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Control of Competing N−H Insertion and Wolff Rearrangement in Dirhodium(II)-Catalyzed Reactions of 3-Indolyl Diazoketoesters. Synthesis of a Potential Precursor to the Marine 5-(3-Indolyl)oxazole Martefragin A

James R. Davies,[†] Peter D. Kane,[‡] Christopher J. Moody,*[,†] and Alexandra M. Z. Slawin[§]

Department of Chemistry, University of Exeter, Stocker Road, Exeter, EX4 4QD, United Kingdom, Tripos Receptor Research Ltd, Bude-Stratton Business Park, Bude, Cornwall, EX23 8LY, United Kingdom, and School of Chemistry, University of St. Andrews, Fife, Scotland, KY16 9ST, United Kingdom

c.j.moody@ex.ac.uk

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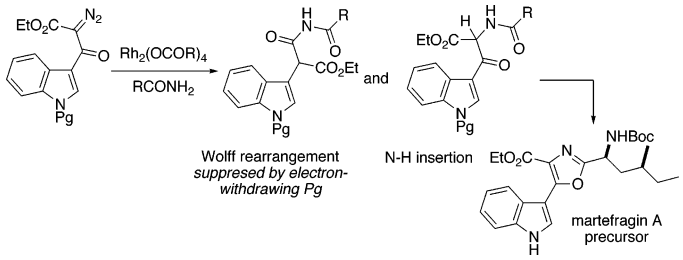

Dirhodium(II)-catalyzed reaction of 3-indolyl α-diazo-*β*-ketoester **25** in the presence of hexanamide results in competing metal carbene N−H insertion and Wolff rearrangement. The corresponding phenyl diazoketoester **32**, on the other hand, gives only the product of N−H insertion, suggesting that the indole moiety is more prone to 1,2-rearrangement. The competing processes were investigated in a range of 3-indolyl α-diazo-*β*-ketoesters (**36**, **38**, **40**, **44**); these studies established that the Wolff rearrangement could be effectively suppressed by the presence of a strong electron-withdrawing group on the indole nitrogen. Dirhodium(II) catalysts were also more effective than copper or Lewis acid catalysts in favoring the insertion process. The products of N−H insertion, the ketoamides (**26**, **47**, **49**, **51**, **53**), were readily cyclodehydrated to the corresponding 5-(3-indolyl)-oxazoles. The N−H insertion/cyclodehydration methodology was used in a formal synthesis of the marine natural product martefragin A. Thus the *N*-Boc homoisoleucine amide **23**, prepared by asymmetric hydrogenation of a dehydro amino acid, underwent N−H insertion with the rhodium carbene derived from the *N*-nosyl indolyl diazoester **40**, followed by cyclodehydration and deprotection to give the 5-(3-indolyl)oxazole martefragin A precursor **75**.

Introduction

The 5-(3-indolyl)oxazole ring system occurs in a small number of natural products. These range from the simple pimprinine alkaloids, pimprinine **1** itself,[1,2] pimprinethine **2**,[3,4] WS-30581A and B **3** and **4**,[5] and pimprinaphine **5**,[3,6] through martefragin A **6**,[7,8] to the complex marine natural product diazonamide A **7** (Figure 1).[9]

The synthetic challenges posed by diazonamide A have stimulated much interest in indolyloxazoles, although there remain relatively few methods to access this ring

* To whom correspondence should be addressed. Fax: +44 1392 263434.
[†] University of Exeter.
[‡] Tripos Receptor Research.
[§] University of St Andrews.

(1) Bhate, D. S.; Hulyalker, R. K.; Menon, S. K. *Experientia* **1960**, *16*, 504.
(2) Joshi, B. S.; Taylor, W. I.; Bhate, D. S.; Karmarkar, S. S. *Tetrahedron* **1963**, *19*, 1437.
(3) Koyama, Y.; Yokose, K.; Dolby, L. J. *Agric. Biol. Chem.* **1981**, *45*, 1285−1287.
(4) Noltenmeyer, M.; Sheldrick, G. M.; Hoppe, H.-U.; Zeeck, A. *J. Antibiot.* **1982**, *35*, 549−555.
(5) Umehara, K.; Yoshida, K.; Okamoto, M.; Iwami, M.; Tanaka, H.; Kohsaka, M.; Imanaka, H. *J. Antiobiot.* **1984**, *37*, 1153−1160.
(6) The APHE natural products appear to be identical with the pimprinine alkaloids: Kelly, T. R.; Fu, Y.; Xie, R. L. *Tetrahedron Lett.* **1999**, *40*, 1857−1860.
(7) Takahashi, S.; Matsunaga, T.; Hasegawa, C.; Saito, H.; Fujita, D.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1527−1529.
(8) Nishida, A.; Fuwa, M.; Fujikawa, Y.; Nakahata, E.; Furuno, A.; Nakagawa, M. *Tetrahedron Lett.* **1998**, *39*, 5983−5986.
(9) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303−2304.

