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# The Diazo Route to Diazonamide A. Studies on the Indole Bis-oxazole Fragment

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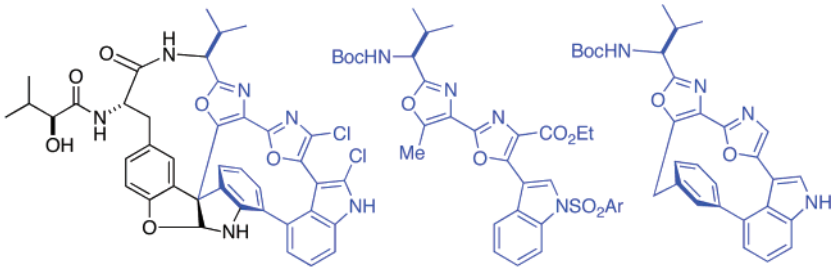


Various approaches to the indole bis-oxazole fragment of the marine secondary metabolite diazonamide A are described, all of which feature dirhodium(II)-catalyzed reactions of diazocarbonyl compounds in key steps. Thus, 3-bromophenylacetaldehyde is converted into an α-diazo-β-ketoester, dirhodium(II)-catalyzed reaction of which with *N*-Boc-valinamide resulted in N-H insertion of the intermediate rhodium carbene to give a ketoamide that readily underwent cyclodehydration to give (*S*)-2-(1-*tert*-butoxycarbonylamino)-2-methylpropyl]-5-(3-bromobenzyl)oxazole-4-carboxamide, after ammonolysis of the initially formed ester. This aryl bromide was then coupled to a 3-formylindole-4-boronate under Pd catalysis to give the expected biaryl. Subsequent conversion of the aldehyde group into a second α-diazo-β-ketoester gave a substrate for an intramolecular carbene N-H insertion, although attempts to effect this cyclization were unsuccessful. A second approach to an indole bis-oxazole involved an intermolecular rhodium carbene N-H insertion, followed by oxazole formation to give (*S*)-2-[1-*tert*-(butoxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxamide. A further N-H insertion of this carboxmide with the rhodium carbene derived from ethyl 2-diazo-3-[1-(2-nitrobenzenesulfonyl)indol-3-yl]-3-oxopropanoate gave a ketoamide, cyclodehydration of which gave the desired indole bis-oxazole. Finally, the boronate formed from 4-bromotryptamine was coupled to another diazocarbonyl-derived oxazole to give the corresponding biaryl, deprotection and cyclization of which produced a macrocyclic indole−oxazole derivative. Subsequent oxidation and cyclodehydration incorporated the second oxazole and gave the macrocyclic indole bis-oxazole.

## Introduction

The marine secondary metabolite diazonamide A, isolated from the colonial ascidian *Diazona chinensis*, was reported to have potent in vitro cytoxicity against human tumor cell lines.[1] This biological activity,[2] together with the unique and complex structure, assigned as **1** on the basis of an X-ray crystallographic study of a derivative,[1] ensured that diazonamide A immediately captured the imagination of synthetic organic chemists. Therefore, in the 15 years since the structure of diazonamide A was reported in 1991, more than 10 research groups have published approaches to this fascinating natural product.[3−30] The story acquired a new twist in 2001 when

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Harran and co-workers completed a total synthesis of structure **1** only to discover that not only was it rather unstable, but it was also different from the natural product.[31,32] On the basis of his own studies and a reexamination of the original X-ray data, Harran proposed the alternative structure **2** for diazonamide A (Figure 1). Not only did this subsequently prove to be correct, it also better fits a biosynthetic route in which the bicyclic core derives from modification of a Tyr-Val-Trp-Trp tetrapeptide. Unequivocal proof that the revised structure **2** was indeed that of diazonamide A came in 2002, when Nicolaou and co-workers published the first total synthesis of the natural product.[33,34] Subsequently, the Nicolaou group reported a second route to diazonamide A,[35,36] while Harran and co-workers completed their own total synthesis of the correct structure.[37] Despite the fact that Nicolaou's and Harran's endeavors in total synthesis have now solved the structural problem of diazonamide A, such is its attraction as a target molecule that it continues to hold the attention of a number of research groups.

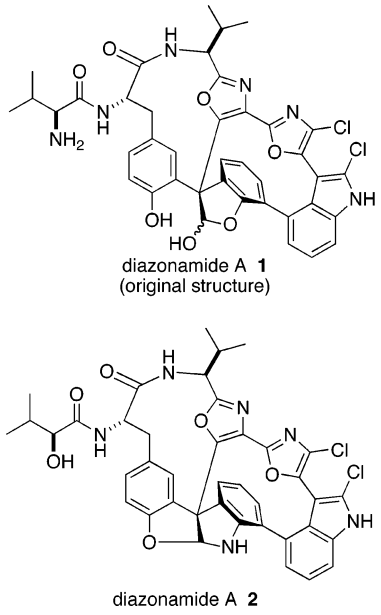


**FIGURE 1.** Original and revised structures for the marine secondary metabolite diazonamide A.

Our own interest in diazonamide A started over a decade ago when we reported an approach to a benzofuranone related to the original structure and an approach to 5-(3-indolyl)oxazoles using dirhodium(II)-catalyzed reactions of diazocarbonyl compounds.[38,39] We have also reported preliminary results on a second approach to the benzofuran unit of the original structure using the Claisen rearrangement[40] and further studies on the indole fragments.[41,42] We have continued to exploit diazocarbonyl compounds in the synthesis of oxazoles,[43−45] including the oxazole building blocks of the natural products nostocyclamide[46] and promothiocin A,[47] and recently completed the synthesis of a precursor to the 5-(3-indolyl)oxazole martefragin A.[48] The method is based on the chemoselective N-H insertion reactions of rhodium carbene intermediates, derived by dirhodium(II) catalyzed reactions of diazocarbonyl compounds, with carboxamides, followed by Robinson−Gabriel cyclodehydration (Scheme 1). This is an efficient and versatile route to a wide range of oxazoles, subsequently adapted to solid

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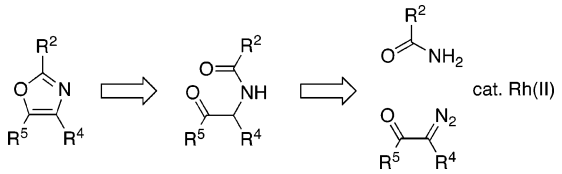
**SCHEME 1. Diazo Route to Oxazoles**




phase by others,[49,50] and therefore seemed an ideal method for the synthesis of both oxazoles in the indole bis-oxazole heterocyclic core of diazonamide A, using both intra- and intermolecular rhodium carbene insertion approaches.[51] It is also highly appealing and appropriate that *diazo* chemistry should be used at key stages in synthetic approaches to a molecule named *diazo*namide.

## Results and Discussion

**Retrosynthetic Analysis.** Although originally devised some years ago for the "old" structure, our retrosynthetic analysis of diazonamide A **2** remains largely unaltered in its overall strategy in which the construction of both oxazole rings by the aforementioned diazocarbonyl methodology plays a key role. In common with most other reported strategies, our initial simplification was to disconnect the α-hydroxy isovaleric acid side chain and the two chlorine atoms. It was established early on in the diazonamide saga that both these chlorines could be introduced by a late-stage electrophilic chlorination reaction.[5,12] However, as did Magnus and co-workers,[12] we recognized an additional possibility that the 4-chlorooxazole might derive by a decarboxylative chlorination of the corresponding oxazole-4-carboxylic acid. This relates to the putatitive biosynthetic precursor to diazonamide A in that C-4 of the oxazole derives from the α-carbon of tryptophan and therefore would originally bear a carboxylic acid. This initial analysis of diazonamide A **2** leads back to the bicycle **3**, which is further simplified to the macrocycle **4** by lactamization and aminal formation onto a reduced oxindole (Scheme 2). The stage is now set for the novel intramolecular rhodium carbene N-H insertion reaction to form the indole bis-oxazole macrocycle by dirhodium(II)-catalyzed reaction of the diazocarbonyl compound **5**. A second oxazole formation by *inter*molecular N-H insertion and a standard Pd-catalyzed formation of the biaryl bond reveals the valine-derived carboxamide **6** and the two α-diazo-*β*-ketoesters **7** and **8** as precursors. The choice of an ester substituent in diazo compound **8** correlates with a tryptophan (rather than tryptamine) in the putative biosynthetic pathway. Finally, it was envisaged that both diazocarbonyl compounds **7** and **8** would derive from the corresponding aldehydes by our previously developed diethylzinc-mediated reactions of ethyl diazoacetate.[52] This reveals the 3-formyloxindole **9** (which is not discussed here) and the simple indole-3-carboxaldehyde **10**.

This paper describes our studies on the diazo route to the indole bis-oxazole fragment and, in particular, a model for the key step—the rhodium carbene intramolecular N-H insertion reaction as exemplified by the simplified substrate **11** (Scheme 2).

**Synthesis of the Intramolecular N-H Insertion Precursor 11.** Our route to the model precursor **11** for the key intramolecular N-H insertion reaction started with 3-bromophenylacetaldehyde **12** prepared from commercially available 3-bromophenylacetic acid by DIBAL reduction of the corresponding methyl ester or by $LiAlH_4$ reduction of the Weinreb amide. Although the desired α-diazo-*β*-ketoester **14** could in principle be prepared from aldehyde **12** by diethylzinc-mediated addition of ethyl diazoacetate[52] followed by oxidation of the resulting α-diazo-*β*-hydroxyester with IBX (see below), the preferred route used the Roskamp protocol,[53] whereby tin(II) chloride mediated addition of ethyl diazoacetate gave the *β*-ketoester **13**. Diazo transfer using 4-acetamidobenzenesulfonyl azide[54] and triethylamine gave the diazocarbonyl compound **14** (Scheme 3). Dirhodium tetraoctanoate catalyzed reaction of diazo compound **14** with (*S*)-*N*-Boc-valinamide[44] resulted in chemoselective insertion into the carboxamide N-H bond to give ketoamide **15** in 73% yield. No products resulting from alternative rhodium carbene pathways, such as Wolff rearrangement, intermolecular insertion into the carbamate N-H, or intramolecular aromatic C-H insertion, were isolated. As expected, the ketoamide **15**, a 1,4-dicarbonyl compound, underwent Robinson–Gabriel cyclodehydration using the Wipf $Ph_3P/I_2/Et_3N$ protocol[55] to give the oxazole **16**. Finally, in preparation for a further rhodium carbene N-H insertion reaction, the oxazole ester **16** was converted into the corresponding carboxamide **17** (Scheme 3).

