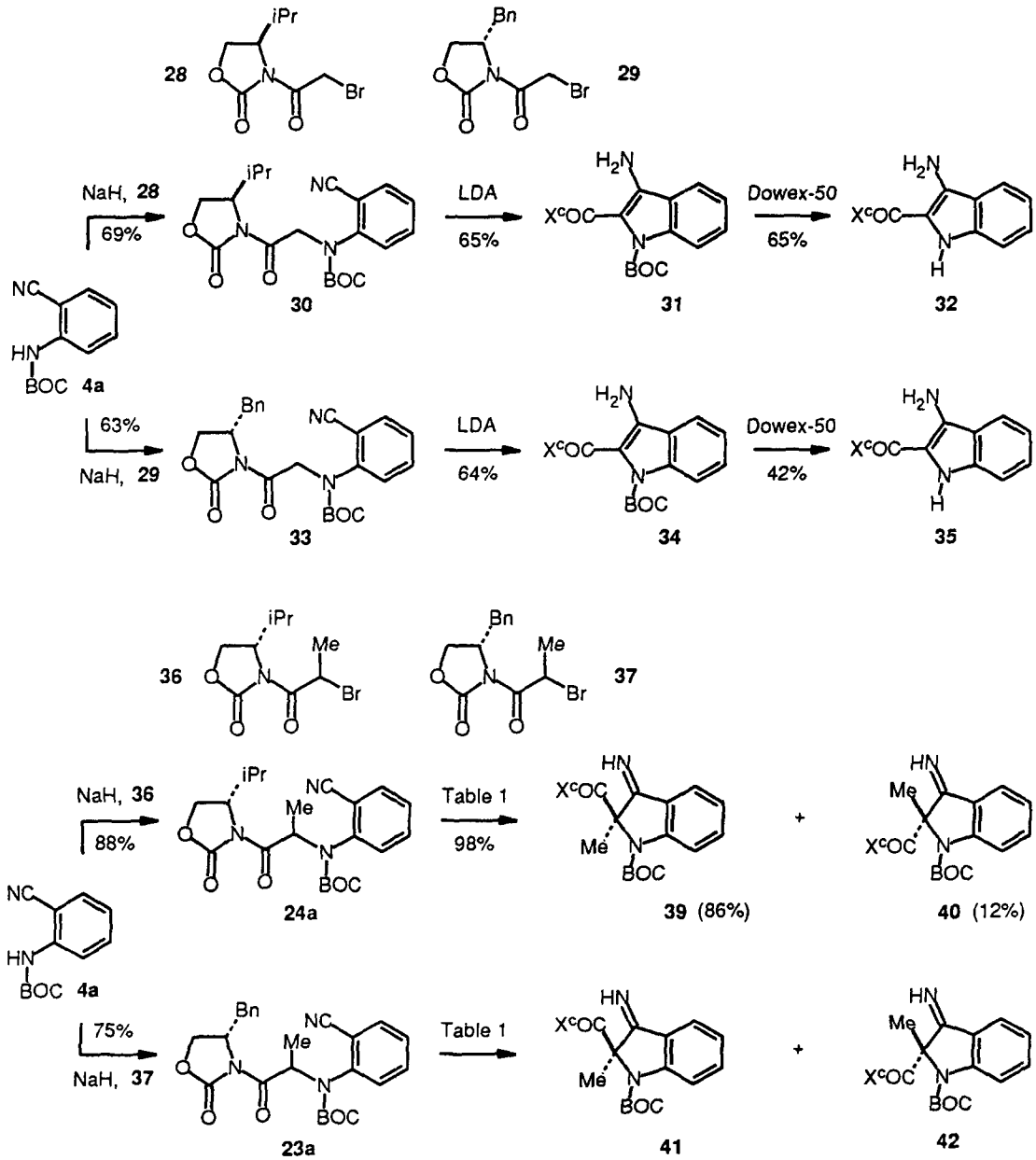


Scheme 4.

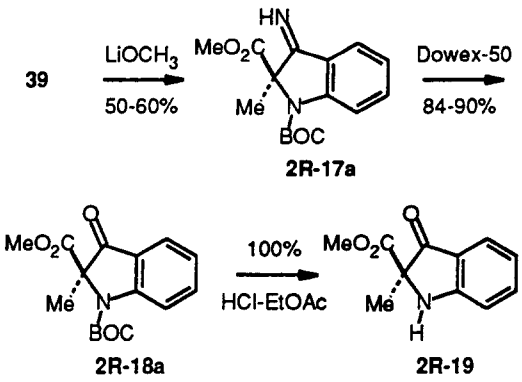
rapidly, the level of diastereoselection diminished (5 min, 99%, 4:1) or even reversed (< 10 s, 92%, 1:2) and the origin of these intriguing observations are under present investigation. A single-crystal X-ray structure determination[51] of the minor diastereomer **40** derived from the Dieckmann condensation of **24a** unambiguously established the relative configuration and, hence, the absolute stereochemistry of the newly introduced C2 center as 2*S* (Fig. 1). Consequently, the major diastereomer depicted in Scheme 5 was found to correspond to the natural 2*R* configuration.

Methanolysis of the major diastereomer **39** with lithium methoxide in THF served to remove the chiral auxiliary (50–60%), and treatment of the resulting methyl ester (2*R*)-**17a** with Dowex 50 (25 °C, CH_3OH–H_2O, 3 h, 84–90%) resulted in imine hydrolysis to provide (2*R*)-**18a** (Scheme 6). Alternative methods to remove the chiral auxiliary were less successful including LiOOH and $NaOCH_3/CH_3OH$ and efforts to first hydrolyze the imine prior to oxazolidinone removal (Dowex 50, CH_3OH–H_2O, 25 °C) were not as successful although these were not examined in detail.[52] Chiral phase HPLC analysis of (2*R*)-**18a** on an analytical Daicel Chiralcel OJ column where the two enantiomers of **18a** exhibit a remarkably large separation (α = 2.2, 10% *i*-PrOH–hexane, 1.0 mL min^{-1}, 0.46 × 25 cm OJ column) indicated an optical purity of > 99.9% (> 99.9% *e.e.*). Final acid-catalyzed *N*-BOC deprotection provided the desired (2*R*)-**19**.