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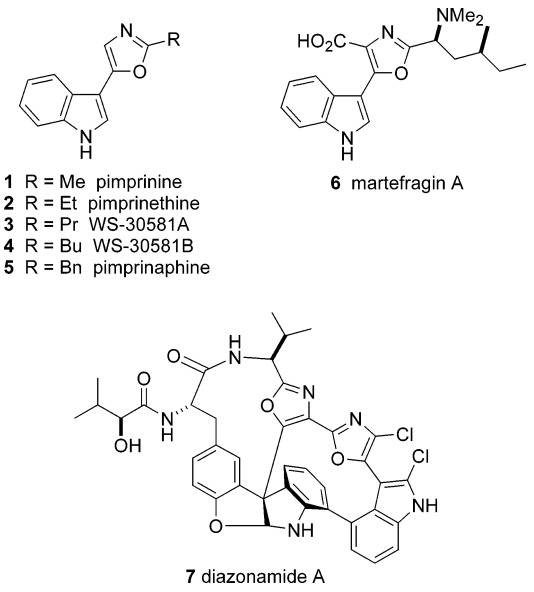
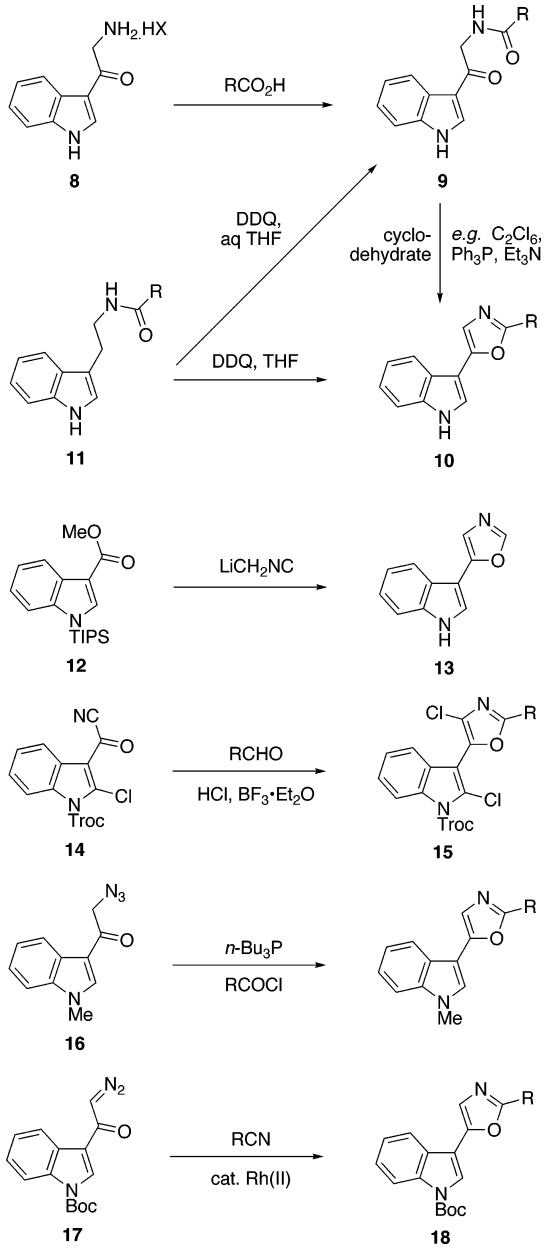


FIGURE 1. Structures of naturally occurring 5-(3-indolyl)-oxazoles.

system. Most routes rely on some variation of the classical Robinson−Gabriel method whereby a 3-aminoacetylindole **8** is acylated and the resulting ketoamide 1,4-dicarbonyl compound **9** cyclodehydrated to the indolyloxazole **10** with reagents such as $POCl_3$/pyridine, the Burgess reagent, or the Wipf hexachloroethane/triphenylphosphine protocol (Scheme 1).[10−12]

Alternatively, the 1,4-dicarbonyl ketoamide **9** can be accessed by Yonemitsu DDQ-oxidation of the *N*-acyltryptamine **11**,[13−16] subsequent cyclodehydration leading to the indolyloxazole **10**. Under anhydrous conditions, the Yonemitsu oxidation of *N*-acyltryptamines **11** can lead directly to the indolyloxazole **10** (Scheme 1).[13,14,17,18] Other methods employed include the Schöllkopf lithioisonitrile method as exemplified by the conversion of indole-3-carboxylate **12** to indolyloxazole **13**,[19] methods based on TOSMIC,[20] the HCl/BF_3·Et_2O mediated reaction of aldehydes with indolylacyl cyanides **14** that gives dichloro indolyloxazoles **15** directly related to diazonamide A,[21] reactions proceeding via iminophosphoranes derived by reaction of tri-*n*-butylphosphine with 3-azidoacetylindole **16**,[22] and palladium-catalyzed coupling of 3-tri-*n*-butylstannylindoles with 5-bromooxazoles.[23]

SCHEME 1

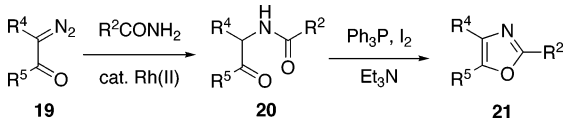


Our own interest in indolyloxazoles started over a decade ago when we developed a simple route based on rhodium carbene chemistry. Thus dirhodium(II)-catalyzed decomposition of *N*-Boc-diazoindole **17** in the presence of simple alkyl nitriles gave the Boc-protected derivatives **18**, subsequently deprotected to the indolyloxazole alkaloids pimprinine **1**, pimprinethine **2**, and WS-30581A **3** (Scheme 1).[24]

However, attempted extension of this reaction to more highly functionalized nitriles (derived by dehydration of the corresponding amides), and hence to structurally more complex oxazoles, was unsatisfactory. Therefore an alternative was developed in which the starting amide was reacted directly with the diazocarbonyl compound **19** under dirhodium(II) catalysis in an N−H insertion

(10) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223−2226.
(11) Wipf, P.; Methot, J.-L. *Org. Lett.* **2001**, *3*, 1261−1264.
(12) Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2001**, *42*, 627−629.
(13) Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457−1462.
(14) Yoshioka, T.; Mohri, K.; Oikawa, Y.; Yonemitsu, O. *J. Chem. Res.* (*S*) **1981**, 194−195; *J. Chem. Res.* (*M*) **1981**, 2252−2281.
(15) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765−4770.
(16) Nicolaou, K. C.; Snyder, S. A.; Huang, X.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.* **2004**, *126*, 10162−10173.
(17) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831−834.
(18) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961−4966.
(19) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033−1035.
(20) Dhar, T. G. M.; Shen, Z.; Fleener, C. A.; Rouleau, K. A.; Barrish, J. C.; Hollenbaugh, D. L.; Iwanowicz, E. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3305−3308.
(21) Radspieler, A.; Liebscher, J. *Synthesis* **2001**, 745−750.
(22) Molina, P.; Fresneda, P. M.; Almendros, P. *Synthesis* **1993**, 54−56.
(23) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167−8170.
(24) Doyle, K. J.; Moody, C. J. *Synthesis* **1994**, 1021−1022.