As outlined in the retrosynthetic analysis (Scheme 2), the synthesis of the required indole fragment started with indole **10**, readily prepared from the known 4-bromoindole-3-carboxaldehyde **18**.[56] Model studies of biaryl coupling reactions of the bromobenzyl oxazole **17** quickly established that Pd-catalyzed reactions with boronic acid derivatives proceeded more smoothly than with stannanes, and therefore, Suzuki conditions were used to form the biaryl bond. Thus, the 4-bromoindole **10** was first reacted with bis(pinacolato)diboron in dioxane in the presence of potassium acetate and $PdCl_2(dppf)\cdot CH_2Cl_2$ complex[57] to give the 4-indolylboronic acid derivative **19**. A second Pd-catalyzed reaction under Suzuki conditions then combined the indole **19** and oxazole **17** fragments to give the biaryl compound **20** (Scheme 4). The required diazo functionality was installed using our diethylzinc protocol,[52] the two-step procedure—diethylzinc-mediated addition of ethyl diazoacetate to the aldehyde followed by oxidation of the resulting α-diazo alcohol using IBX in DMSO—proceeding with reasonable efficiency even in a relatively complex substrate such as aldehyde **20**. Thus, a sequence involving diazo compounds at three separate stages (Schemes 3 and 4) gave the key model diazo compound **11**. Attempts to bring about the intramolecular

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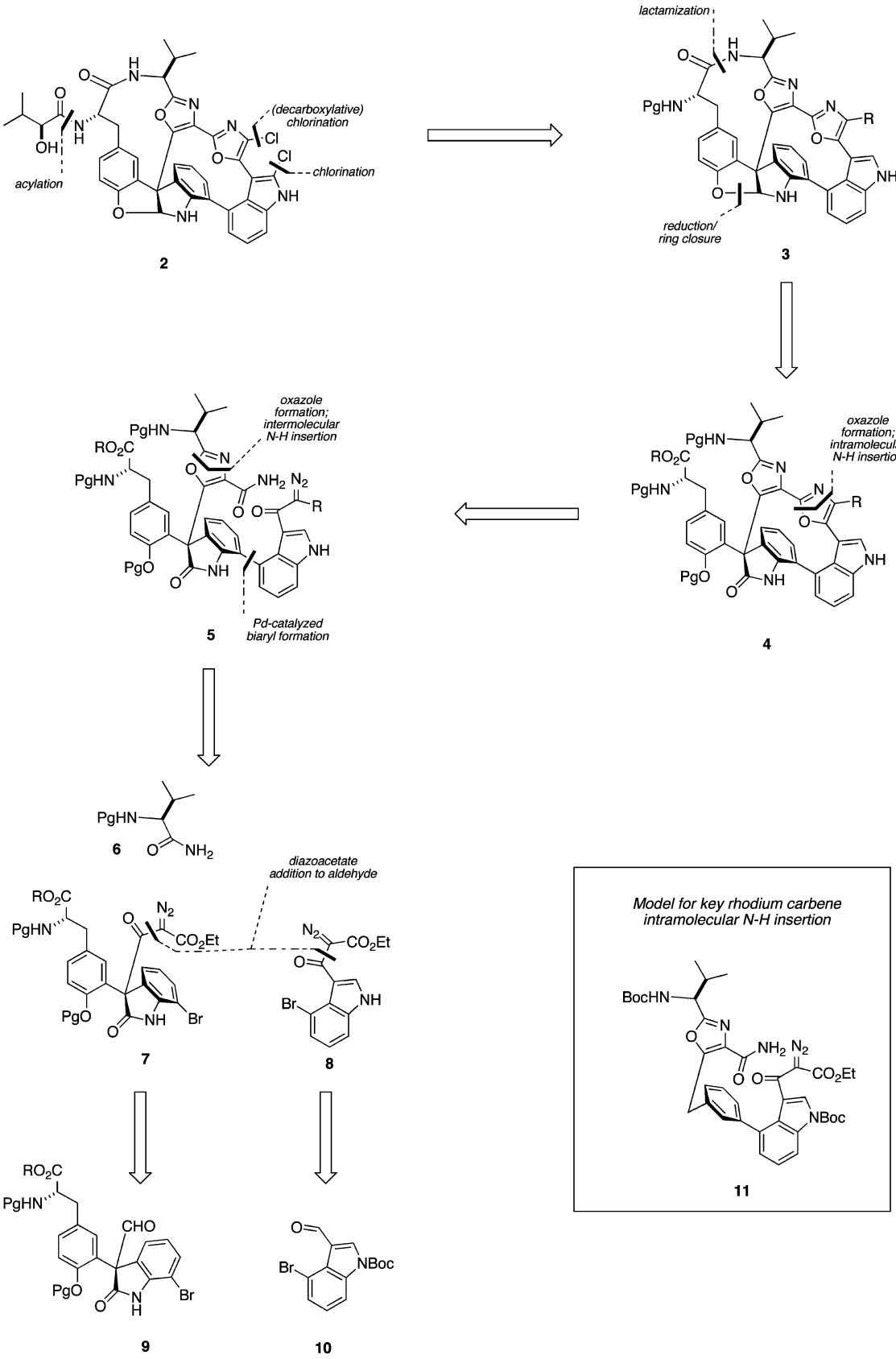
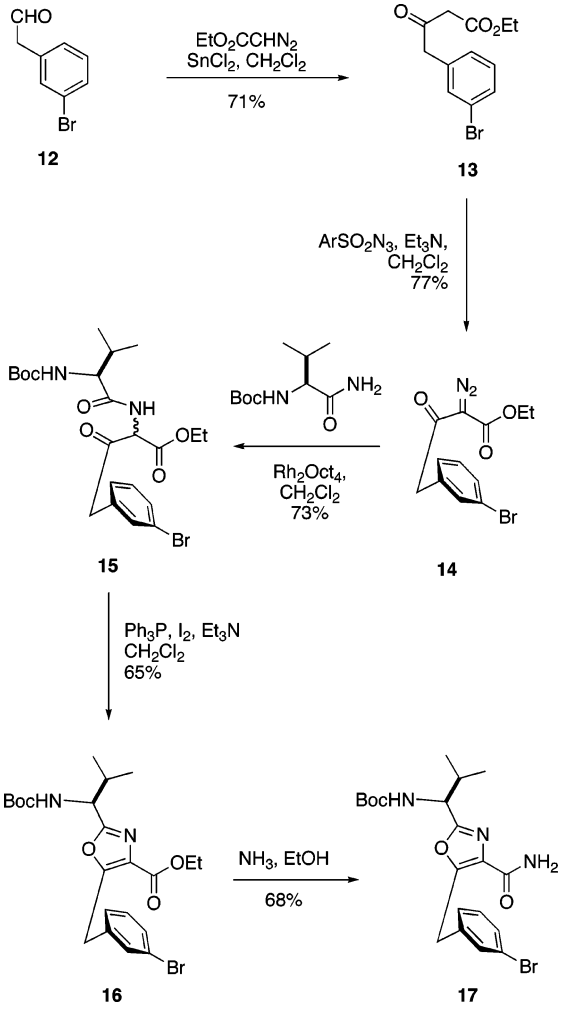
**SCHEME 2. Retrosynthetic Analysis of Diazonamide A 2**[a]




[a] Pg = Protecting Group; R = H or $CO_2R'$.

carbene N-H insertion reaction involved the addition of a dilute dichloromethane solution of diazo compound **11** to a heated solution of the dirhodium(II) catalyst. Both dirhodium tetraoctanoate and dirhodium tetra(perfluo-

**SCHEME 3. Preparation of the Oxazole Carboxamide 17**[a]

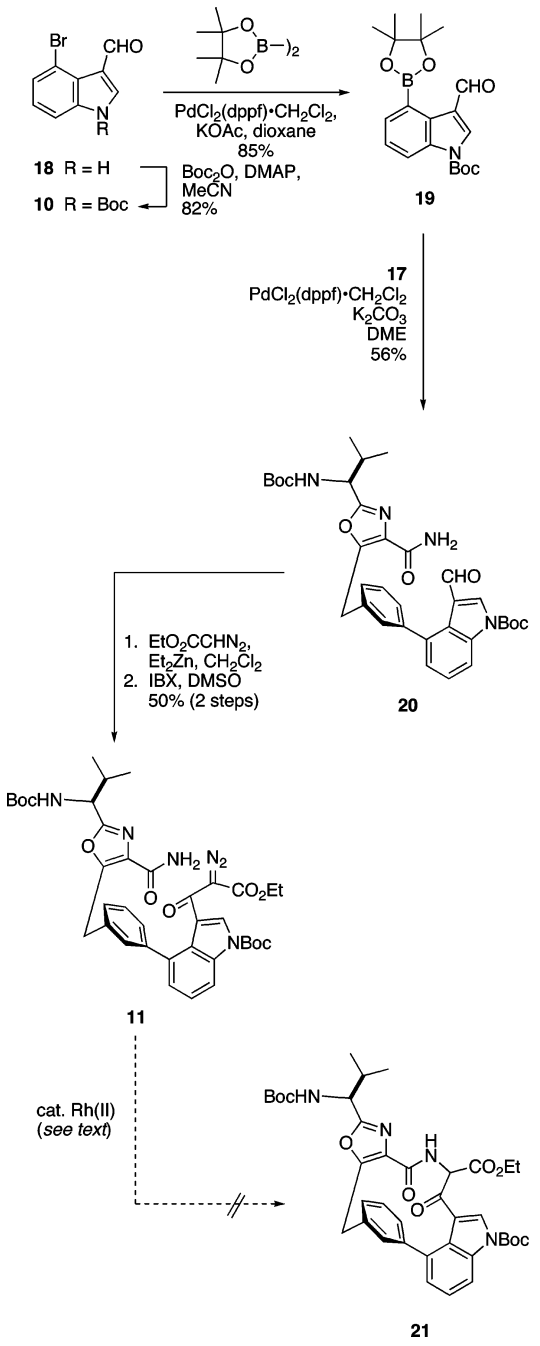



[a] Ar = 4-AcNH-$C_6H_4$; Oct = $OCOC_7H_{15}$.

robutyramide) were studied as catalysts, but in both cases a complex mixture of products was observed, none of which appeared to show signals expected from the desired N-H insertion product **21** in the $^1$H NMR spectrum of the mixture. It was at this juncture, in a parallel study aimed at a simpler 5-(3-indolyl)oxazole martefragin A, that it was discovered that *N*-Boc-indol-3-yl diazoketoesters are prone to undergo Wolff rearrangement in competition with insertion reactions.[48] However, the presence of Wolff rearrangement products from the diazo compound **11** was also not apparent from the $^1$H NMR spectrum of the mixture, although the possibility of products derived by competing aromatic C-H insertion, as observed previously,[39] could not be excluded. Hence, it appears that the proposed intramolecular rhodium carbene N-H insertion reaction as evidenced by the model diazo compound **11** is apparently not a viable route to the indole bis-oxazole fragment of diazonamide A, and therefore a less ambitious *inter*molecular N-H insertion route was investigated.

**Synthesis of Indole Bis-oxazoles.** We have already shown in preliminary work that the oxazole carboxylic acid **22**, prepared in three steps from methyl 2-diazo-3-oxobutanoate,[44] could be readily coupled to tryptophan methyl ester to give the tryptophan derivative **23**.