The application of these and related efforts on the divergent, diastereoselective synthesis of duocarmycin A and SA are in progress and will be reported in due course.



Scheme 5.



Scheme 6.

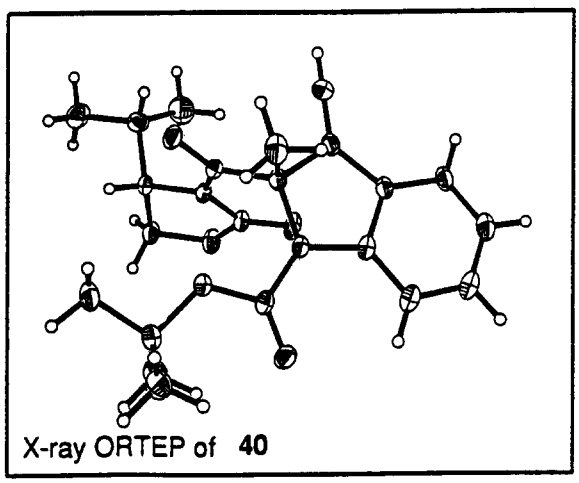


Figure 1.

Experimental

2-N-(tert-Butyloxycarbonyl)aminobenzonitrile (4a). A solution of 2-aminobenzonitrile (2.67 g, 22.6 mmol) in anhydrous dioxane (30 mL) was treated with di-*tert*-butyl dicarbonate (29.59 g, 140 mmol, 6 eq.), and the resulting reaction mixture was stirred at 90 °C for 48 h under N_2. Removal of the solvent *in vacuo* and flash chromatography (SiO_2, 5% EtOAc–hexane) provided **4a** (2.67 g, 4.93 g theoretical, 54%) as a white solid: mp 75–77 °C (hexane, white needles); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (*d*, 1H, *J* = 8.4 Hz), 7.49–7.58 (*m*, 2H), 7.08 (*dd*, 1H, *J* = 7.6 and 7.6 Hz), 7.03 (*br s*, 1H), 1.54 (*s*, 9H); IR (KBr) ν_{max} 3263, 2982, 2223, 1700, 1585, 1530, 1450, 1371, 1294, 1251, 1156, 1056 cm^{-1}; FABHRMS (NBA) m/z 219.1130 ($[M + H]^+$, $C_{12}H_{14}N_2O_2$ requires 219.1134).

N-(tert-Butyloxycarbonyl)-N-(2-cyanophenyl)glycine methyl ester (5). A suspension of NaH (66 mg, 60% in oil, 1.65 mmol, 1.2 eq.) in DMF (5 mL) at 0 °C under N_2 was treated with **4a** (300 mg, 1.37 mmol) and the mixture was stirred for 30 min. Methyl bromoacetate (0.16 mL, 1.69 mmol, 1.2 eq.) was added to the mixture at 0 °C and the reaction mixture was stirred for 4 h at 25 °C. The reaction mixture was poured into ice-cold 10% aqueous HCl (50 mL) and extracted with EtOAc (20 mL × 3). The organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 25% EtOAc–hexane) afforded **5** (399 mg, 399 mg theoretical, 100%) as a colorless oil: ^1H NMR (CD_3OD, 400 MHz) (major rotomer): δ 7.74 (*br d*, 1H, *J* = 7.7 Hz), 7.68 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 7.57 (*br d*, 1H, *J* = 7.7 Hz), 7.44 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 4.36 (*s*, 2H), 3.75 (*s*, 3H), 1.39 (*s*, 9H); IR (film) ν_{max} 2979, 2230, 1752, 1711, 1597, 1492, 1452, 1369, 1327, 1214, 1156 cm^{-1}; FABHRMS (NBA–NaI) m/z 291.1350 ($[M + H]^+$, $C_{15}H_{18}N_2O_4$ requires 291.1345).

Methyl 3-amino-1-tert-butyloxycarbonylindole-2-carboxylate (6). A stirred solution of freshly prepared LDA (1.2 eq.) in anhydrous THF (5 mL) at –78 °C under Ar was treated with a solution of **5** (397 mg, 1.37 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred for 2 h at –78 °C before the reaction was quenched with the addition of saturated aqueous NH_4Cl (20 mL). The resulting mixture was extracted with EtOAc (20 mL × 3). The combined organic extract was dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash chromatography (SiO_2, 20–30% EtOAc–hexane gradient elution) afforded **6** (354 mg, 397 mg theoretical, 89%) as a white solid: mp 142–144 °C (hexane, white needles); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (*d*, 1H, *J* = 8.4 Hz), 7.50 (*d*, 1H, *J* = 8.4 Hz), 7.47 (*dd*, 1H, *J* = 8.4 and 7.4 Hz), 7.24 (*dd*, 1H, *J* = 8.4 and 7.4 Hz), 5.15 (*s*, 2H), 3.89 (*s*, 3H), 1.59 (*s*, 9H); IR (KBr) ν_{max} 3478, 3449, 3350, 2981, 1740, 1680, 1629, 1455, 1328, 1281, 1227, 1161, 1111 cm^{-1}; FABHRMS (NBA–NaI) m/z 290.1270 ($[M^+]$, $C_{15}H_{18}N_2O_4$ requires 290.1267).