SCHEME 2



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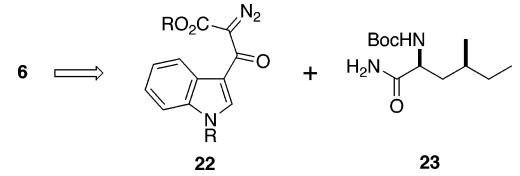


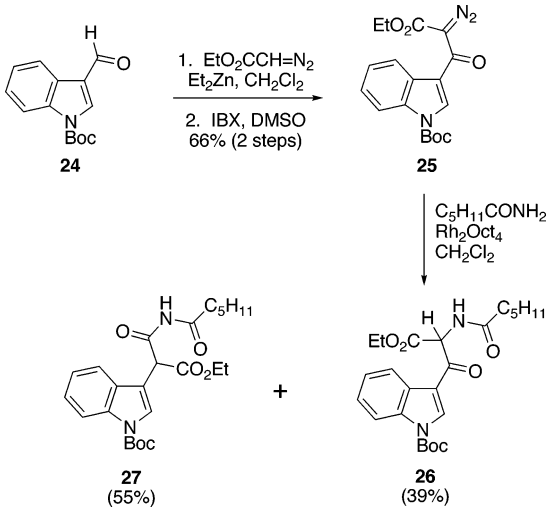
reaction to give a ketoamide 1,4-dicarbonyl compound **20** that subsequently underwent a Robinson−Gabriel cyclodehydration to the oxazole **21**.[25] Although this is a very general route to 2,5-di- or 2,4,5-trisubstituted oxazoles **21** (Scheme 2),[26] our preliminary studies on its application to more complex oxazoles, such as the indolylbisoxazole fragment of diazonamide A,[27] did not, for reasons that will become apparent later, prove entirely satisfactory. Therefore, before continuing with this approach to diazonamide A, we undertook the less daunting challenge posed by martefragin A **6**.

Results and Discussion

Martefragin A **6** was isolated from the Japanese alga *Martensia fragilis* Harvey and shown to be a potent inhibitor of lipid peroxidation.[7] The structure and stereochemistry were subsequently confirmed by synthesis by Nishida et al., the indolyloxazole being formed by Yonemitsu DDQ oxidation (cf. **11** to **10**).[8] Subsequently, Nishida et al. have reported the synthesis of a range of analogues of martefragin, again using DDQ oxidation to establish the indolyloxazole system.[28] To apply our diazocarbonyl methodology, we required a 3-indolyl-α-diazo-*β*-ketoester **22** and the amide **23** (Scheme 3). However, before using the precious 2-amino-4-methylhexanoic amide derivative **23**, the *N*-protected amide derivative of homoisoleucine, we undertook a model study using the readily available hexanoic amide.

Model Study and Advent of Competing Wolff Rearrangement. The required 3-indolyl-α-diazo-*β*-ketoester **25** was prepared from *N*-Boc-indole-3-carboxaldehyde **24** with use of our diethylzinc mediated addition of ethyl diazoacetate protocol,[29] followed by IBX oxidation of the intermediate α-diazo-*β*-hydroxyester. The diazocarbonyl compound **25** was then added over 16 h to a mixture of hexanamide and dirhodium tetraoctanoate in boiling dichloromethane. Much to our surprise, the reaction gave two major products, of which the desired carbene N−H insertion product **26** was formed in only 39% yield. This is in direct contrast to earlier work with related diazoketoesters (**19**, R^4 = CO_2Et; R^5 = alkyl or aryl) where the N−H insertion product was essentially the only observed product of reaction.[26] The structure of the ketoamide N−H insertion product **26** was confirmed by its subsequent cyclodehydration to the oxazole (see below) and also by X-ray crystallography (see the Supporting Information).

SCHEME 4



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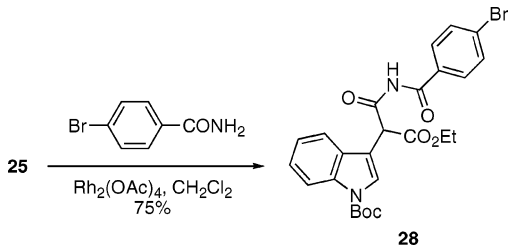
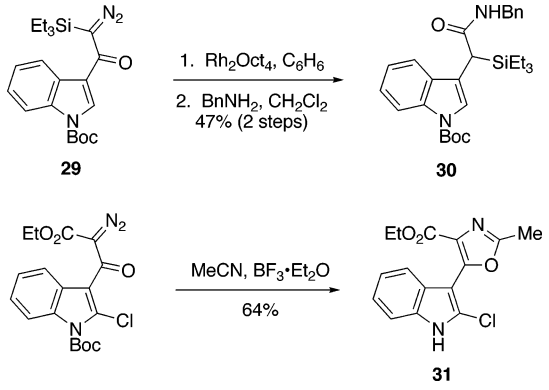


The second product formed from the diazocarbonyl compound **25** was spectroscopically very similar to the ketoamide **26** with one main exception, the absence of coupling between the NH and CH. When the reaction was repeated with 4-bromobenzamide in place of hexanamide, only the analogous "unknown" product was formed, X-ray crystallography (see the Supporting Information) establishing its structure as imide **28** (Scheme 5), the product of Wolff rearrangement followed by interception of the ketene by the amide. These experiments, therefore, established the structure of the second hexanamide derived product as the imide **27** (Scheme 4).