**SCHEME 4**




Subsequent Yonemitsu oxidation with DDQ in aqueous THF[58,59] gave the ketoamide **24** in modest yield, cyclodehydration of which gave the indole bis-oxazole **25** (Scheme 5).[41]

In line with our desire to use diazocarbonyl chemistry to prepared *both* oxazoles of diazonamide A, the challenge now lay in adapting the above route to incorporate a second dirhodium(II)-catalyzed step. As a prelude to this, we repeated the earlier work using the diazoindole **27**, readily prepared from *N*-Boc-indole-3-carboxaldehyde by

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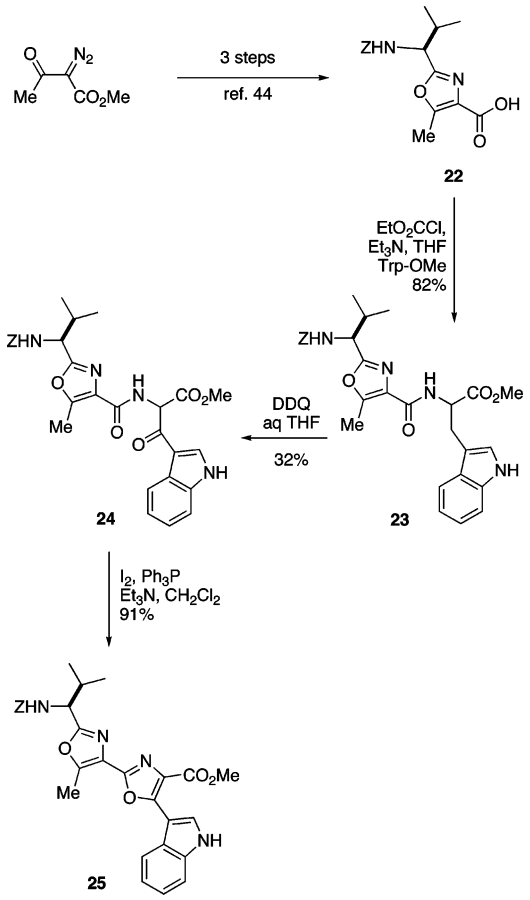
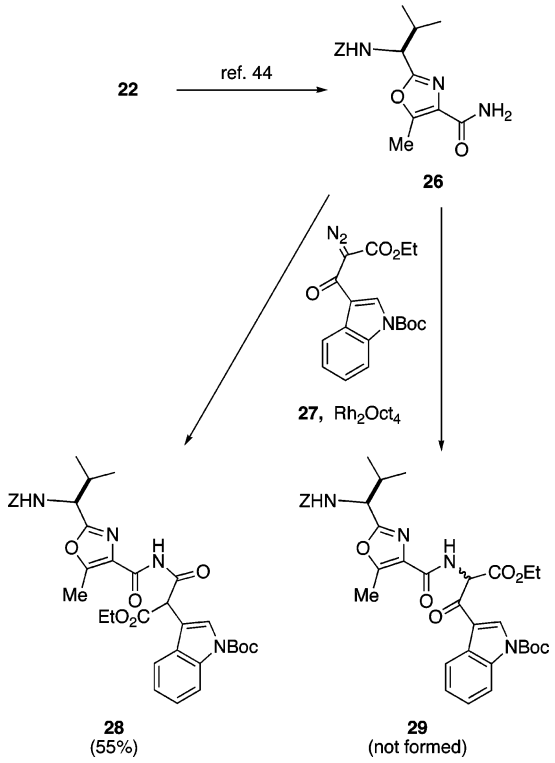
**SCHEME 5. Our Previously Reported Route to Indole Bis-oxazole 25[41]**




the diethylzinc−ethyl diazoacetate protocol.[41,48,52] Dirhodium(II) tetraoctanoate catalyzed reaction of diazoindole **27** with oxazole-4-carboxamide **26** resulted in exclusive Wolff rearrangement and the formation of the imide **28** as a single diastereomer (of unknown relative stereochemistry) (Scheme 6). Although the imide **28** was only formed in 55% yield, there was no evidence for the formation of the N-H insertion product **29** as suggested in our preliminary communication.[41]

Fortunately, in our parallel studies on martefragin A we had developed a solution to the Wolff rearrangement problem,[48] and this was now adopted in the diazonamide case. The starting oxazole-4-carboxamide **31** was prepared by our standard diazocarbonyl route via the ketoamide **30** (Scheme 7); the change in N-protecting group (i.e., Z in **26** to Boc in **31**) was carried out to increase solubility. Two diazo indoles were investigated, the *N*-benzenesulfonyl derivative **32** and the nosyl (2-nitrobenzenesulfonyl) compound **33**, both prepared by diethylzinc-mediated addition of ethyl diazoacetate to the corresponding indole-3-carboxaldehydes followed by IBX oxidation as previously described.[48] Dirhodium(II) tetraoctanoate catalyzed reaction of the *N*-benzenesulfonyldiazoindole **32** with the oxazole-4-carboxamide **31** gave the desired N-H insertion product, the ketoamide **34** in only 12% yield, the major product being imide **35**, a result of Wolff rearrangement followed by trapping of the ketene with amide **31**. Nevertheless, despite the small quantity of ketoamide **34** obtained, it was readily cyclodehydrated to the indole bis-oxazole **36** in reasonable yield (Scheme

**SCHEME 6**[a]

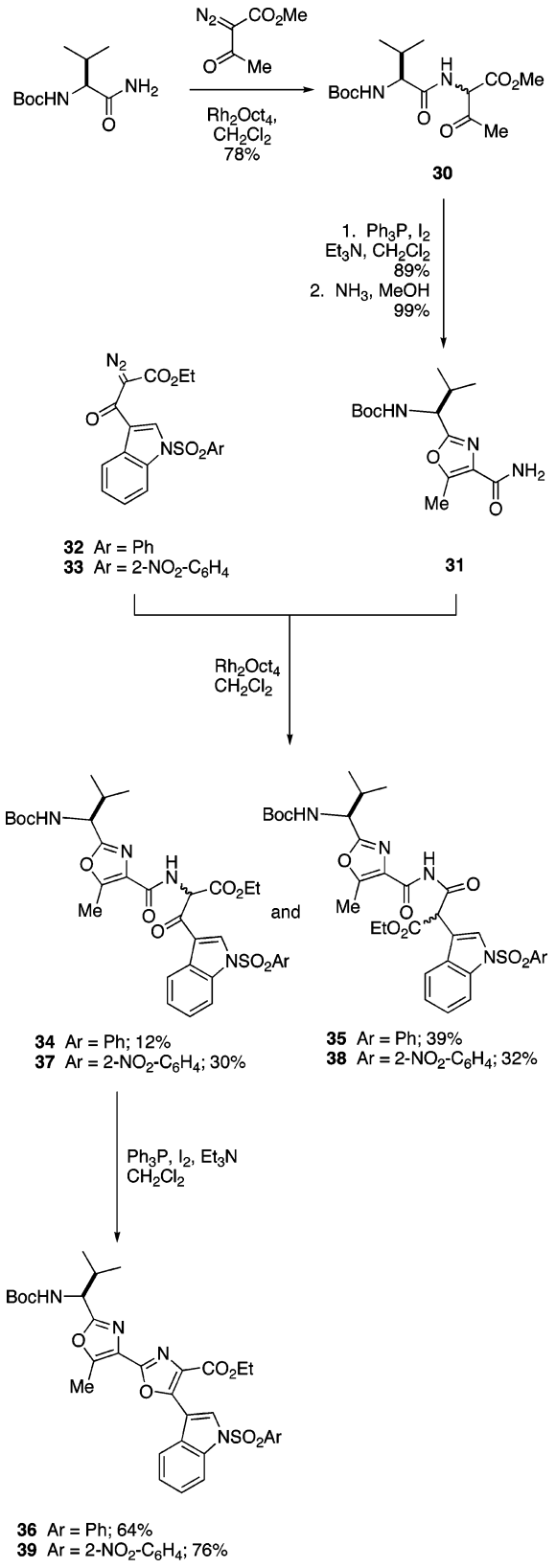



[a] Oct = $OCOC_7H_{15}$.

7). However, the use of the *N*-nosyldiazoindole **33** proved more satisfactory, resulting in the formation of the N-H insertion product **37** in 30% yield (plus 32% of Wolff rearrangement product **38**), cyclodehydration of which gave the indole bis-oxazole **39** in good yield (Scheme 7).

**Synthesis of the Macrocyclic Indole Bis-oxazole 45.** Although the diazocarbonyl methodology could be successfully applied to the synthesis of the simple indole bis-oxazole **39** albeit in modest yield because of competing Wolff rearrangement, the current failure to effect an intramolecular variant prompted a reevaluation of our synthetic route to the complete indole bis-oxazole macrocycle. Thus, we decided to combine the successful aspects of the current work with the more conventional peptide coupling approach used in our preliminary study (Scheme 5). The coupling partners were the 4-bromotryptamine **40** and the bromobenzyl oxazole **41**, the terminal amino and carboxyl protecting groups both being removable by hydrogenolysis. The 4-bromotryptophan **40** was prepared in a conventional manner from 4-bromoindole-3-carboxaldehyde **18** by condensation with nitromethane, lithium aluminum hydride reduction of the nitroalkene, and protection of the amino group as its benzyl carbamate. The oxazole benzyl ester **41** was prepared in a manner similar to that of its ethyl ester analogue starting by transesterification of the ethyl ester **13**, followed by diazo transfer, dirhodium(II)-catalyzed N-H insertion, and cyclodehydration (Scheme 8). After some experimentation, it was decided to delay the Yonemitsu DDQ-oxidation of the tryptamine side chain until after the biaryl coupling. Likewise, it was also found to be better to attach the boronic acid unit to the indole rather than the oxazole for the Suzuki coupling. Therefore, 4-bromo-*N*-Z-tryptamine **40** was subject to boration

**SCHEME 7. Diazo Route to Indole Bis-oxazoles 36 and 39**[a]




[a] Oct = $OCOC_7H_{15}$.

using Baudoin's modification of Masuda's method,[60,61] involving $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)biphenyl as ligand. This gave the required boronate, although it was always contaminated with significant and inseparable amounts of *N*-Z-tryptamine and, therefore, was coupled directly with the bromobenzyl oxazole **41**. The Suzuki coupling could be conducted under standard conditions ($Ph_3P$, aq $Na_2CO_3$, DME), although the $PdCl_2(dppf)\cdot CH_2Cl_2$ catalyst gave slightly better results. This gave the desired biaryl **42** in a modest 38% yield. The terminal protecting groups were removed by hydrogenolysis over Pearlman's catalyst and the resulting amino acid diluted in DMF and treated with diphenylphosphoryl azide (DPPA) and Hünig's base to effect macrocyclization to **43** in good yield. The macrocycle **43** exhibits a complex $^1H$ NMR spectrum at room temperature that simplifies considerably at 60 °C. We believe that this is due to the presence of two interconverting atropisomers. The issue of biaryl atropisomerism in diazonamide A precursors has been discussed by Vedejs and co-workers[21] and results when the biaryl bond is formed before the macrocycle is established. The macrocycle **44** was subjected to Yonemitsu oxidation with DDQ in aqueous THF, although this only proceeded as far as the alcohol stage and a subsequent IBX oxidation was required to give the ketone **44**. A similarly incomplete DDQ oxidation was also noted by Nicolaou and coworkers in their synthetic efforts on diazonamide A when a bulky substituent was present at the indole 4-position.[26] The final cyclodehydration of ketoamide **44** was effected using a variation of the Wipf protocol with hexachloroethane in place of iodine.[6] This resulted in the formation of the desired indole bis-oxazole macrocycle **45** (Scheme 8).