Methyl 1-tert-butyloxycarbonyl-2,3-dihydro-3-oxo-1H-indole-2-carboxylate (7). A solution of **6** (1.66 g, 5.72 mmol) in CH_3OH (20 mL) and H_2O (10 mL) at 25 °C was treated with Dowex 50X8-200 ion-exchange resin (3.32 g), and the reaction mixture was stirred for 3 d. The mixture was diluted with EtOAc (50 mL) and filtered to remove the resin. The filtrate was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 20–30% EtOAc–hexane gradient elution) provided **7** (1.33 g, 1.67 g theoretical, 80%) as a white solid: mp 138–140 °C (hexane–EtOAc, white needles); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.29 (*br d*, 1H, *J* = 7.6 Hz), 7.71 (*d*, 1H, *J* = 7.6 Hz), 7.67 (*dd*, 1H, *J* = 7.6 and 7.6 Hz), 7.15 (*dd*, 1H, *J* = 7.6 and 7.6 Hz), 4.90 (*s*, 1H), 3.84 (*s*, 3H), 1.52 (*s*, 9H); IR (KBr) ν_{max} 2947, 1757, 1711, 1604, 1468, 1372, 1313, 1274, 1257, 1158, 1065 cm^{-1}; FABHRMS (NBA–CsI) m/z 424.0146 ($[M^+ + Cs]^+$, $C_{15}H_{17}NO_5$ requires 424.0161).

Methyl (2R,3S*)-1-tert-butyloxycarbonyl-2,3-dihydro-3-hydroxy-1H-indole-2-carboxylate (8).* A solution of **7** (115 mg, 0.40 mmol) in EtOH (5 mL) was treated with $NaBH_4$ (30 mg, 0.79 mmol, 2 eq.) under N_2 at 0 °C and the mixture was stirred for 3 h at 0 °C. The solvent was removed *in vacuo*, and EtOAc (20 mL) was added to the residue. The mixture was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in*

vacuo. Flash chromatography (SiO_2, 20–30% EtOAc–hexane gradient elution) afforded **8** (102 mg, 116 mg theoretical, 88%) as a white solid: mp 113–115 °C (hexane, white needles); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (*m*, 1H), 7.38 (*d*, 1H, *J* = 7.7 Hz), 7.34 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 7.05 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 5.52 (*dd*, 1H, *J* = 8.8 and 8.8 Hz), 4.89 (*br d*, 1H, *J* = 8.8 Hz), 3.81 (*s*, 3H), 2.26 (*d*, 1H, *J* = 8.8 Hz), 1.51 (*s*, 9H); IR (KBr) ν_{max} 3432, 2979, 1761, 1701, 1607, 1484, 1383, 1208, 1158, 1308 cm^{-1}; FABHRMS (NBA–NaI) m/z 316.1167 ($[M^+ + Na]^+$, $C_{15}H_{19}NO_5$ requires 316.1161).

Methyl 1-tert-butyloxycarbonylindole-2-carboxylate (9). A solution of **8** (53 mg, 0.18 mmol) in anhydrous THF (2 mL) was treated with Ph_3P (70 mg, 0.27 mmol, 1.5 eq.) and diethyl azodicarboxylate (42 μL, 0.27 mmol, 1.5 eq.) under N_2, and the reaction mixture was stirred for 4 h at 25 °C. The solvent was removed *in vacuo*. Flash chromatography (SiO_2, 10–20% EtOAc–hexane gradient elution) provided **9** (29 mg, 50 mg theoretical, 58% unoptimized) as a white solid: mp 65–67°C (hexane–EtOAc, white needles); ^1H NMR ($CDCl_3$): δ 8.09 (*dd*, 1H, *J* = 8.1 and 0.9 Hz), 7.60 (*dd*, 1H, *J* = 7.8 and 0.9 Hz), 7.41 (*ddd*, 1H, *J* = 8.1, 7.8 and 0.9 Hz), 7.27 (*ddd*, 1H, *J* = 7.8, 7.8 and 0.9 Hz), 7.10 (*d*, 1H, *J* = 0.7 Hz), 3.92 (*s*, 3H), 1.58 (*s*, 9H); IR (KBr) ν_{max} 3447, 2981, 2946, 1739, 1713, 1551, 1440, 1374, 1322, 1240, 1204, 1158, 1071 cm^{-1}; FABHRMS (NBA–NaI) m/z 276.1227 ($[M^+ + H]^+$, $C_{15}H_{17}NO_4$ requires 276.1236).

Methyl indole-2-carboxylate (10). From **9**: A solution of **9** (9.6 mg, 0.04 mmol) in 4N HCl–EtOAc (1 mL) was stirred for 1 h at 25 °C under N_2. The reaction mixture was diluted with EtOAc (10 mL), and washed with saturated aqueous $NaHCO_3$. The organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 20% EtOAc–hexane) afforded **10** (6.1 mg, 6.1 mg theoretical, 100%) as white solid identical in all respects with authentic material: mp 149–151 °C (EtOAc–hexane, white needles), lit.[53] mp 151–152 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.89 (*br s*, 1H), 7.70 (*d*, 1H, *J* = 8.0 Hz), 7.43 (*d*, 1H, *J* = 8.0 Hz), 7.33 (*dd*, 1H, *J* = 8.0 and 8.0 Hz), 7.23 (*s*, 1H), 7.16 (*dd*, 1H, *J* = 8.0 and 8.0 Hz), 3.95 (*s*, 3H); IR (KBr) ν_{max} 3338, 2952, 1707, 1618, 1528, 1441, 1380, 1342, 1312, 1258, 1212, 1142 cm^{-1}; FABHRMS (NBA–NaI) m/z 175.0641 ($[M]^+$, $C_{10}H_9NO_2$ requires 175.0633).

From **12:** A suspension of NaH (16.7 mg, 60% in oil, 0.42 mmol, 3 eq.) in DMF (2 mL) at 0 °C under N_2 was treated with **12**[54] (20.7 mg, 0.14 mmol), and the mixture was stirred for 30 min. Methyl bromoacetate (0.017 mL, 0.18 mmol, 1.3 eq.) was added to the mixture at 0 °C and the reaction mixture was stirred for 5 d at 25 °C. The reaction mixture was poured into ice-cold 10% aqueous HCl (5 mL) and extracted with EtOAc (5 mL × 3). The organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 25% EtOAc–hexane) afforded **10** (17.8 mg, 24.3 mg theoretical, 73% without optimization) as a white solid identical in all respects to that detailed above.