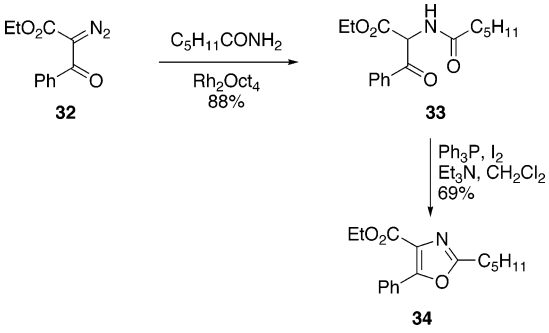
Although the origin of imide **27** by Wolff rearrangement is clear, it remained a puzzle since similar products had not been observed in related reactions.[26] Indeed, the use of dirhodium(II) catalysts for the decomposition of diazoketones rarely results in Wolff rearrangement. However, this is clearly not the case, and there are examples of competing or predominating Wolff rearrangement in dirhodium(II)-catalyzed reactions of diazoketones.[30,31] Of particular relevance is the observation by Marsden and co-workers that the triethylsilyl analogue **29** of our indolyl diazoketoester gave only Wolff

(25) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 591−600.
(26) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967−3977.
(27) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897−6900.
(28) Nishida, A.; Fuwa, M.; Naruto, S.; Sugano, Y.; Saito, H.; Nakagawa, M. *Tetrahedron Lett.* **2000**, *41*, 4791−4794.
(29) Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, 1039−1042.
(30) Dayoub, W.; Diab, Y.; Doutheau, A. *Tetrahedron Lett.* **2001**, *42*, 8455−8457.
(31) Ronan, B.; Bacqué, E.; Barrière, J.-C. *Tetrahedron* **2004**, *60*, 3819−3824.

SCHEME 6



SCHEME 7



rearrangement product **30** upon dirhodium(II) tetraoctanoate- catalyzed decomposition.[32] In contrast, Konopelski observed only oxazole **31** formation on Lewis acid-catalyzed reaction of an indolyl diazoketoester with acetonitrile (Scheme 6).[33]

Wolff Rearrangement vs Insertion: Effect of Indole Structure. Our rationale was that the prevalence for Wolff rearrangement of the indolyl diazoketone **25** was due to the electronic properties of the indole heterocycle. This view was reinforced when the analogous phenyldiazoketone **32**[26] when treated with dirhodium(II) tetraoctanoate in the presence of hexanamide underwent clean N−H insertion (88%) to give ketoamide **33**, cyclodehydration of which gave the expected oxazole **34** in good yield (Scheme 7).

Therefore we investigated a range of other indolyl diazoketones in which the electronic properties of the indole ring were modified by the presence of a chlorine at the 2-position, or attenuated by different substituents on nitrogen [methyl, Boc, benzenesulfonyl (Bs), 2-nitrobenzenesulfonyl (Ns)]. Indolyl diazoketoesters (**36**, **38**, **40**) were readily prepared from the corresponding indole-3-carboxaldehydes (**35**, **37**, **39**) by using the same two step procedure as for diazo compound **25**. The benzothiophene derivative **42** was also prepared from benzothiophene-3-carboxaldehyde **41** for comparison. The *N*-methylindole diazoketone **44** was prepared from 3-acetyl-1-methylindole **43** by acylation of the enolate with ethyl cyanoformate followed by diazo transfer reaction, using 4-acetamidobenzenesulfonyl azide.[34] Finally, the 2-indolyl diazoketoester **46** was prepared from the aldehyde **45** in the same way as the analogous 3-indolyl isomer **25** (Scheme 8).

SCHEME 8

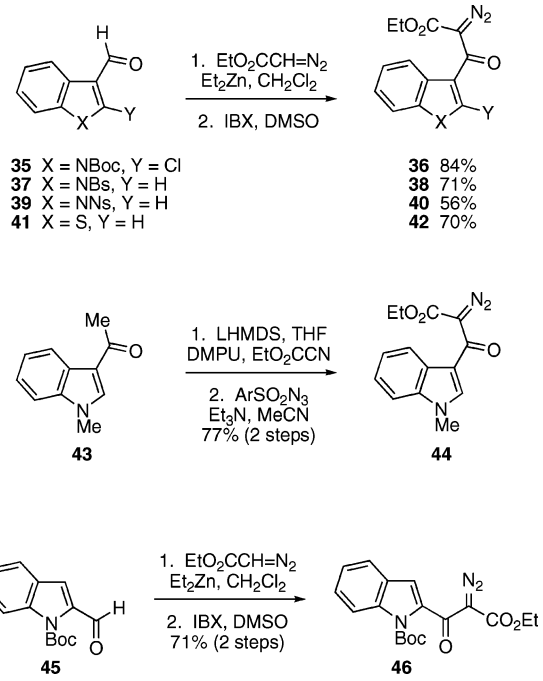
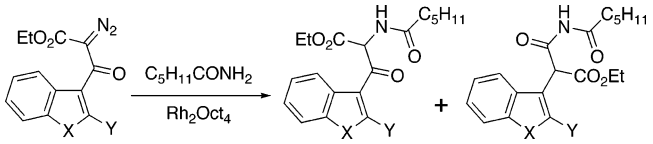