**Conclusions.** The present study has highlighted the use of diazocarbonyl chemistry in the synthesis of oxazoles many of which are relatively complex. However, to date, an intramolecular variant of the key N-H insertion reaction to form a macrocyclic ring of diazonamide A has eluded us, and in some circumstances, the competing Wolff rearrangement cannot be completely suppressed. Nevertheless, despite these setbacks, successful syntheses of a range of oxazoles and indole bis-oxazoles related to diazonamide A have been achieved using diazocarbonyl methodology.

## Experimental Section

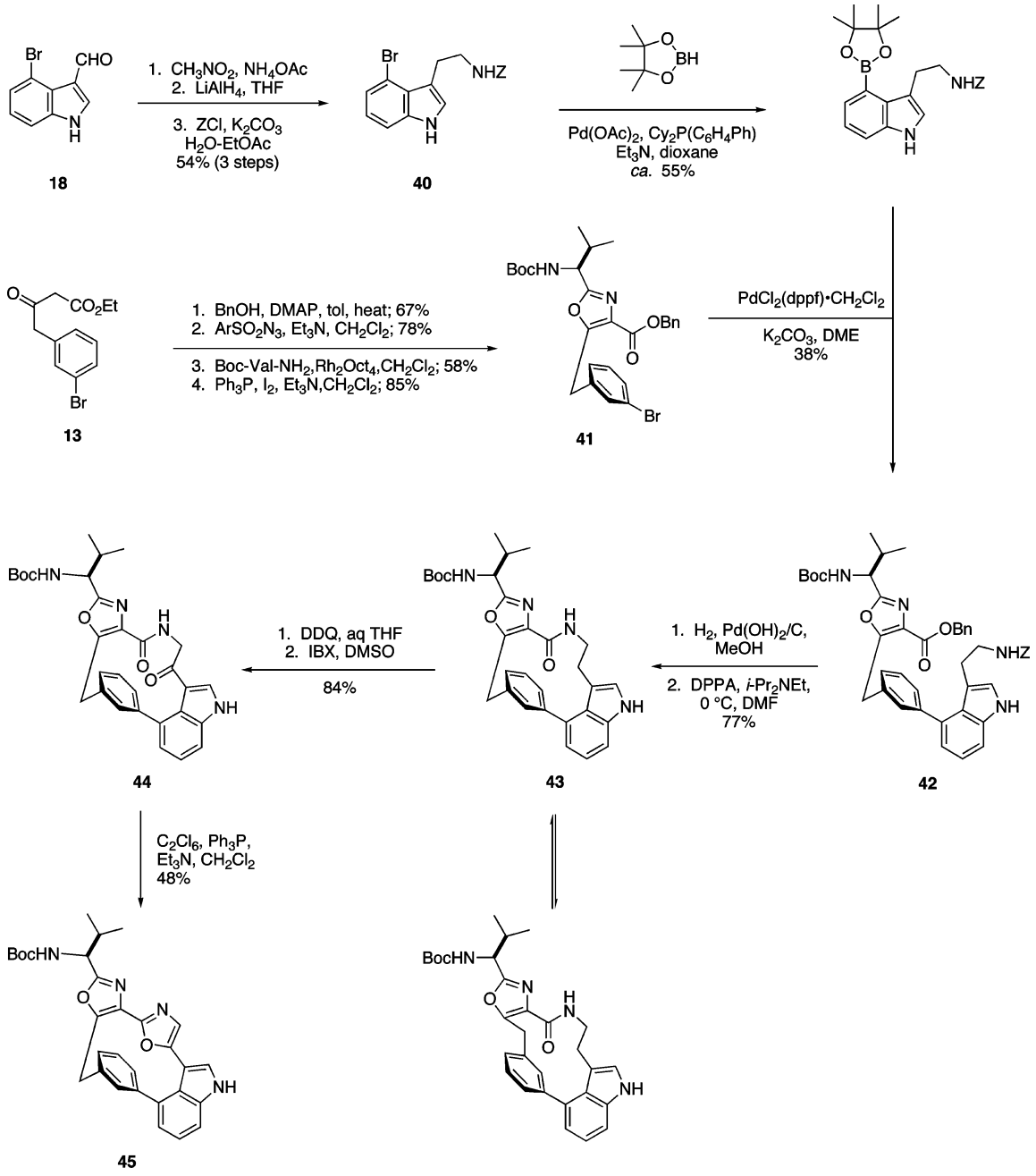
Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40−60 °C, and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Chromatography was carried out on Merck Kieselgel 60H or Matrex silica 60. Fully characterized compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000−600 $cm^{-1}$. $^1H$ and $^{13}C$ NMR spectra were recorded at 300 or 400 MHz ($^1H$ frequencies, corresponding $^{13}C$ frequencies are 75 and 100 MHz); *J* values are recorded in Hz. In the $^{13}C$ NMR spectra, signals corresponding to CH, $CH_2$, or $CH_3$ groups, as assigned from DEPT, are noted; all others are C.

**General Experimental Procedures. A. Synthesis of β-Ketoesters from Aldehydes Using Ethyl Diazoacetate and Tin(II) Chloride.**[53] Anhydrous tin(II) chloride (1.3 mmol)

(60) Baudoin, O.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271.

(61) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458−6459.

**SCHEME 8. Construction of the Model Indole Bis-oxazole Macrocycle 45**[a]




[a] DPPA = diphenylphosphoryl azide; Ar = 4-AcNH-$C_6H_4$; Oct = $OCOC_7H_{15}$.

was suspended in dichloromethane (40 mL) to which was added ethyl diazoacetate (14 mmol). Then the aldehyde (13 mmol) in dichloromethane (10 mL) was added dropwise, and the mixture was stirred for 4 h. Dilute HCl (2 M; 25 mL) was added and the mixture stirred for 30 min and then extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo, and the resulting oil was purified by column chromatography (dichloromethane–light petroleum) to yield the product.

**B. Diazo Transfer.** To a stirred mixture of the $\beta$-ketoester (10 mmol) and 4-acetamidobenzenesulfonyl azide[54] (11 mmol) in acetonitrile (60 mL) at 0 °C was added triethylamine (30 mmol) dropwise. After being stirred at room temperature for 16 h, the reaction mixture was concentrated in vacuo and the resulting solid was triturated with ether–light petroleum. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel eluting with ethyl acetate–light petroleum (1:4) to yield the product.

**C. Rhodium Carbene N-H Insertion Reactions: Preparation of Ketoamides.** To a solution of the carboxamide (5.00 mmol) and dirhodium tetraoctanoate (unless otherwise stated) (2.5 mol %) in a suitable solvent (10 mL), heated to reflux, was added a solution of the diazo compound (6.50 mmol) in the same solvent dropwise over 16 h. The reaction mixture was heated for a further 2–4 h and evaporated in vacuo and the residue purified on silica gel eluting with ethyl acetate–light petroleum (1:4) to yield the product.

**D. Cyclodehydration of Ketoamides to Oxazoles.** To a solution of triphenylphosphine (0.20 mmol) and iodine (0.20 mmol) in dry dichloromethane (10 mL) was added triethylamine (0.41 mmol); a solution of the ketoamide (0.10 mmol) in dry dichloromethane (3 mL) was added. The reaction mixture was stirred for 16 h and evaporated in vacuo and the

residue purified on silica gel eluting with ethyl acetate−light petroleum to yield the product.

**E. Synthesis of α-Diazo-β-ketoesters by Reaction of Aldehydes with Ethyl Diazoacetate and Diethylzinc Followed by IBX Oxidation.**[52] To a solution of ethyl diazoacetate (1.9 mmol) in dichloromethane (5 mL) cooled to −60 °C was added diethylzinc (1.0 M in hexanes; 1.9 mmol) maintaining the temperature below −50 °C, and the mixture was stirred for 30 min. A solution of the aldehyde (1.9 mmol) in dichloromethane (5 mL) was added, and the solution was stirred for 2 h maintaining the temperature below −50 °C before being allowed to warm to room temperature overnight. The mixture was quenched with concentrated aqueous ammonia (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (ethyl acetate−light petroleum) (1:4) to give impure α-diazo-β-hydroxy ester that was carried through to the next stage without further purification.

Iodoxybenzoic acid (2.1 mmol) was dissolved in DMSO (5 mL) over 20 min, the crude α-diazo-β-hydroxyester (1.4 mmol) in DMSO (5 mL) was added, and the mixture was stirred for 3 h. The reaction mixture was poured onto water (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (ethyl acetate−light petroleum) (1:9) to yield the product.

**(*S*)-*N*$^2$-*tert*-Butoxycarbonyl-*N*$^1$-[1-ethoxycarbonyl-3-(3-bromophenyl)-2-oxopropyl]valinamide 15.** According to general procedure C, the *title compound* was prepared from (*S*)-*N*-Boc-valinamide[44] (1.0 g, 4.6 mmol), diazo compound **14** (2.16 g, 6.9 mmol) (see the Supporting Information), and dirhodium tetraoctanoate (90 mg, 0.12 mmol) in dichloromethane (50 mL), as a mixture of diastereomers, as a colorless solid (1.7 g, 3.4 mmol, 73%): mp 99−102 °C; IR (KBr/cm$^{-1}$) 3308 (N-H), 1748 (C=O), 1720 (C=O), 1691 (C=O), 1653 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) δ 7.42 (1H, d, $J$ = 7.9), 7.37 (1H, s), 7.24−7.14 (3H, m), 5.30 (1H, d, $J$ = 5.0), 5.06 (1H, m), 4.29−4.18 (2H, m), 4.10−3.93 (3H, m), 2.25−2.18 (1H, m), 1.45 (9H, s), 1.33−1.25 (3H, m), 1.06−0.92 (6H, m); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 198.0 + 179.9 (diast), 171.7, 165.6 + 165.5 (diast), 155.8, 134.7, 132.7 + 132.6 (CH, diast), 130.5 (CH), 130.2 + 130.1 (CH, diast), 128.4 + 128.3 (CH, diast), 122.6, 80.1 + 80.0 (diast), 62.9 ($CH_2$), 62.0 (CH), 59.5 (CH), 46.9 + 46.8 ($CH_2$, diast), 30.8 + 30.7 (CH, diast), 28.3 (Me), 19.2 + 19.1 (Me, diast), 17.5 + 17.4 (Me, diast), 14.0 (Me); MS (CI) 501/499 (MH$^+$, 4), 473 (5), 401/399 (77), 337/335 (23), 72 (100) (found MH$^+$, 499.1446, $C_{22}H_{32}{}^{79}BrN_2O_6$ requires 499.1444).