Methyl 1-tert-butyloxycarbonyl-2,3-dihydro-3-imino-2-methyl-1H-indole-2-carboxylate (17a). A suspension of NaH (110 mg, 60% in oil, 3.75 mmol, 3 eq.) in DMF (2 mL) at 0 °C under N_2 was treated with **4a** (200 mg, 0.92 mmol), and the mixture was stirred for 30 min. Methyl 2-bromopropionate (0.123 mL, 1.10 mmol, 1.2 eq.) was added to the mixture at 0 °C and the reaction mixture was stirred for 12 h at 25 °C. The reaction mixture was poured into ice-cold 10% aqueous HCl (50 mL) and extracted with EtOAc (30 mL × 3). The organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 5–20% EtOAc–hexane gradient elution) afforded **17a** (212 mg, 279 mg theoretical, 76%) as a white amorphous solid: ^1H NMR ($CDCl_3$, 400 MHz): δ 9.42 (*br s*, 1H), 8.18 (*d*, 1H, *J* = 8.0 Hz), 7.68 (*m*, 1H), 7.53 (*dd*, 1H, *J* = 8.0 and 7.6 Hz), 7.14 (*dd*, 1H, *J* = 7.6 and 7.6 Hz), 3.72 (*s*, 3H), 1.82 (*s*, 3H), 1.52 (*s*, 9H); IR (film) ν_{max} 3258, 2978, 1751, 1718, 1653, 1605, 1468, 1378, 1364, 1248, 1161, 1139, 1068 cm^{-1}; FABHRMS (NBA–CsI) m/z 437.0481 ($[M + Cs]^+$, $C_{16}H_{20}N_2O_4$ requires 437.0477).

Methyl 1-tert-butyloxycarbonyl-2,3-dihydro-2-methyl-3-oxo-1H-indole-2-carboxylate (18a). A solution of **17a** (79 mg, 0.26 mmol) in CH_3OH (4 mL) and H_2O (2 mL) at 25 °C was treated with Dowex 50X8-200 ion-exchange resin (158 mg), and the reaction mixture was stirred for 3 h. The mixture was diluted with EtOAc (50 mL) and filtered to remove the resin. The filtrate was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 5–15% EtOAc–hexane gradient elution) afforded **18a** (65 mg, 79 mg theoretical, 82%): mp 132–134 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.32 (*br d*, 1H, *J* = 7.7 Hz), 7.74 (*d*, 1H, *J* = 7.7 Hz), 7.68 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 7.18 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 3.71 (*s*, 3H), 1.78 (*s*, 3H), 1.54 (*s*, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.1, 167.2, 153.4, 149.9, 137.7, 124.9, 123.5, 121.3, 116.8, 83.1, 72.4, 53.1, 28.1, 20.1; IR (KBr) ν_{max} 3414, 2983, 1766, 1736, 1601, 1589, 1463, 1378, 1159, 1138, 1071 cm^{-1}; FABHRMS (NBA–CsI) m/z 438.0326 ($[M + Cs]^+$, $C_{16}H_{19}NO_5$ requires 438.0318).

Methyl 2,3-dihydro-2-methyl-3-oxo-1H-indole-2-carboxylate (19). A solution of **18a** (50 mg, 0.16 mmol) in 4 N HCl–EtOAc (2 mL) was stirred for 4 h at 25 °C under N_2. The reaction mixture was diluted with EtOAc (20 mL), and washed with saturated aqueous $NaHCO_3$. The organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 20% EtOAc–hexane) afforded **19** (31 mg, 34 mg theoretical, 91%) as a pale yellow solid: mp 110–112 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (*dd*, 1H, *J* = 7.8 and 1.0 Hz), 7.50 (*ddd*, 1H, *J* = 7.8, 7.8 and 1.0 Hz), 6.96 (*dd*, 1H, *J* = 7.8 and 1.0 Hz), 6.90 (*ddd*, 1H, *J* = 7.8, 7.8 and 1.0 Hz), 5.18 (*s*, 1H), 3.77 (*s*, 3H), 1.66 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 169.8, 161.0, 137.6, 125.3, 120.3, 119.6,

113.4, 70.4, 53.5, 21.9; IR (KBr) ν_{max} 3396, 2951, 1729, 1672, 1620, 1582, 1495, 1467, 1326, 1294, 1261, 1119 cm^{-1}; FABHRMS (NBA) m/z 206.0827 ([M + H]$^+$, $C_{11}H_{11}NO_3$ requires 206.0817).

*3-[2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-cyanophenyl)]-amino]propionyl-(4*S*)-isopropyl-2- oxazolidinone (**24a**).* A suspension of NaH (110 mg, 60% in oil, 2.75 mmol, 1.2 eq.) in DMF (5 mL) at 0 °C under N_2 was treated with **4a** (500 mg, 2.29 mmol), and the mixture was stirred for 30 min. A solution of 3-[(2*R*,*S*)-bromopropionyl]-(4*S*)-isopropyl-2-oxazolidinone[50] (**36**, 908 mg, 3.44 mmol, 1.5 eq.) in DMF (5 mL) was added dropwise at 0 °C under N_2. The reaction mixture was stirred for 3 h at 0 °C. The mixture was diluted with EtOAc (50 mL), and the mixture was washed with ice-cold 10% aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 15–30% EtOAc–hexane gradient elution) afforded **24a** (810 mg, 920 mg theoretical, 88%) as a single diastereomer as a white solid: mp 154–155 °C (diisopropyl ether, white needles); $[\alpha]^{25}_D$ –12.9 (*c* 0.51, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (*br d*, 1H, *J* = 7.8 Hz), 7.67 (*br d*, 1H, *J* = 7.8 Hz), 7.62 (*dd*, 1H, *J* = 7.8 and 7.8 Hz), 7.41 (*dd*, 1H, *J* = 7.8 and 7.8 Hz), 6.01 (*q*, 1H, *J* = 7.2 Hz), 4.55 (*m*, 1H), 4.42 (*dd*, 1H, *J* = 8.9 and 8.9 Hz), 4.25 (*dd*, 1H, *J* = 8.9 and 2.5 Hz), 2.37 (*m*, 1H), 1.47 and 1.34 (two *s*, 9H), 1.18 (*d*, 3H, *J* = 7.2 Hz), 0.93 (*d*, 3H, *J* = 6.9 Hz), 0.88 (*d*, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0, 153.6, 153.3, 141.8, 133.0, 132.5, 131.1, 127.8, 116.7, 115.5, 81.6, 63.8, 58.3, 54.8, 28.4, 27.9, 17.8, 15.5, 14.7; IR (KBr) ν_{max} 3400, 2982, 2227, 1772, 1705, 1597, 1491, 1455, 1405, 1312, 1255, 1211, 1166, 1120, 1057, 1021 cm^{-1}; FABHRMS (NBA) m/z 402.2020 ([M$^+$ + H]$^+$, $C_{21}H_{27}N_3O_5$ requires 402.2029). Anal. calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.63; H, 6.92; N, 10.39.