TABLE 1. Competing N−H Insertion and Wolff Rearrangement in the Dirhodium Tetraoctanoate-Catalyzed Reactions of 3-Indolyl and 3-Benzothienyl Diazoketoesters



diazo	X	Y	N−H insertion	yield/%	Wolff	yield/%
25	NBoc	H	**26**	39	**27**	55
36	NBoc	Cl	**47**	47	**48**	38
38	NBs	H	**49**	52	**50**	23
40	NNs	H	**51**	52		0
44	NMe	H		0	**52**	81
42	S	H	**53**	38	**54**	30

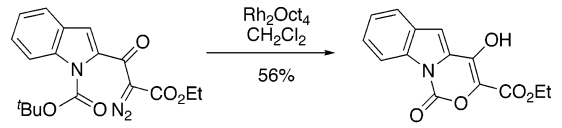
The six new diazoketones were all reacted with hexanamide under similar conditions in the presence of dirhodium(II) tetraoctanoate and the results are shown in Table 1. The most significant result to emerge is that the Wolff rearrangement is suppressed by more electron-withdrawing substituents on the indole nitrogen. Thus the *N*-methyl derivative **44** leads to only Wolff rearrangement whereas the *N*-(2-nitrobenzenesulfonyl) derivative **40** gives only N−H insertion, with the *N*-Boc and *N*-Bs compounds being intermediate in reactivity. The effect of the chlorine substituent is less marked, although less Wolff rearrangement is observed than with its unchlorinated analogue. The benzothiophene diazoketoester **42** behaves similarly to the *N*-Boc-2-chloroindole

(32) Marsden, S. P.; Pang, W.-K. *J. Chem. Soc., Chem. Commun.* **1999**, 1199−1200.

(33) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Véliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609−611.

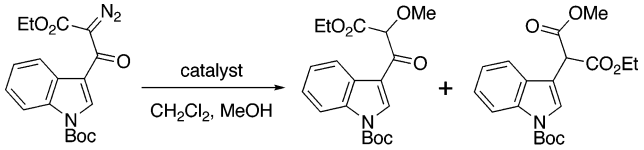
(34) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709−1716.

SCHEME 9



46 55

TABLE 2. Competing O−H Insertion and Wolff Rearrangement in Catalyzed Reactions of 3-Indolyl Diazoketoester 25: Ratio of Insertion Product 56 to Wolff Rearrangement 57



25 56 57

entry	catalyst	O−H insertion[a] **56**	Wolff rearrangement[a] **57**
1	$Rh_2(OAc)_4$	1	2
2	Rh_2Oct_4	2	1
3	$Rh_2(OCOCF_3)_4$	1	3
4	$Rh_2(NHCOC_3F_7)_4$	4	1
5	$Cu(acac)_2$		trace[b]
6	$RuCl_2(Ph_3P)_3$	6	1[b]
7	$FeCl_3$		trace[b]
8	$Sc(OTf)_3$		trace[b]
9	$BF_3{\cdot}Et_2O$		trace[b]

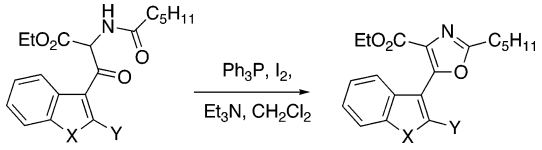
[a] Ratio as determined by ^{1}H NMR. [b] Diazoketoester is recovered largely unchanged.

36. The results are consistent with more electron-rich groups migrating more easily to the electron-deficient carbene (or rhodium carbene) center.

In the case of 2-indolyl diazoketoester **46**, an entirely different result was observed upon dirhodium(II)-catalyzed reaction in the presence of hexanamide. Neither N−H insertion nor Wolff rearrangement occurred; instead intramolecular capture of the rhodium carbene by the Boc-group carbonyl oxygen supervened to give, after loss of isobutene, the oxazinoindole **55** in 56% yield (Scheme 9).

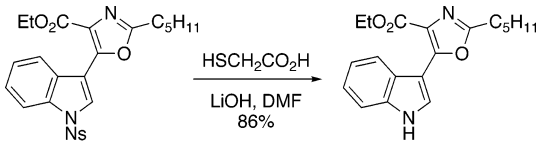
Wolff Rearrangement vs Insertion: Effect of Catalyst. To study the effect of catalyst, the indolyl diazoketoester **25** was decomposed in dichloromethane in the presence of methanol (ca. 10 equiv). Methanol was chosen as the reactant to facilitate analysis of the reaction mixture by ^{1}H NMR spectroscopy since the O−H insertion product **56** is readily distinguishable from the product **57** of Wolff rearrangement/ketene trapping. The results are shown in Table 2. Although the catalysts were studied under identical conditions, only the dirhodium(II) catalysts were effective in causing rapid reaction of the diazoketoester **25**. As expected on the basis of our previous work,[35] the fluorinated amide ligand proved the most effective for carbene insertion. Although others have reported that $Cu(acac)_2$,[36] $Sc(OTf)_3$,[37] and $RuCl_2(Ph_3P)_3$[38] are effective catalysts for diazo decomposition and subsequent N−H insertion reactions, they proved ineffective in the present case. Likewise iron(III) chloride and boron trifluoride etherate also proved ineffective.