**(*S*)-Ethyl 5-(3-Bromobenzyl)-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]oxazole-4-carboxylate 16.** According to general procedure D, the *title compound* was prepared from **15** (1.5 g, 3.0 mmol) as a colorless oil (941 mg, 2.0 mmol, 65%): [α]$^{30}$ −14.0 (*c* 1.0, $CHCl_3$); IR (KBr/cm$^{-1}$) 3350 (N-H), 1706 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) δ 7.41−7.36 (2H, m), 7.20−7.18 (2H, m), 5.27 (1H, d, $J$ = 5.9), 4.75 (1H, dd, $J$ = 9.1, 5.9), 4.43 (2H, q, $J$ = 7.1), 4.34 (2H, s), 2.18−2.11 (1H, m), 1.46−1.39 (12H, m), 0.90 (3H, d, $J$ = 6.5), 0.88 (3H, d, $J$ = 6.5); $^{13}$C NMR (75 MHz; $CDCl_3$) δ 161.6, 160.6, 155.1, 154.0, 136.9, 130.3 (CH), 128.9 (CH), 128.85 (CH), 126.5, 125.9 (CH), 121.3, 78.6, 59.9 ($CH_2$), 52.8 (CH), 31.6 (CH), 30.3 ($CH_2$), 26.9 (Me), 17.3 (Me), 16.6 (Me), 13.0 (Me); MS (CI) 483/481 (MH$^+$, 26), 427/425 (100), 383/381 (34), 366/364 (20); (found MH$^+$, 481.1335, $C_{22}H_{30}{}^{79}BrN_2O_5$ requires 481.1338).

**(*S*)-2-[(1-*tert*-Butoxycarbonylamino)-2-methylpropyl]-5-(3-bromobenzyl)oxazole-4-carboxamide 17.** The oxazole ester **16** (500 mg, 1.0 mmol) was dissolved in a solution of ethanol (5 mL) and ammonia (5 mL) and the mixture stirred overnight before being reduced in vacuo and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the the combined organic layers were washed with saturated sodium hydrogen carbonate (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and reduced in vacuo. The residue was purified by column chromatography (ethyl acetate−light petroleum) to yield the *title compound* as a colorless solid (320 mg, 0.7 mmol, 68%): mp 103−105 °C; [α]$^{30}$ −33.7 (*c* 1.05, $CHCl_3$); IR (KBr/cm$^{-1}$) 3483 (N-H), 3457 (N-H), 3360 (N-H), 1690 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) δ 7.43−7.34 (2H, m), 7.24−7.13 (2H, m), 6.85 (1H, s), 5.71 (1H, s), 5.09 (1H, d, $J$ = 8.7), 4.69 (1H, dd, $J$ = 8.7, 5.8), 4.38 (2H, s), 2.18−2.09 (1H, m), 1.44 (9H, s), 0.89 (3H, d, $J$ = 6.6), 0.88 (3H, d, $J$ = 6.6); $^{13}$C NMR (75 MHz; $CDCl_3$) δ 163.3, 161.5, 155.1, 154.1, 138.5, 131.5 (CH), 130.0 (CH), 129.8 (CH), 128.6, 127.3 (CH), 122.4, 80.0, 53.9 (CH), 32.3 (CH), 31.1 ($CH_2$), 28.1 (Me), 18.4 (Me), 17.7 (Me); MS (CI) 454/452 (MH$^+$, 21), 398/396 (100) (found MH$^+$, 452.1179, $C_{20}H_{27}{}^{79}BrN_3O_4$ requires 452.1185).

**(*S*)-5-[3-(1-*tert*-Butoxycarbonyl-3-formylindol-4-yl)]benzyl-2-(1-*tert*-butoxycarbonylamino)-2-methylpropyl]oxazole-4-carboxamide 20.** To a solution of boronic indole **19** (219 mg, 0.6 mmol) (see the Supporting Information), oxazole amide **17** (320 mg, 0.7 mmol), and potassium carbonate (407 mg, 2.9 mmol) in DME (15 mL) was added $PdCl_2$(dppf)·$CH_2Cl_2$ (86 mg, 0.1 mmol), and the resulting solution was heated to 85 °C for 20 h. The mixture was then diluted with ether (20 mL), and the mixture was washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to yield the *title compound* as a pale yellow foam (205 mg, 0.3 mmol, 56%): [α]$^{31}$ −30.6 (*c* 0.12, $CHCl_3$); IR (KBr/cm$^{-1}$) 3437 (N-H), 1752 (C=O), 1716 (C=O), 1675 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) δ 9.37 (1H, s), 8.33 (1H, s), 8.27 (1H, d, $J$ = 8.4), 7.44−7.32 (5H, m), 7.27−7.22 (1H, m), 6.95 (1H, s), 5.91 (1H, s), 4.68−4.64 (1H, m), 4.50−4.35 (2H, br m), 2.11 − 2.08 (1H, m), 1.69 (9H, s), 1.37 (9H, s), 0.90 (3H, d, $J$ = 6.2), 0.84 (3H, d, $J$ = 6.7), valine NH not observed; $^{13}$C NMR (100 MHz; $CDCl_3$) δ 187.4 (CH), 163.9, 161.7, 155.6, 154.9, 148.8, 141.6, 137.1, 136.3, 135.3, 131.6 (CH), 129.5 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 125.5, 125.4 (CH), 125.2 (CH), 121.2, 114.7 (CH), 85.6, 79.7, 75.0, 65.9 ($CH_2$), 54.4 (CH), 32.4 (CH), 28.3 (Me), 28.1 (Me), 18.8 (Me), 18.1 (Me); MS (CI) 617 (M$^+$, 100) (found MH$^+$, 617.2968, $C_{34}H_{41}N_4O_7$ requires 617.2970).

**(*S*)-Ethyl {1-*tert*-Butoxycarbonyl-4-{3-[2-(1-*tert*-butoxycarbonylamino-2-methylpropyl)-4-carbamoyloxazol-5-ylmethyl]phenyl}indol-3-yl}-2-diazo-3-oxopropanoate 11.** According to general procedure E, biaryl aldehyde **20** (140 mg, 0.22 mmol) was treated with ethyl diazoacetate (0.04 mL, 0.22 mmol) and diethylzinc (1 M in hexanes; 0.22 mL, 0.22 mmol) in dichloromethane (5 mL) followed in a second step by IBX (95 mg, 0.34 mmol) in DMSO (3 mL) to yield the *title compound* as a yellow oil (83 mg, 0.11 mmol, 50%): [α]$^{31}$ −13.9 (*c* 0.12, $CHCl_3$); IR (film/cm$^{-1}$) 3350 (N-H), 2136 (C=N$_2$), 1711 (C=O), 1680 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) δ 8.15 (1H, d, $J$ = 8.3), 7.88 (1H, s), 7.24−7.38 (1H, m), 7.34−7.33 (2H, m), 7.29 − 7.26 (1H, m), 7.24−7.22 (1H, m), 7.19−7.17 (1H, m), 6.88 (1H, d, $J$ = 2.7), 5.67 (1H, d, $J$ = 3.0), 5.51 (1H, m), 4.72 (1H, dd, $J$ = 6.2, 9.2), 4.43 (2H, s), 3.91 (2H, q, $J$ = 7.1), 2.19−2.16 (1H, m), 1.67 (9H, s), 1.40 (9H, s), 0.95−0.85 (9H, m); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 182.8, 163.8, 161.5, 160.1, 155.5, 154.8, 149.0, 141.2, 137.0, 135.22, 135.16, 129.2 (CH), 128.7, 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 125.8, 125.2 (CH), 124.4 (CH), 121.2, 114.5 (CH), 84.8, 79.8, 78.1, 61.2 ($CH_2$), 54.2 (CH), 32.2 (CH), 31.6 ($CH_2$), 28.3 (Me), 28.1 (Me), 18.8 (Me), 17.9 (Me), 13.8 (Me); MS (ES+) 729 (MH$^+$, 100) (found MH$^+$, 729.3250, $C_{38}H_{45}N_6O_9$ requires 729.3243).

**Ethyl 2-(1-*tert*-Butoxycarbonylindol-3-yl)-*N*-{[1-benzyloxycarbonylamino-2-(*S*)-methylpropyl)-4-methyloxazole-5-carbonyl]amino}malonamate 28.** According to general procedure C, using oxazole amide **26**[44] (200 mg, 0.60 mmol) and diazo compound **27**[48] (647 mg, 1.8 mmol) with dirhodium tetraoctanoate (12 mg, 0.02 mmol) in dichloromethane (22 mL), the *title compound* was isolated as a yellow solid (220 mg, 0.33 mmol, 55%): mp 59−62 °C; IR (KBr/cm$^{-1}$)

3361 (N-H), 1734 (C=O), 1701 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 9.44 (0.5H) 9.41 (0.5H, s), 7.97 (1H, d, $J$ = 7.6), 7.56 (1H, s), 7.45 (1H, d, $J$ = 7.7), 7.18 − 7.07 (7H, m), 5.66 (1H, s), 5.11−5.05 (1H, m), 4.96−4.93 (2H, m), 4.58 (1H, dd, $J$ = 5.7, 8.7), 4.11−4.01 (2H, m), 2.45 (3H, s), 2.01−1.95 (1H, m), 1.48 (9H, s), 1.08 (3H, t, $J$ = 6.4), 0.75 (6H, d, $J$ = 6.6); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 167.1, 166.7, 160.1, 158.7, 155.7, 154.9, 148.4, 135.0, 134.3, 128.3, 127.6 (CH), 127.3 (CH), 127.2 (CH), 126.8, 124.8 (CH), 123.7 (CH), 121.8 (CH), 118.7 (CH), 114.3 (CH), 111.2, 82.9, 66.3 ($CH_2$), 61.0 ($CH_2$), 53.5 (CH), 50.1 (CH), 31.2 (CH), 27.2 (Me), 17.7 (Me), 16.8 (Me), 13.0 (Me), 11.0 (Me); MS (ES+) 661 ($MH^+$, 100) (found $MH^+$, 661.2870, $C_{35}H_{41}N_4O_9$ requires 661.2868).