*(2*R*)-1-*tert*-Butyloxycarbonyl-2,3-dihydro-3-imino-2-[(4*S*)-isopropyl-2-oxo-3-oxazolidinyl]carbonyl-2-methyl-1*H*-indole (2*R*-39) and (2*S*)-1-*tert*-butyloxycarbonyl-2,3-dihydro-3-imino-2-[(4*S*)-isopropyl-2-oxo-3-oxazolidin-yl]-carbonyl-2-methyl-1*H*-indole (2*S*-40).* A solution of **24a** (300 mg, 0.75 mmol) in anhydrous THF (6 mL) was added dropwise over a period of 30 min to a stirred solution of freshly prepared LDA (1.2 eq.) in anhydrous THF (3 mL) at –78 °C under Ar. The reaction mixture was stirred for 1 h at –78 °C, and quenched with the addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with EtOAc (10 mL x 3), and the combined organic extract was dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 20–50% EtOAc–hexane gradient elution) provided the minor (2*S*)–isomer **40** (38 mg, 300 mg theoretical, 13%) as a white solid and the major (2*R*)–isomer **39** (257 mg, 300 mg theoretical, 86%) as a white solid, respectively. For the minor (2*S*)–isomer **40**: mp 160–162 °C (diisopropyl ether, white plates); $[\alpha]^{25}_D$ +8.7 (*c* 0.15, CH_3OH); TLC R_f 0.78 (50% EtOAc–hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.32 (*br s*, 1H), 8.12 (*br d*, 1H, *J* = 7.4 Hz), 7.3–7.7 (m, 2H), 7.14 (*dd*, 1H, *J* = 7.4 and 7.4 Hz), 4.37 (*m*, 1H), 4.1–4.3 (*m*, 2H), 2.61 (*m*, 1H), 1.79 (*s*, 3H), 1.52 and 1.60 (two *s*, 9H), 0.95 (*d*, 3H, *J* = 7.0 Hz), 0.87 (*d*, 3H, *J* = 7.0 Hz); IR (KBr) ν_{max} 3428, 3264, 2982, 1784, 1724, 1691, 1656, 1606, 1470, 1375, 1322, 1239, 1138, 1053 cm^{-1}; FABHRMS (NBA) m/z 402.2012 ([M + H]$^+$, $C_{21}H_{27}N_3O_5$ requires 402.2029). Anal. calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.60; H, 6.54; N, 10.27. A single-crystal X-ray structure determination of (2*S*)-**40** conducted on white plates grown from diisopropyl ether unambiguously established the relative and absolute stereochemistry of this product. (Fig. 1).[51] For the major (2*R*)–isomer **39**: mp 126–128 °C (diisopropyl ether, white plates); $[\alpha]_D^{25}$ +94 (*c* 0.3, CH_3OH); TLC R_f = 0.40 (50% EtOAc–hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.18 (*br s*, 1H), 7.68 (*br d*, 1H, *J* = 7.5 Hz), 7.4–7.6 (m, 2H), 7.12 (*dd*, 1H, *J* = 7.5 and 7.5 Hz), 4.63 (*m*, 1H), 4.1–4.3 (*m*, 2H), 2.47 (*m*, 1H), 1.81 (*s*, 3H), 1.60 (*s*, 9H), 0.92 (*d*, 3H, *J* = 8.0 Hz), 0.90 (*d*, 3H, *J* = 8.0 Hz); IR (KBr) ν_{max} 3448, 3261, 3206, 2962, 1795, 1718, 1682, 1654, 1606, 1472, 1363, 1330, 1245, 1143, 1062 cm^{-1}; FABHRMS (NBA–NaI) m/z 402.2020 ([M + H]$^+$, $C_{21}H_{27}N_3O_5$ requires 402.2029). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.48; H, 6.54; N, 10.32.

*Methyl (2*R*) - 1 -* tert *- butyloxycarbonyl - 2 , 3 -dihydro-3-imino-2-methyl-1*H*-indole-2-carboxylate (2*R*-**17a**).* A sample of 2*R*-**39** (58.3 mg, 0.15 mmol) was added to a stirred solution of CH_3OLi prepared from lithium (20.2 mg, 2.91 mmol, 20 eq.) and CH_3OH (0.12 mL, 2.96 mmol, 20 eq.) in anhydrous THF (2 mL) at 0 °C. The reaction mixture was stirred for 24 h at 25 °C under N_2. The mixture was quenched with the addition of saturated aqueous NaCl (10 mL) and extracted with EtOAc (15 mL x 3). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2, 10–20% EtOAc–hexane gradient elution) afforded 2*R*-**17a** (22.2 mg, 44.2 mg theoretical, 50%, typically 50–60%) as a white amorphous solid: $[\alpha]^{25}_D$ +43 (*c* 0.14, CH_3OH); identical in all other respects with racemic **17a**.