TABLE 3. Cyclodehydration of Ketoamides to 5-(3-Indolyl)oxazoles and a 5-(3-Benzothienyl)oxazole



ketoamide	X	Y	oxazole	yield/%
26	NBoc	H	**58**	78
47	NBoc	Cl	**59**	80
49	NBs	H	**60**	65
51	NNs	H	**61**	85
53	S	H	**62**	75

SCHEME 10



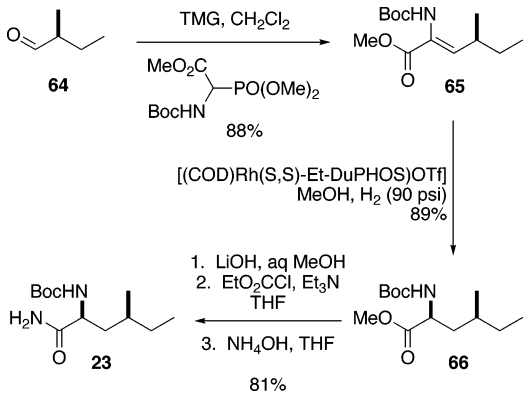
61 63

Cyclodehydration of Ketoamides: Synthesis of 5-(3-Indolyl)oxazoles. Although the dirhodium(II)-catalyzed reactions of diazoketoesters led to mixtures of ketoamides (from N−H insertion) and imides (from Wolff rearrangement), the ketoamides were isolated in sufficient quantity to allow subsequent Robinson−Gabriel cyclodehydration. Thus the ketoamides **26**, **47**, **49**, **51**, and **53** were readily cyclodehydrated to the corresponding oxazoles **58**−**62**, using the Wipf $Ph_3P/I_2/Et_3N$ method (Table 3).[39] The structure of the 5-(3-indolyl)oxazole **58** was confirmed by X-ray crystallography (see the Supporting Information), and the nosyl protecting group was readily removed from indolyloxazole **61** to give **63** in high yield (Scheme 10) with use of the standard Fukuyama protocol.[40]

Formal Synthesis of Normartefragin A and Martefragin A. To adapt our indolyl diazocarbonyl methodology to the synthesis of martefragin A, the amide derivative **23** of (*S,S*)-homoisoleucine was required (Scheme 3). In their synthesis, Nishida et al. prepared (*S,S*)-*N*-Boc-homoisoleucine in a linear nine-step sequence starting from (*R*)-citronellol and introducing the second stereogenic center by azidation of an Evans' oxazolidinone.[8] We elected to use a shorter sequence starting from commercially available (*S*)-2-methylbutanol, oxidation of which with $TEMPO/NaClO_2$ gave the corresponding aldehyde **64**,[41] a compound reported to participate in Wittig olefination reactions without racemization.[41−43] The Horner−Wadsworth−Emmons reaction of aldehyde **64** with trimethyl 2-(*tert*-butoxycarbonylamino)-phosphonoacetate, itself prepared in an N−H insertion

(35) Cox, G. G.; Kulagowski, J. J.; Moody, C. J.; Sie, E.-R. H. B. *Synlett* **1992**, 975−976.
(36) Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2277−2280.
(37) Pansare, S. V.; Jain, R. P.; Bhattacharyya, A. *Tetrahedron Lett.* **1999**, *40*, 5255−5258.
(38) Sengupta, S.; Das, D.; Sen Sarma, D. *Tetrahedron Lett.* **1996**, *37*, 8815−8818.
(39) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.
(40) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353−359.
(41) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Omura, S. *Org. Lett.* **2001**, *3*, 2289−2291.