***N*$^2$-(*tert*-Butoxycarbonyl)-*N*$^1$-(1-methoxycarbonyl-2-oxopropyl)valinamide 30.** According to general procedure C, the title compound was prepared from (*S*)-*N*-(*tert*-butoxycarbonyl)valinamide[44] (1.2 g, 5.6 mmol) and methyl 2-diazo-3-oxobutanoate (1.0 g, 7.2 mmol) in dichloromethane, as a mixture of diastereomers, as a colorless solid (1.4 g, 4.1 mmol, 78%): mp 110−112 °C (lit.[44] mp 111−113 °C); IR (KBr/cm$^{-1}$) 3319 (N-H), 1752 (C=O), 1721 (C=O), 1690 (C=O), 1655 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 7.15 (1H, d, $J$ = 5.8), 5.25 (1H, d, $J$ = 6.2), 5.05 (1H, d, $J$ = 6.2) 4.08 (1H, m), 4.85, 4.83 (3H, 2 × s), 2.42, 2.40 (3H, 2 × s), 2.25−2.19 (1H, m), 1.47 (9H, s), 1.00 (3H, d, $J$ = 6.8), 0.93 (3H, d, $J$ = 6.8); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 197.3 + 197.2 (diast), 170.7, 165.6 + 165.5 (diast), 155.0, 79.4, 62.2 + 62.1 (CH, diast), 58.8 (CH), 52.6 + 52.5 (Me, diast), 30.1 + 29.9 (Me, diast), 27.5 (Me), 27.3 + 27.2 (CH, diast), 18.5 + 18.4 (Me, diast), 16.7 + 16.5 (Me, diast); MS (CI) 331 ($MH^+$, 12), 231 (100) (found $MH^+$, 331.1862, $C_{15}H_{27}N_2O_6$ requires 331.1869).

**(*S*)-2-[1-*tert*-(Butoxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxamide 31.** (a) According to general procedure D, (*S*)-methyl 2-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxylate was prepared from **30** (1.2 g, 3.6 mmol) as a colorless crystalline solid (1.0 g, 3.2 mmol, 89%): mp 88−90 °C (lit.[62] oil; lit.[63] mp 57 °C); [α]$^{26}$ −39.0 (*c* 1.0, $CHCl_3$) (lit.[62] [α]$^{23}$ 20.9 (*c* 11.7, $CHCl_3$)); IR (KBr/cm$^{-1}$) 3394 (N-H), 1715 (C=O), 1700 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 5.26−5.23 (1H, d, $J$ = 9.4), 4.73−4.70 (1H, dd, $J$ = 9.4, 6.1), 3.88 (3H, s), 2.59 (3H, s), 2.19−2.13 (1H, m), 1.41 (9H, s), 0.90 (3H, d, $J$ = 6.7), 0.89 (3H, d, $J$ = 6.7); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 163.1, 162.5, 156.7, 155.8, 127.6, 80.3, 54.5 (CH), 52.4 (Me), 33.3 (CH), 28.7 (Me), 19.2 (Me), 18.3 (Me), 12.4 (Me); MS (CI) 313 ($MH^+$, 32), 257 (100) (found $MH^+$, 313.1761, $C_{15}H_{25}N_2O_5$ requires 313.1763). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.7; H, 7.7; N, 9.0. Found: C, 57.7; H, 7.9; N, 8.9.

(b) The above oxazole ester (1.0 g, 3.2 mmol) was dissolved in a solution of methanol (10 mL) and ammonia (0.88; 10 mL), and the mixture was stirred overnight. The mixture was reduced in vacuo and partitioned with ethyl acetate (40 mL) and water (20 mL) and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate (60 mL) and brine (60 mL), dried ($MgSO_4$), filtered, and reduced in vacuo to yield the *title compound* as a colorless oily solid (940 mg, 3.2 mmol, 99%): [α]$^{30}$ −58.3 (*c* 1.04, $CHCl_3$); IR (KBr/cm$^{-1}$) 3473 (N-H), 3355 (N-H), 1680 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 6.81 (1H, s), 5.78 (1H, s), 5.15−5.12 (1H, d, $J$ = 8.9), 4.70−4.65 (1H, dd, $J$ = 6.1, 8.9), 2.60 (3H, s), 2.17−2.10 (1H, m), 1.44 (9H, s), 0.92 (3H, d, $J$ = 6.8), 0.91 (3H, d, $J$ = 6.8); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 164.9, 161.7, 156.2, 154.6, 129.4, 81.0, 55.0 (CH), 33.4 (CH), 29.2 (Me), 19.6 (Me), 18.8 (Me), 12.6 (Me); MS (CI) 298 ($MH^+$, 11), 242 (100) (found $MH^+$, 298.1763, $C_{14}H_{24}N_3O_4$ requires 298.1767).

**Reaction of Ethyl 3-(1-Benzenesulfonylindol-3-yl)-2-diazo-3-oxopropanoate 32 with (*S*)-2-[1-*tert*-Butoxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxamide 31.** To a solution of oxazole amide **31** (300 mg, 1.0 mmol) and dirhodium tetraoctanoate (20 mg, 0.03 mmol) in dichloromethane (10 mL) heated under reflux was added diazo indole **32**[48] (521 mg, 1.3 mmol) in dichloromethane (12 mL) over 16 h. The reaction mixture was heated for a further 30 min, allowed to cool, evaporated in vacuo, and purified by flash chromatography (ethyl acetate−light petroleum). From the reaction two products were isolated:

**(i) Ethyl 2-(1-benzenesulfonylindol-3-yl)-*N*-{[(1-tert-butoxycarbonylamino-2(*S*)-methylpropyl)-4-methyloxazole-5-carbonyl]amino}malonamate 35:** colorless oil (260 mg, 0.39 mmol, 39%); IR (film/cm$^{-1}$) 3360 (N-H), 1711 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 9.57 (1H, s), 7.97 (1H, d, $J$ = 8.2), 7.88 (2H, d, $J$ = 7.9), 7.81 (1H, s), 7.64 (1H, d, $J$ = 7.8), 7.49−7.46 (1H, m), 7.41−7.35 (2H, m), 7.32−7.20 (2H, m), 5.87 (1H, s), 5.11−5.09 (1H, m), 4.69 (1H, dd, $J$ = 5.9, 8.8), 4.26−4.16 (2H, m), 2.62 (3H, s), 2.16−2.09 (1H, m), 1.43 (9H, s), 1.23 (3H, t, $J$ = 7.1), 0.91 (3H, d, $J$ = 6.6), 0.90 (3H, d, $J$ = 6.6); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 168.6, 167.9, 162.0, 160.1, 157.0, 155.8, 138.4, 135.3, 134.3 (CH), 130.2, 129.7 (CH), 128.1, 127.2 (CH), 126.8 (CH), 125.4 (CH), 123.9 (CH), 120.8 (CH), 114.6, 113.9 (CH), 80.7, 62.4 ($CH_2$), 54.5 (CH), 51.4 (CH), 32.8 (CH), 28.7 (Me), 19.2 (Me), 18.3 (Me), 14.4 (Me), 12.4 (Me); MS (ES+) 667 ($MH^+$, 30), 611 (100), 568 (22), 567 (63) (found $MH^+$, 667.2438, $C_{33}H_{39}N_4O_9S$ requires 667.2432). **(ii) Ethyl 3-(1-benzenesulfonylindol-3-yl)-2-{[(1-*tert*-butoxycarbonylamino-2(*S*)-methylpropyl)-4-methyloxazole-5-carbonyl]amino}-3-oxopropanoate 34:** colorless oil (82 mg, 0.12 mmol, 12%), used directly in the next step, without any characterization.

**(*S*)-Ethyl 5-(1-Benzenesulfonylindol-3-yl)-2′-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]-5′-methyl-[2,4′]ioxazolyl-4-carboxylate 36.** According to general procedure D, the *title compound* was prepared from **34** (80 mg, 0.12 mmol) as a colorless solid (50 mg, 0.08 mmol, 64%): mp 160−162 °C; [α]$^{30}$ −38.5 (*c* 0.96, $CHCl_3$); IR (KBr/cm$^{-1}$) 3350 (N-H), 1711 (C=O), 1685 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 8.99 (1H, s), 8.11 (1H, d, $J$ = 7.8), 8.06 (1H, d, $J$ = 8.0), 7.99 (2H, d, $J$ = 7.5), 7.57−7.55 (1H, m), 7.49−7.46 (2H, m), 7.39−7.36 (2H, m), 5.33 (1H, d, $J$ = 8.8), 4.79 (1H, dd, $J$ = 5.7, 8.8), 4.49 (2H, q, $J$ = 7.1), 2.74 (3H, s), 2.25−2.20 (1H, m), 1.47−1.44 (12H, m), 0.95 (6H, d, $J$ = 6.7); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 163.0, 162.1, 155.5, 154.0, 150.6, 150.4, 137.8 134.6, 134.3 (CH), 129.8 (CH), 129.5 (CH), 127.90, 127.88, 127.1 (CH), 125.5 (CH), 124.5, 124.3 (CH), 121.8 (CH), 113.7 (CH), 109.2, 79.9, 61.5 ($CH_2$), 54.1 (CH), 32.9 (CH), 28.3 (Me), 18.8 (Me), 17.9 (Me), 14.4 (Me), 12.0 (Me); MS (CI) 649 ($MH^+$, 8), 593 (25), 549 (61), 409 (100) (found $MH^+$, 649.2316, $C_{33}H_{37}N_4O_8S$ requires 649.2332).

**Reaction of Ethyl 2-Diazo-3-[1-(2-nitrobenzenesulfonyl)indol-3-yl]-3-oxopropanoate 33 with (*S*)-2-[1-*tert*-Butoxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxamide 31.** To a solution of oxazole amide **31** (347 mg, 1.2 mmol) and dirhodium tetraoctanoate (23 mg, 36 μmol) in dichloromethane (10 mL) heated under reflux was added diazo indole **33**[48] (670 mg, 1.5 mmol) in dichloromethane (12 mL) over 16 h. The reaction mixture was heated for a further 30 min, allowed to cool, evaporated in vacuo, and purified by flash chromatography (ethyl acetate−light petroleum). From the reaction two products were isolated:

**(i) Ethyl 3-{[2-(1-*tert*-butoxycarbonylamino-2-methylpropyl)-5-methyloxazole-4-carbonyl]amino}-2-[1-(2-nitrobenzenesulfonyl)-1*H*-indol-3-yl]-3-oxopropionate 38:** mixture of diastereomers, as a yellow oil (272 mg, 0.4 mmol, 32%); IR (film/cm$^{-1}$) 3352 (N-H), 1724 (C=O), 1703 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 9.63, 9.61 (1H, 2 × s), 7.80−7.77 (2H, m), 7.71−7.65 (4H, m), 7.59−7.54 (1H, m), 7.29−7.26 (2H, m), 5.93 (1H, s), 5.27−5.26 (1H, m), 4.68 (1H, dd, $J$ = 6.0, 8.5) 4.28−4.22 (2H, m), 2.62 (3H, s), 2.15−2.12 (1H, m), 1.44, 1.42 (9H, 2 × s), 1.24 (3H, t, $J$ = 7.1), 0.91 (3H, d, $J$ = 6.4), 0.90 (3H, d, $J$ = 6.7); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 167.60 + 167.58

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(63) Haberhauer, G.; Rominger, F. *Eur. J. Org. Chem.* **2003**, 3209−3218.