*Methyl (2*R*)-1-*tert*-butyloxycarbonyl-2,3-dihydro-2-methyl-3-oxo-1*H*-indole-2-carboxylate (2*R*-**18a**).* A solution of (2*R*)-**17a** (19.6 mg, 0.06 mmol) in CH_3OH (1 mL) and H_2O (0.5 mL) at 25 °C was treated with Dowex 50X8-200 ion-exhange resin (39.2 mg), and the reaction mixture was stirred for 3 h under N_2. The mixture was diluted with EtOAc (15 mL) and filtered to remove the resin. The filtrate was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 5–15% EtOAc–hexane gradient elution) afforded (2*R*)–**18a** (16.6 mg, 19.7 mg theoretical, 84%, typically 84–90%) as a white solid: mp 133–135 °C (hexane, white needles); $[\alpha]^{25}_D$ +167 (*c* 0.1, CH_3OH); identical in all other respects with racemic material. Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 3.30; N, 4.59. Found: C, 62.57; H, 3.03; N, 4.41. The enantiomeric purity of (2*R*)-**18a** was established to be > 99.9% *e.e.* by HPLC analysis (Daicel ChiralCel OJ 4.6 × 250 mm analytical column, 10% *i*-PrOH–hexane, 1.0

mL min^{-1} flow rate). The enantiomeric esters (2*S*)-**18a** and (2*R*)-**18a** eluted with retention times of 6.8 and 15.2 min, respectively (α = 2.2).

Methyl (2R)-2,3-dihydro-2-methyl-3-oxo-1H-indole-2-carboxylate (2R-19). A solution of (2*R*)-**18a** (14.5 mg, 0.048 mmol) in 4 N HCl–EtOAc (1 mL) was stirred for 4 h at 25 °C under N_2. The reaction mixture was diluted with EtOAc (10 mL), and washed with saturated aqueous $NaHCO_3$. The organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 20% EtOAc–hexane) afforded (2*R*)-**19** (9.7 mg, 9.7 mg theoretical, 100%) as a yellow solid: mp 112–114 °C (hexane, yellow needles); $[\alpha]^{25}_D$ +36 (*c* 0.1, CH_3OH); identical in all other respects with racemic material.

Acknowledgments

We gratefully acknowledge the financial support of the National Institutes of Health (CA 55276) and Sankyo Company, Ltd for Dr. T. Nishi's sabbatical (1992–1994).

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39. For 2-*N*,*N*-bis(methoxycarbonylmethyl)aminobenzonitrile: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.03 (*d*, 1H, *J* = 8.3 Hz), 7.4–7.5 (*m*, 2H), 7.21 (*dd*, 1H, *J* = 8.3 and 8.3 Hz), 5.24 (*s*, 2H), 4.82 (*s*, 2H), 3.83 (*s*, 3H), 3.74 (*s*, 3H).

40. The similar sequence with **4b** provided the corresponding benzoyl derivatives. For **4b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (*br d*, 1H, *J* = 8.6 Hz), 8.41 (*br s*, 1H), 7.9–8.0 (*m*, 2H), 7.5–7.7 (*m*, 5H), 7.23 (*ddd*, 1H, *J* = 7.7, 7.7 and 0.9 Hz). For **5b** (93%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (*d*, 1H, *J* = 7.4 Hz), 7.1–7.5 (*m*, 8H), 5.08 (*br d*, 1H, *J* = 20.8 Hz), 4.28 (*br d*, 1H, *J* = 20.8 Hz), 3.78 (*s*, 3H). For **6b** (53%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (*d*, 1H, *J* = 8.4 Hz), 7.70–7.72 (*m*, 2H), 7.59 (*br d*, 1H, *J* = 7.9 Hz), 7.42–7.54 (*m*, 4H), 7.30 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 5.30 (*br s*, 2H), 3.33 (*s*, 3H). For **7b** (91%), ^{1}H NMR ($CDCl_3$ 400 MHz): δ 8.11 (*br d*, 1H, *J* = 7.4 Hz), 7.76 (*br d*, 1H, *J* = 7.4 Hz), 7.4–7.6 (*m*, 6H), 7.21 (*dd*, 1H, *J* = 7.4 and 7.4 Hz), 5.20 (*s*, 1H), 3.68 (*s*, 3H).

41. For **13**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.16 (*s*, 1H), 8.23 (*s*, 1H), 7.91 (*dd*, 1H, *J* = 7.7 and 1.5 Hz), 7.63 (*ddd*, 1H, *J* = 7.7, 7.7 and 1.5 Hz), 7.50 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 7.41 (*dd*, 1H, *J* = 7.7 and 0.8 Hz), 4.47 (*s*, 2H), 3.67 (*s*, 3H).

42. Although this was not investigated in detail, treatment of **18a** with pH 4 phosphate buffer (50 °C, 3 d) provided only recovered **18a** and limited efforts to deprotect **18b** (conc. aqueous HCl:CH_3OH 1:4, reflux, 48 h; $PrNH_2$, CH_2Cl_2, 25–50 °C, 24–48 h; $(Me_2N)_2C$=NH, CH_3OH, 25 °C, 12 h) were not successful.

43. For **16b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.1–7.8 (*m*, 9H), 5.39 and 4.36 (two *br q*, 1H, *J* = 7.3 Hz), 3.84 and 3.81 (two *s*, 3H), 1.91 and 1.35 (two *d*, 3H, *J* = 7.3 Hz); FABHRMS (NBA) m/z 309.1234 ([M + H]$^+$, $C_{18}H_{16}N_2O_3$ requires 309.1239). For **17b**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 9.50 (*br s*, 1H), 7.0–8.0 (*m*, 8H), 6.13 (*br d*, 1H, *J* = 6.3 Hz), 3.77 (*s*, 3H), 1.98 (*s*, 3H). For **18b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (*d*, 1H, *J* = 7.7 Hz), 7.48–7.63 (*m*, 5H), 7.33 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 7.31 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 6.33 (*br d*, 1H, *J* = 8.4 Hz), 3.77 (*s*, 3H), 1.93 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 167.7, 166.6, 152.2, 136.7, 135.3, 131.6, 129.0, 127.4, 125.3, 124.0, 122.6, 116.1, 73.4, 53.2, 19.2; IR (KBr) ν_{max} 1764, 1717, 1667, 1602, 1466, 1341, 1267, 1178, 1127 cm^{-1}; FABHRMS (NBA) m/z 310.1072 ([M + H]$^+$, $C_{18}H_{15}NO_4$ requires 310.1079).