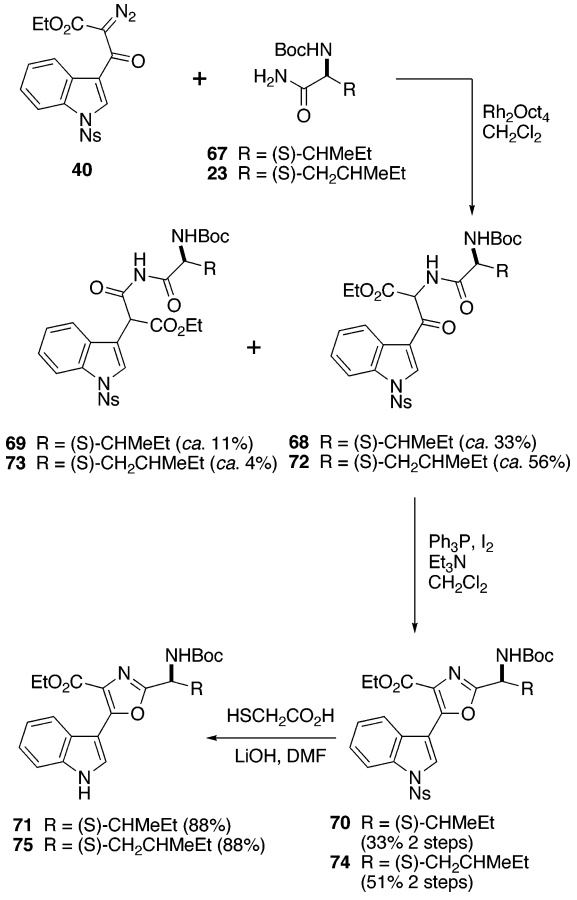
SCHEME 11



reaction by dirhodium(II)-catalyzed reaction of trimethyl diazophosphonoacetate with *tert*-butyl carbamate,[44] using DBU as base at room temperature, gave the desired dehydro amino acid **65**. NOE studies established the geometry of the dehydro amino acid as (*Z*), as expected from the use of the Schmidt method,[45] but unfortunately, HPLC analysis on a chiral stationary phase suggested that some epimerization had occurred during the olefination step (**65**, ca. 75% ee). The amount of epimerization could be reduced significantly by running the reaction at 0 °C, although the yield was reduced from 78% to 42%. However, use of tetramethylguanidine (TMG) as base resulted in both high yield (88%) and improved ee (ca. 95%), although the material could never be obtained as a pure single enantioner. Asymmetric hydrogenation of the dehydro amino acid **65** in methanol with Burk's (*S*,*S*)-EtDuPHOS system, [(+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate],[46,47] gave the protected (S,S)-homoisoleucine **66** in high yield. The Et-DuPHOS catalyst system is extremely effective for the asymmetric hydrogenation of dehydro amino acids and generally proceeds with excellent stereocontrol. Hence the fact that small amounts of another diastereomer of **66** were observed in the ^{13}C NMR spectrum were attributed to the fact that the starting alkene **65** was not enantiomerically pure; unfortunately, the presence of small amounts of a diastereomer persisted to the end of the synthesis. Finally, the homoisoleucine ester **66** was converted into the required amide **23** by standard methodology (Scheme 11).

On the basis of the earlier studies on the competing N−H insertion and Wolff rearrangement processes, we elected to use the *N*-(2-nitrobenzenesulfonyl) (nosyl) indole derivative **40** as the diazoketoester component together with a dirhodium(II) catalyst. However, before committing our precious homoisoleucine amide **23**, we

SCHEME 12



ran through the sequence of reactions using the readily available isoleucine derived amide **67**. The dirhodium-(II)-catalyzed reaction of **40** with **67** did indeed give the required N−H insertion product **68**, although the yield was poor (ca. 33%) and it could not be separated from the Wolff rearrangement product **69** (ca. 11%). Nevertheless, when the mixture was subjected to standard cyclodehydration conditions, the indolyloxazole **70** was readily obtained in pure form (33% over two steps) and deprotected to give the normartefragin A precursor **71** (Scheme 12). Fortunately, when the homoisoleucine amide **23** was used in the dirhodium(II)-catalyzed reaction of diazoketoester **40**, not only was the overall yield better (ca. 60%), but the ratio of N−H insertion **72** to Wolff rearrangement **73** was also much improved (ca. 16:1), with the Wolff rearrangement effectively completely suppressed. Again, the two products **72/73** could not be separated, so the mixture was cyclodehydrated. This resulted in the formation of the desired indolyl oxazole **74** (51% over the two steps), deprotection of which gave indolyl oxazole **75**, a potential precursor to martefragin A **6** (Scheme 12), since Nishida et al. have shown that the NHBoc substituent can be converted into the dimethylamino substituent of the natural product.[8]

Conclusions

The above work has shown that our previously reported efficient synthesis of 5-R-oxazoles from amides, $RCONH_2$, by rhodium carbene N−H insertion does not necessarily extend to 3-indolyl diazoketoesters owing to

(42) Ley, S. V.; Armstrong, A.; Diez-Martin, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 667−692.
(43) El Hadrami, M.; Lavergne, J.-P.; Viallefont, P.; Itto, M. Y. A.; Hasnaoui, A. *Tetrahedron Lett.* **1991**, *32*, 3985−3988.
(44) Ferris, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2885−2888.
(45) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.
(46) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.
(47) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37−44.

the propensity of the indole moiety to migrate in Wolff rearrangements. However, the competing Wolff rearrangement and the desired N−H insertion processes can be effectively controlled by the appropriate choice of indole *N*-protecting group, strong electron-withdrawing groups favoring the carbene (rhodium carbene) insertion. Armed with this knowledge, the diazocarbonyl methodology has been applied in a synthesis of a potential precursor to the marine natural product martefragin A.

Experimental Section

General Experimental Details. 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. 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 were 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. Specific rotations are quoted in 10^{-1} deg cm^2 g^{-1}.

Reaction of Aldehydes with Ethyl Diazoacetate and Diethylzinc for the Formation of β-Ketodiazoesters. (a) 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 then the mixture was stirred for 30 min. A solution of the aldehyde (1.9 mmol) in dichloromethane (5 mL) was then added and the resulting solution was stirred for 2 h maintaining the temperature below −50 °C and then allowed to warm to room temperature overnight. The reaction was then quenched with concentrated aqueous ammonia (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (ethyl acetate−light petroleum) (1:4) to give the still impure hydroxydiazoindole that was carried through to the next stage without further purification.

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

Ethyl (1-*tert*-Butoxycarbonylindol-3-yl)-2-diazo-3-oxopropanoate, 25. According to the above general procedure, the title product was isolated from 1-*tert*-butoxycarbonylindole-3-carboxaldehyde **24**[48] (4.5 g, 18.3 mmol) as a yellow crystalline solid (4.3 g, 12.1 mmol, 66%); mp 89−91 °C; IR (KBr/cm^{-1}) 2139 (C=N_2), 1740 (C=O); ^1H NMR (300 MHz; $CDCl_3$) δ 8.61 (1H, s), 8.20 (1H, m), 8.13 (1H, m), 7.35 (2H, m), 4.32 (2H, q, *J* = 7.2), 1.70 (9H, s), 1.32 (3H, t, *J* = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 178.4, 160.6, 148.3, 134.1, 132.8 (CH), 127.6, 124.5 (CH), 123.4 (CH), 121.3 (CH), 116.7, 114.2 (CH), 84.4, 60.8 (CH_2), 27.3 (Me), 13.5 (Me), diazo carbon not observed; *m/z* (CI) 357 (MH^+, 6%), 302 (100). Found: C, 60.8; H, 5.2; N, 11.6. $C_{18}H_{19}N_3O_5$ requires: C, 60.5; H, 5.4; N, 11.8.