(diast), 167.5, 161.58 + 161.55 (diast), 159.8, 156.8, 155.4, 147.8, 135.0 (CH), 134.8, 132.6 (CH), 131.7, 129.8 (CH), 128.7, 127.7, 127.30 + 127.26 (CH) (diast), 125.3 (CH), 125.0 (CH), 124.0 (CH), 120.9 (CH), 114.1 + 114.0 (diast), 113.3 (CH), 80.3, 62.2 ($CH_2$), 54.1 (CH), 51.0 (CH), 32,4 (CH), 28.3 (Me), 18.8 (Me), 17.9 (Me), 14.0 (Me), 12.0 (Me); MS (ES+) 734 (M + Na, 100), 712 ($MH^+$, 76), 656 (66), 612 (55), 320 (38), 264 (58), 242 (40), 196 (50), 181 (76) (found $MH^+$, 712.2277, $C_{33}H_{38}N_5O_{11}S$ requires 712.2283). **(ii) Ethyl 2-{[2-(1-*tert*-butoxycarbonylamino-2-methylpropyl)-5-methyloxazole-4-carbonyl]amino}-3-[1-(2-nitrobenzenesulfonyl)-1*H*-indol-3-yl]-3-oxopropionate 37:** mixture of diastereomers, as a yellow oil (252 mg, 0.4 mmol, 30%); IR (film/$cm^{-1}$) 3402 (N-H), 1747 (C=O), 1709 (C=O), 1666 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 8.75 (1H, s), 8.39−8.36 (1H, m), 8.19−8.15 (2H, m), 7.83−7.77 (4H, m), 7.40−7.37 (2H, m), 6.09 (1H, d, $J$ = 7.1), 5.18 (1H, d, $J$ = 9.0), 4.71 (1H, dd, $J$ = 5.7, 9.0), 4.32−4.25 (2H, m), 2.59 (3H, s), 2.18−2.16 (1H, m), 1.44 (9H, s), 1.26 (3H, t, $J$ = 7.1), 0.93 (3H, d, $J$ = 6.6), 0.92 (3H, d, $J$ = 6.5); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 186.2, 166.6, 161.5, 161.1, 155.5, 153.9, 148.0, 138.0 (CH), 134.5, 132.9 (CH), 131.22 (CH), 131.20 (CH), 130.6, 128.3, 127.5, 126.3 (CH), 125.6 (CH), 125.5 (CH), 123.3 (CH), 118.1, 112.9 (CH), 80.0, 62.9 ($CH_2$), 59.4 + 59.3 (diast) (CH), 54.1 (CH), 32.7 (CH), 28.34 + 28.33 (diast) (Me), 18.8 (Me), 17.9 (Me), 14.0 (Me), 11.7 (Me); MS (ES+) 712 ($MH^+$, 30), 657 (32), 656 (100) (found $MH^+$, 712.2286, $C_{33}H_{38}N_5O_{11}S$ requires 712.2283).

**(*S*)-Ethyl 2′-(1-*tert*-Butoxycarbonylamino-2-methylpropyl)-5′-methyl-5-[1-(2-nitrobenzenesulfonyl)-1*H*-indol-3-yl][2,4′]bioxazolyl-4-carboxylate 39.** According to general procedure D, the *title compound* was prepared from **37** (220 mg, 0.31 mmol) as a colorless solid (163 mg, 0.24 mmol, 76%): mp 125 °C dec; $[\alpha]^{31}$ −57.6 (*c* 0.11, $CHCl_3$); IR (KBr/$cm^{-1}$) 3420 (N-H), 1716 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 8.95 (1H, s), 8.19−8.14 (1H, m), 7.91−7.88 (2H, m), 7.80−7.74 (2H, m), 7.70−7.66 (1H, m), 7.42−7.40 (2H, m), 5.33 (1H. d, $J$ = 9.2), 4.79 (1H, dd, $J$ = 6.1, 9.2), 4.48 (2H, q, $J$ = 7.2), 2.75 (3H, s), 2.25−2.20 (1H, m), 1.47−1.43 (12H, m), 0.95 (6H, d, $J$ = 6.0); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 163.0, 161.9, 155.5, 154.3, 150.8, 149.8, 147.9, 135.3 (CH), 134.5, 132.7 (CH), 131.5, 130.3 (CH), 130.1 (CH), 128.4, 127.8, 125.8 (CH), 125.3 (CH), 124.8 (CH), 124.5, 122.2 (CH), 113.6 (CH), 109.3, 80.0, 61.6 ($CH_2$), 54.2 (CH), 32.9 (CH), 28.3 (Me), 18.8 (Me), 18.0 (Me), 14.3 (Me), 12.0 (Me); MS (ES+) 694 ($MH^+$, 30), 656 (25), 639 (36), 638 (100) (found $MH^+$, 694.2183, $C_{33}H_{36}N_5O_{10}S$ requires 694.2177).

**(*S*)-Benzyl 5-(3-Bromobenzyl)-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]oxazole-4-carboxylate 41.** (a) A solution of ketoester **13** (500 mg, 1.8 mmol), benzyl alcohol (379 mg, 3.6 mmol), and DMAP (100 mg, 0.8 mmol) in toluene was heated under reflux for 48 h. The reaction was quenched with aqueous ammonium chloride (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and reduced in vacuo, and the residue was purified by flash chromatography to yield benzyl 4-(3-bromophenyl)-3-oxobutanoate as an oily yellow solid (410 mg, 1.2 mmol, 67%): IR (KBr/$cm^{-1}$) 1742 (C=O), 1716 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 7.41−7.32 (7H, m), 7.18 (1H, t, $J$ = 7.7), 7.09−7.07 (1H, m), 5.16 (2H, s), 3.78 (2H, s), 3.51 (2H, s); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 199.8, 167.2, 135.7, 135.5, 133.0 (CH), 130.9 (CH), 130.7 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 123.2, 67.7 ($CH_2$), 49.6 ($CH_2$), 48.9 ($CH_2$); MS (EI) 348/346 ($M^+$, 3), 91 (100) (found $M^+$, 346.0216, $C_{17}H_{15}{}^{79}BrO_3$ requires 346.0205). Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.8; H, 4.4. Found: C, 58.5; H, 4.1.

(b) According to general procedure B, the above benzyl ketoester (770 mg, 2.2 mmol) was subjected to diazo transfer to yield benzyl 4-(3-bromophenyl)-2-diazo-3-oxobutanoate as a red oily solid (650 mg, 1.7 mmol, 78%): IR (KBr/$cm^{-1}$) 2154 ($C{=}N_2$), 1717 (C=O), 1698 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 7.43−7.33 (7H, m), 7.22−7.14 (2H, m), 5.28 (2H, s), 4.15 (2H, s); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 189.8, 161.4, 136.5, 135.4, 131.1 (CH), 130.7 (CH), 130.4 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 122.9, 67.6 ($CH_2$), 45.7 ($CH_2$), diazo C not observed; MS (CI) 375/373 ($MH^+$, 9), 107 (30), 91 (100) (found $MH^+$, 373.0172, $C_{17}H_{14}{}^{79}BrN_2O_3$ requires 373.0188).

(c) According to general procedure C, (*S*)-$N^1$-[1-benzyloxycarbonyl-3-(2-bromophenyl)-2-oxopropyl]-$N^2$-*tert*-butoxycarbonylvalinamide was prepared from (*S*)-*N*-Boc-valinamide (591 mg, 2.7 mmol), the above diazo compound (1.7 g, 5.5 mmol), and dirhodium tetraoctanoate (106 mg, 0.14 mmol) in dichloromethane, as a mixture of diastereomers, as a colorless solid (880 mg, 1.6 mmol, 58%): mp 122−124 °C (ethyl acetate/light petroleum); IR (KBr/$cm^{-1}$) 3426 (N-H), 3314 (N-H), 1759 (C=O), 1724 (C=O), 1688 (C=O); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 7.40−7.32 (6H, m), 7.20−7.11 (3H, m), 6.99−6.96 (1H, m), 5.34 (1H, d, $J$ = 6.0), 5.30−5.14 (2H, m), 5.00−4.98 (1H, m), 4.10−4.04 (1H, m), 3.99−3.83 (2H, m), 2.21−2.17 (1H, m), 1.44 (9H, s), 0.98−0.94 (3H, m), 0.90−0.87 (3H, m); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 197.9, 172.0, 165.9, 156.2, 134.9, 134.7, 133.0 (CH), 131.0 (CH), 130.5 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 123.0, 80.6, 69.0 ($CH_2$), 62.4 (CH), 59.9 (CH), 47.3 ($CH_2$), 31.1 (CH), 28.7 (Me), 19.6 (Me), 17.7 (Me); MS (CI) 563/561 ($MH^+$, 35), 507/505 (100), 463/461 (83), 311/309 (59) (found $MH^+$, 561.1589, $C_{27}H_{34}{}^{79}BrN_2O_6$ requires 561.1600). Anal. Calcd for $C_{27}H_{33}BrN_2O_6$: C, 57.8; H, 5.9; N, 5.0. Found: C, 57.6; H, 6.0; N, 4.8.

(d) According to general procedure D, the above ketoamide (280 mg, 0.53 mmol) was cyclodehydrated to give the title compound as an orange oily solid (230 mg, 0.45 mmol, 85%): $[\alpha]^{31}$ −33.3 (*c* 0.10, $CHCl_3$); IR (film/$cm^{-1}$) 3348 (N-H), 1713 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 7.41−7.30 (7H, m), 7.11−7.07 (2H, m), 5.39 (1H, d, $J$ = 12.2), 5.35 (1H, d, $J$ = 12.2), 5.30 (1H, d, $J$ = 9.2), 4.72 (1H, dd, $J$ = 5.8, 9.2), 4.21 (2H, s), 2.17−2.09 (1H, m), 1.44 (9H, s), 0.88 (3H, d, $J$ = 6.7), 0.87 (3H, d, $J$ = 6.7); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 163.1, 161.7, 156.6, 155.4, 138.1, 135.4, 131.6 (CH), 130.3 (CH), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.7, 127.2 (CH), 122.7, 80.0, 67.0 ($CH_2$), 54.1 (CH), 32.9 (CH), 31.7 ($CH_2$), 28.3 (Me), 18.7 (Me), 17.9 (Me); MS (CI) 545/543 ($MH^+$, 72), 489/487 (100), 445/443 (22), 91 (39) (found $MH^+$, 543.1479, $C_{27}H_{32}{}^{79}BrN_2O_5$ requires 543.1495).