44. These include C_6H_6 (80 °C) and toluene (110 °C), Dean–Stark trap –H_2O, 12–72 h, no reaction; C_6H_6, cat. BF_3–OEt_2, 16 h (starting material and *N*-BOC deprotection).

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46. For **30**: white amorphous solid; $[\alpha]^{25}_D$ –73 (*c* 0.1, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz) (major rotomer): δ 7.67 (*d*, 1H, *J* = 7.8 Hz), 7.57 (*dd*, 1H, *J* = 7.8 and 7.8 Hz), 7.48 (*d*, 1H, *J* = 7.8 Hz), 7.34 (*ddd*, 1H, *J* = 7.8, 7.8 and 1.4 Hz), 5.04 (*d*, 1H, *J* = 18.0 Hz), 4.85 (*d*, 1H, *J* = 18.0 Hz), 4.47 (*m*, 1H), 4.34 (*dd*, 1H, *J* = 8.7 and 8.7 Hz), 4.26 (*m*, 1H), 2.42 (*m*, 1H), 1.59 and 1.50 (two *s*, 9H), 0.92 (*d*, 3H, *J* = 7.0 Hz), 0.89 (*d*, 3H, *J* = 7.0 Hz); IR (KBr) ν_{max} 2972, 2231, 1784, 1718, 1598, 1491, 1453, 1370, 1261, 1209, 1157, 1105, 1056, 1018 cm^{-1}; FABHRMS (NBA–NaI) m/z 410.1711 ([M + Na]$^+$, $C_{20}H_{25}N_3O_5$ requires 410.1692). For **31**: white amorphous solid; $[\alpha]^{25}_D$ –12 (*c* 0.05, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.55 (*br s*, 2H), 8.16 (*br d*, 1H, *J* = 7.8 Hz), 7.86 (*d*, 1H, *J* = 7.8 Hz), 7.58 (*dd*, 1H, *J* = 7.8 and 7.8 Hz), 7.37 (*dd*, 1H, *J* = 7.8 and 7.8 Hz), 4.90 (*m*, 1H), 4.30 (*br dd*, 1H, *J* = 11.9 and 6.8 Hz), 3.99 (*br d*, 1H, *J* = 11.9 Hz), 2.80 (*m*, 1H), 1.65 (*s*, 9H), 1.18 (*d*, 3H, *J* = 6.7 Hz), 0.88 (*d*, 3H, *J* = 6.7 Hz); IR (film) ν_{max} 2964, 1774, 1714, 1653, 1457, 1367, 1316, 1280, 1244, 1149 cm^{-1}; FABHRMS (NBA–NaI) m/z 410.1705 ([M + Na]$^+$, $C_{20}H_{25}N_3O_5$ requires 410.1692).

47. For **33**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (*br d*, 1H, *J* = 7.6 Hz), 7.60 (*br dd*, 1H, *J* = 7.6 and 7.6 Hz), 7.52 (*br d*, 1H, *J* = 8.3 Hz), 7.27–7.40 (*m*, 4H), 7.18–7.23 (*m*, 2H), 5.04 (*br d*, 1H, *J* = 17.5 Hz), 4.85 (*br d*, 1H, *J* = 17.5 Hz), 4.73 (*m*, 1H),

4.28 (*dd*, 1H, *J* = 9.1 and 9.1 Hz), 4.22 (*br d*, 1H, *J* = 9.1 Hz), 3.34 (*br d*, 1H, *J* = 13.2 Hz), 2.83 (*br dd*, 1H, *J* = 13.2 and 9.7 Hz), 1.53 and 1.44 (two *s*, 9H); FABHRMS (NBA–CsI) m/z 568.0844 ([M + Cs]$^+$, $C_{24}H_{25}N_3O_5$ requires 568.0849). For **34**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.14 (*br d*, 1H, *J* = 7.8 Hz), 7.85 (*br d*, 1H, *J* = 7.8 Hz), 7.56 (**dd**, 1H, *J* = 7.8 and 7.8 Hz), 7.36 (*dd*, 1H, *J* = 7.8 and 7.8 Hz), 7.20 (*br m*, 5H), 5.52 (*m*, 1H), 4.30 (*m*, 1H), 3.9–4.1 (*m*, 2H), 3.35 (*m*, 1H), 1.66 (*s*, 9H); FABHRMS (NBA–CsI) m/z 568.0849 ([M + Cs]$^+$, $C_{24}H_{25}N_3O_5$ requires 568.0849).

48. Treatment of **31** and **34** with Dowex 50 (CH_3OH–H_2O, 25 °C, 7 d) led only to *N*-BOC deprotection to provide **32** and **35**.

49. For **23a:** $[\alpha]^{25}_D$ +40 (*c* 0.1, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5–8.1 (*m*, 2H), 7.0–7.4 (*m*, 7H), 5.94 (*m*, 1H), 4.6–4.9 (*m*, 1H), 4.2–4.4 (*m*, 2H), 3.25 (*br d*, 1H, *J* = 13.3 Hz), 2.84 (*br dd*, 1H, *J* = 13.3 and 9.2 Hz), 1.47 and 1.35 (two *s*, 9H), 1.18 and 1.13 (two *d*, 3H, *J* = 6.8 Hz); IR (KBr) ν_{max} 2981, 2231, 1781, 1701, 1491, 1457, 1395, 1254, 1215, 1169, 1129, 1051, 1020 cm^{-1}; FABHRMS (NBA) m/z 450.2040 ([M + H]$^+$, $C_{25}H_{27}N_3O_5$ requires 450.2029). For **41**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.1–7.7 (*m*, 10H), 4.83 (*m*, 1H), 4.13 (*dd*, 1H, *J* = 8.7 and 8.7 Hz), 4.06 (*dd*, 1H, *J* = 8.7 and 4.0 Hz), 3.64 (*br d*, 1H, *J* = 13.1 Hz), 2.51 (*dd*, 1H, *J* = 13.1 and 13.1 Hz), 1.87 (*s*, 3H), 1.63 (*s*, 9H); FABHRMS (NBA) m/z 450.2020 ([M + H]$^+$, $C_{25}H_{27}N_3O_5$ requires 450.2029). **42:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.0–8.2 (*m*, 10H), 4.60 (*m*, 1H), 4.0–4.2 (*m*, 2H), 3.43 (*m*, 1H), 2.79 (*m*, 1H), 1.85 (*s*, 3H), 1.58 and 1.56 (two *s*, 9H); FABHRMS (NBA) m/z 450.2034 ([M + H]$^+$, $C_{25}H_{27}N_3O_5$ requires 450.2029). For the Dieckmann product derived from **25a** (1.4:1): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.4–8.3 (*m*, 2H), 6.9–7.3 (*m*, 6H), 6.50 (*m*, 2H), 4.79 (*m*, 1H), 2.11 (*s*, 3H), 1.85 (*s*, 3H), 1.57 (*s*, 9H), 1.26 (*s*, 3H), 0.8–1.9 (*m*, 8H), 0.80 (*d*, 3H, *J* = 5.5 Hz); FABHRMS (NBA–NaI) m/z 505.3075 ([M + H]$^+$, $C_{31}H_{40}N_2O_4$ requires 505.3066). For the Dieckmann product derived from **26a** (1.3:1): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (*br s*, 1H), 7.65 and 7.78 (*m*, 2H), 6.8–7.2 (*m*, 5H), 4.59 and 4.50 (two *s*, 1H), 2.9–3.3 (*m*, 3H), 2.6–2.8 (*m*, 1H), 1.81 and 1.69 (two *s*, 3H), 1.60 and 1.57 (two *s*, 9H), 1.2–1.5 (*m*, 5H), 0.82 and 0.77 (two *s*, 3H), 0.72 and 0.70 (two *s*, 3H), FABHRMS (NBA) m/z 505.3075 ([M + H]$^+$, $C_{31}H_{40}N_2O_4$ requires 505.3066).

(*Received in U.S.A.* 6 Octo*b*er 1994)

50. The oxazolidinone **36** was prepared by treatment of the cyclic carbamate of *S*-valinol with *n*-BuLi (1.2 eq., THF, –78 °C, 30 min) followed by 2–bromopropionyl bromide (1.2 eq., THF, –78 °C, 1 h, 96%). The resulting two diastereomers could be separated by chromatography but were found to equilibrate to an approximately 2:1 mixture at 4 °C (refrigerator) overnight. For the less polar isomer: oil; R_f 0.76 (33% EtOAc–hexane); $[\alpha]^{25}_D$ +69 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.76 (*q*, 1H, *J* = 6.7 Hz), 4.44 (*m*, 1H), 4.35 (*dd*, 1H, *J* = 9.0 and 9.0 Hz), 4.26 (*dd*, 1H, *J* = 9.0 and 2.4 Hz), 2.40 (*m*, 1H), 1.86 (*d*, 3H, *J* = 6.8 Hz), 0.94 (*d*, 3H, *J* = 6.9 Hz), 0.89 (*d*, 3H, *J* = 6.9 Hz); IR (film) ν_{max} 2960, 1776, 1709, 1386, 1372, 1297, 1250, 1189 cm^{-1}. For the more polar isomer: oil; R_f 0.59 (33% EtOAc–hexane); $[\alpha]^{25}_D$ +70 (*c* 0.90, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.76 (*q*, 1H, *J* = 6.7 Hz), 4.50 (*m*, 1H), 4.32 (*dd*, 1H, *J* = 9.1 and 9.1 Hz), 4.26 (*dd*, 1H, *J* = 9.1 and 3.6 Hz), 2.40 (*m*, 1H), 1.83 (*d*, 3H, *J* = 6.7 Hz), 0.96 (*d*, 3H, *J* = 6.9 Hz), 0.94 (*d*, 3H, *J* = 6.9 Hz); IR (film) ν_{max} 2960, 1776, 1701, 1386, 1368, 1297, 1250, 1203, 1119, 1058 cm^{-1}.

51. The author has deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates may be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

52. Treatment of **39** with $PhCH_2OLi$ (5.0 eq., THF, 25 °C, 6 h, 80%) similarly provided the corresponding benzyl ester: benzyl (2*R*)-1-*tert*-butyloxycarbonyl-2,3-dihydro-3-imino-2-methyl-1*H*-indole-2-carboxylate: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.34 (*br d*, 1H, *J* = 7.7 Hz), 7.74 (*d*, 1H, *J* = 7.7 Hz), 7.67 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 7.2–7.4 (*m*, 5H), 7.16 (*dd*, 1H, *J* = 7.7 and 7.7 Hz), 5.17 (*s*, 2H), 1.80 (*s*, 3H), 1.40 (*s*, 9H).

53. Ciamician, G.; Zatti, C. *Chem. Ber.* **1888**, *21*, 1929.

54. For **11**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.87 (*s*, 1H), 7.49 (*dd*, 1H, *J* = 7.8 and 1.6 Hz), 7.32 (*ddd*, 1H, *J* = 7.8, 7.8 and 1.6 Hz), 6.75 (*ddd*, 1H, *J* = 7.8, 7.8 and 1.6 Hz), 6.65 (*br d*, 1H, *J* = 7.8 Hz), 6.11 (*br s*, 1H). For **12**: white solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.10 (*s*, 1H), 9.94 (*s*, 1H), 8.73 (*br d*, 1H, *J* = 8.0 Hz), 8.54 (*s*, 1H), 7.72 (*br d*, 1H, *J* = 8.0 Hz), 7.63 (*dd*, 1H, *J* = 8.0 and 8.0 Hz), 7.29 (*dd*, 1H, *J* = 8.0 and 8.0 Hz).