**(*S*)-Benzyl 5-{3-[3-(2-Benzyloxycarbonylaminoethyl)-1*H*-indol-4-yl]-benzyl}-2-(1-*tert*-butoxycarbonylamino-2-methylpropyl)oxazole-4-carboxylate 42.** To a solution of bromotryptamine **40** (1.0 g, 2.7 mmol) (see the Supporting Information) in dioxane (10 mL) were added triethylamine (1.1 mL, 8.0 mmol), palladium acetate (36 mg, 0.16 mmol), and 2-(dicyclohexylphosphino)biphenyl (94 mg, 0.27 mmol). The mixture was degassed for 10 min, and then 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 mL, 11 mmol) was added cautiously to the mixture, which was then heated to 70 °C for 45 min. The mixture was allowed to cool, carefully quenched with ammonium chloride solution (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic extractions were dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by column chromatography to yield impure pinacolatoboronic tryptamine (ca. 55%; contaminated with the debromo compound). The impure boronate (310 mg, 0.7 mmol), oxazole **41** (200 mg, 0.4 mmol), and potassium carbonate (510 mg, 3.6 mmol) were dissolved in DME (20 mL) and degassed for 10 min. $PdCl_2(dppf)\cdot CH_2Cl_2$ (54 mg, 75 $\mu$mol) was added to the mixture, which was then heated to 85 °C for 3 h. The mixture was allowed to cool, diluted with ether (30 mL), and washed with brine. The aqueous wash was extracted with ether (30 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by column chromatography to yield the title compound as a colorless oil (105 mg, 0.14 mmol, 38%): $[\alpha]^{33}$ −5.6 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$/$cm^{-1}$) 3479 (N-H), 3442 (N-H), 1714 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 8.49 (1H, s), 7.38−7.34 (4H m), 7.32−7.24 (9H, m), 7.21−7.16 (3H, m), 7.00 (1H, s), 6.90 (1H, d, $J$ = 6.6), 5.46 (1H, d, $J$ = 8.8), 5.33 (2H, s), 5.02 (2H, s), 4.72 (1H, dd, $J$ = 6.1, 8.8), 4.51 (1H, m), 4.35 (2H, s), 2.85 (2H, m), 2.45 (2H, t, $J$ = 6.4), 2.12−2.09 (1H, m),

1.40 (9H, s), 0.85 (3H, d, $J$ = 6.6), 0.83 (3H, d, $J$ = 6.6); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 163.0, 161.9, 157.6, 156.2, 155.5, 142.3, 137.1, 136.7, 135.4, 135.3, 135.0, 129.8 (CH), 128.64 (CH), 128.57 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.13 (CH), 128.10 (CH) 128.0 (CH), 127.4, 127.2 (CH), 124.3, 123.6 (CH), 121.7 (CH), 121.3 (CH), 112.9, 110.6 (CH), 79.9, 66.9, 66.5, 54.2 (CH), 41.1 ($CH_2$), 32.8 (CH), 32.1 ($CH_2$), 28.3 (Me), 27.4 (Me), 18.7 (Me), 17.9 (Me); MS (ES+) 757 ($M^+$, 27), 658 (48), 657 (100) (found $MH^+$, 757.3590, $C_{45}H_{49}N_4O_7$ requires 757.3596).

**Macrocycle 43.** A solution of the biaryl **42** (130 mg, 0.17 mmol) in methanol was evacuated and purged with nitrogen five times. Palladium hydroxide on carbon (20 w/w; 12 mg, 17 $\mu$mol) was added to the solution, and the reaction vessel was then evacuated and purged with nitrogen five times and then evacuated and purged with hydrogen five times and left under an atmosphere of hydrogen for 1 h. The mixture was filtered through Celite and concentrated in vacuo. The residue was dissolved in DMF (170 mL) and cooled to 0 °C, diisopropylethylamine (300 $\mu$l, 1.7 mmol) followed by DPPA (76 $\mu$l, 0.35 mmol) were added, and the solution was stirred at 0 °C for 3 days. The reaction was quenched with citric acid (1 M; 50 mL) at 0 °C and concentrated in vacuo, partitioned between ethyl acetate (150 mL) and citric acid (1 M; 75 mL), and separated and the aqueous layer extracted further with ethyl acetate (3 × 100 mL). The combined organic extractions were washed with water (50 mL), sodium hydrogen carbonate (2 × 50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography to yield the title compound as a colorless oil (69 mg, 0.13 mmol, 77%) as a mixture of atropisomers: IR ($CHCl_3$/cm$^{-1}$) 3477 (N−H), 3443 (N−H), 3332 (N−H), 1713 (C=O), 1660 (C=O); $^1$H NMR (300 MHz; 25 °C; $CDCl_3$) $\delta$ 8.69 (1H, s), 7.43−7.30 (3H, m), 7.26−7.25 (1H, m), 7.12 (1H, t, $J$ = 7.2), 7.07 (1H, s), 6.81−6.79 (2H, m), 6.18 (1H, m), 5.23 (0.5H, d, $J$ = 9.2), 5.08 (0.5H, d, $J$ = 9.2), 4.72 (0.5H, m), 4.65 (0.5H, m), 4.25 (2H, s), 3.98 (1H, m), 2.88 (1H, m), 2.46−2.32 (2H, m), 2.13−2.02 (1H, m), 1.40 (9H, s), 0.93−0.84 (6H, m); $^{13}$C NMR (100 MHz; 60 °C; $CDCl_3$) $\delta$ 162.6, 155.1, 153.4, 142.2, 136.3, 136.1, 135.5, 132.7, 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 126.0, 123.2 (CH), 121.12 (CH), 121.07 (CH), 115.7, 115.6, 110.4 (CH), 80.0, 54.6 (CH), 43.7 ($CH_2$), 32.7 (CH), 31.9 ($CH_2$), 28.2 (Me), 23.9 ($CH_2$), 18.6 (Me), 17.9 (Me); MS (CI) 515 ($MH^+$, 8), 416 (30), 415 (100), 398 (39) (found $MH^+$, 515.2671, $C_{30}H_{35}N_4O_4$ requires 515.2658).

**Ketoamide Macrocycle 44.** To a solution of DDQ (85 mg, 0.38 mmol) in THF/$H_2O$ (9/1, 3.5 mL) was added a solution of macrocycle **43** (88 mg, 0.17 mmol) in THF/$H_2O$ (9/1, 3.5 mL) dropwise, and the resulting mixture was stirred at ambient temperature for 1 h. The mixture was diluted with ethyl acetate (20 mL) and extracted with sodium hydrogen carbonate (4 × 20 mL), dried ($MgSO_4$), filtered, reduced in vacuo, and purified by column chromatography to yield the hydroxy intermediate as a pale red solid (80 mg, 0.15 mmol, 88%). The resulting solid was dissolved in DMSO (1.0 mL), added to a solution of IBX (80 mg, 0.15 mmol) in DMSO (1.0 mL), and stirred at ambient temperature overnight. The mixture was quenched with water (15 mL) and extracted with dichloromethane (3 × 10 mL), and the combined extracts were dried ($MgSO_4$), filtered, reduced in vacuo, and purified by column chromatography to yield the title compound, as a mixture of atropisomers, as a yellow crystalline solid (75 mg, 0.14 mmol, 95%, 84% over two steps): mp 150 °C dec; IR ($CHCl_3$/cm$^{-1}$) 3459 (N-H), 3281 (N-H), 1713 (C=O), 1661 (C=O); $^1$H NMR (400 MHz; 60 °C; $CDCl_3$) $\delta$ 9.71 (1H, s), 7.45−7.43 (1H, m), 7.36−7.26 (3H, m), 7.21−7.19 (2H, m), 7.12−7.10 (1H, m), 6.80 (1H, br m), 5.21 (1H, br m), 4.76 (1H, br m), 4.14 (4H, br m), 2.20−2.16 (1H, m), 1.48 (9H, s), 0.99 (3H, d, $J$ = 7.1), 0.97 (3H, d, $J$ = 7.1); $^{13}$C NMR (100 MHz; 25 °C; $CDCl_3$) $\delta$ 191.9, 167.3, 161.8, 155.7, 143.0, 137.5, 136.5, 135.9, 130.75 (CH), 130.68, 130.4 (CH), 130.0, 128.6 (CH), 126.6, 125.8 (CH), 124.6 (CH), 123.8 (CH), 122.0 (CH), 119.4, 110.9 (CH), 80.1, 54.3 (CH), 47.8 ($CH_2$), 32.7 (CH), 31.4 ($CH_2$), 28.4 (Me), 18.8 (Me), 18.2 (Me); MS (ES+) 551 (M + Na, 100), 529 ($MH^+$, 15), 495 (40), 473 (60), 445 (10), 412 (found $MH^+$, 529.2445, $C_{30}H_{33}N_4O_5$ requires 529.2457).

**Indole Bis-oxazole Macrocycle 45.** To a solution of triphenylphosphine (30 mg, 113 $\mu$mol) and hexachloroethane (27 mg, 113 $\mu$mol) in dichloromethane (1 mL) was added triethylamine (32 $\mu$l) followed by a solution of ketoamide macrocycle **44** (30 mg, 57 $\mu$mol) in dichloromethane (1 mL). The resulting mixture was stirred overnight and then reduced in vacuo and the residue purified by column chromatography to yield the title compound, as a mixture of atropisomers, as a pale brown solid (14 mg, 27 $\mu$mol, 48%): mp 140 °C dec; IR ($CHCl_3$/cm$^{-1}$) 3470 (N-H), 3442 (N-H), 1711 (C=O); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 9.16 (1H, s), 9.01 (1H, s), 7.86 (2H, d, $J$ = 6.6), 7.47 (2H, t, $J$ = 7.4), 7.37−7.26 (6H, m), 7.17−7.00 (6H, m), 6.80 (1H, s), 6.77 (1H, s), 5.44 (1H, d, $J$ = 9.3), 5.40 (1H, d, $J$ = 9.2), 4.85 (1H, dd, $J$ = 8.9, 5.7), 4.78 (1H, dd, $J$ = 8.6, 6.1), 4.35 (1H, d, $J$ = 16.4), 4.20 (1H, d, $J$ = 16.4), 4.09 (1H, d, $J$ = 16.2), 3.81 (1H, d, $J$ = 16.2), 2.25−2.20 (2H, m), 1.46 (18H, s), 1.00−0.95 (12H, m); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$ 162.4 + 162.2 (atrop), 155.9, 154.5, 152.3, 146.6 + 146.5 (atrop), 139.7 + 139.6 (atrop), 135.9 + 135.8 (atrop), 135.4, 135.3, 132.3, 132.1, 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 126.63 + 126.58 (CH, atrop), 125.7 + 125.5 (CH, atrop), 122.7 + 122.6 (CH, atrop), 121.3 (CH), 111.3 + 111.1 (CH, atrop), 104.0, 80.1 + 79.9 (atrop), 54.4 + 54.0 (CH, atrop), 33.4 + 32.9 (CH, atrop), 33.1 ($CH_2$), 28.3 (Me), 18.9 + 18.7 (Me, atrop), 18.2 + 17.9 (Me, atrop); MS (ES+) 511 ($MH^+$, 48), 478 (15), 477 (42), 455 (100), 433 (13) (found $MH^+$, 511.2347, $C_{30}H_{31}N_4O_4$ requires 511.2340).

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra of compounds *N*-methoxy-*N*-methyl-3-bromophenylacetamide, **10**−**17**, **19**, **20**, **28**, **31**, **35**−**45**, *trans*-4-bromo-3-(2-nitroethenyl)-1*H*-indole, benzyl 4-(3-bromophenyl)-3-oxobutanoate, benzyl 4-(3-bromophenyl)-2-diazo-3-oxobutanoate, and (*S*)-$N^1$-[1-benzyloxycarbonyl-3-(2-bromophenyl)-2-oxopropyl]-$N^2$-*tert*-butoxycarbonylvalinamide; experimental details for compounds **10**, **12**−**14**, **19**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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