Ethyl 3-(1-*tert*-Butoxycarbonyl-2-chloroindol-3-yl)-2-diazo-3-oxopropanoate, 36. According to the above general procedure, the title product was isolated from 1-*tert*-butoxycarbonyl-2-chloroindole-3-carboxaldehyde **35**[49] (1.2 g, 4.3 mmol) as a yellow crystalline solid (1.4 g, 3.6 mmol, 84%), mp 120 °C dec; IR (KBr/cm^{-1}) 2141 (C=N_2), 1752 (C=O; ^1H NMR (300 MHz; $CDCl_3$) δ 7.98 (1H, d, *J* = 7.7), 7.53 (1H, dd, *J* = 1.3, 7.0), 7.27−7.19 (2H, m), 4.16 (2H, q, *J* = 7.1), 1.63 (9H, s), 1.13 (3H, t, *J* = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 179.1, 159.8, 147.5, 134.0, 125.2, 125.1, 124.3 (CH), 123.1 (CH), 118.5 (CH), 117.2, 114.2 (CH), 85.2, 77.2, 60.9 (CH_2), 27.2 (Me), 13.2 (Me); *m/z* (FI) 391 (M^+, 100%). Found: M^+, 391.0939. $C_{18}H_{18}{}^{35}ClN_3O_5$ requires: 391.0935.

Ethyl 3-(1-Benzenesulfonylindol-3-yl)-2-diazo-3-oxopropanoate, 38. According to the above general procedure, the title product was isolated from 1-benzenesulfonylindole-3-carboxaldehyde **37**[50] (1.2 g, 4.2 mmol) as a yellow crystalline solid (1.2 g, 3.0 mmol, 71%), mp 131−133 °C dec; IR (KBr/cm^{-1}) 2136 (C=N_2), 1716 (C=O); ^1H NMR (300 MHz; $CDCl_3$) δ 8.66 (1H, s), 8.19−8.16 (1H, m), 8.00−7.93 (3H, m), 7.61−7.55 (1H, m), 7.51−7.46 (2H, m), 7.36−7.32 (2H, m), 4.35 (2H, q, *J* = 7.0), 1.35 (3H, t, *J* = 7.0); ^{13}C NMR (75 MHz; $CDCl_3$) δ 179.3, 161.5, 138.0, 134.8 (CH), 134.6, 134.2 (CH), 129.9 (CH), 129.1, 127.6 (CH), 126.0 (CH), 125.2 (CH), 123.0 (CH), 118.7, 113.5 (CH), 78.5, 62.1 (CH_2), 14.7 (Me); *m/z* (CI) 398 (MH^+, 100%). Found: C, 57.2; H, 3.6; N, 10.5. $C_{19}H_{15}N_3O_5S$ requires: C, 57.4; H, 3.8; N, 10.6.

Ethyl 2-Diazo-3-[1-(2-nitrobenzenesulfonyl)indol-3-yl]-3-oxopropanoate, 40. According to the above general procedure, 1-(2-nitrobenzenesulfonyl)indole-3-carboxaldehyde **39** (300 mg, 0.9 mmol) was converted to the title compound, which was obtained as a pale yellow crystalline solid (223 mg, 0.5 mmol, 56%), mp 150−151 °C; IR (KBr/cm^{-1}) 2146 (C=N_2), 1706 (C=O); ^1H NMR (300 MHz; $CDCl_3$) δ 8.64 (1H, s), 8.24 (1H, d, *J* = 7.4), 7.97−7.94 (1H, dd, *J* = 0.5, 7.4), 7.81−7.65 (4H, m), 7.38−7.35 (2H, m), 4.34 (2H, q, *J* = 7.1), 1.34 (3H, t, *J* = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 179.3, 161.4, 148.4, 135.8 (CH), 134.7 (CH), 134.5, 133.2 (CH), 131.5, 130.8 (CH), 129.0, 126.2 (CH), 125.7 (CH), 125.5 (CH), 123.3 (CH), 118.7, 113.4 (CH), 78.6, 62.2 (CH_2), 14.7 (Me); *m/z* (CI) 443 (M^+, 6%), 415 (13), 146 (100). Found: MH^+, 443.0663. $C_{19}H_{15}N_4O_7S$ requires: 443.0661.

Ethyl 3-(Benzothien-3-yl)-2-diazo-3-oxopropanoate, 42. According to the above general procedure, the title product was isolated from benzothiophene-3-carboxaldehyde **41** (1.2 g, 7.4 mmol) as a yellow crystalline solid (1.4 g, 5.2 mmol, 70%), mp 35−37 °C; IR (KBr/cm^{-1}) 2136 (C=N_2), 1711 (C=O); ^1H NMR (300 MHz; $CDCl_3$) δ 8.25 (1H, dd, *J* = 0.9, 7.2), 8.20 (1H, s), 7.86 (1H, dd, *J* = 1.5, 7.3), 7.48−7.37 (2H, m), 4.26 (2H, q, *J* = 7.2), 1.25 (3H, t, *J* = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 178.3, 159.5, 137.7 (CH), 135.4, 134.1, 131.0, 123.9 (CH), 123.6 (CH), 122.6 (CH), 120.8 (CH), 60.1 (CH_2), 12.6 (Me), diazo C not observed; *m/z* (FI) 274 (M^+, 100%).Found: C, 56.7; H, 3.4; N, 10.3. $C_{13}H_{10}N_2O_3S$ requires: C, 56.9; H, 3.7; N, 10.2.

Ethyl 3-(1-*tert*-Butoxycarbonylindol-2-yl)-2-diazo-3-oxopropanoate, 46. According to the above general procedure, the title product was isolated from 1-*tert*-butoxycarbonylindole-2-carboxaldehyde **45**[51] (1.2 g 4.9 mmol) as a yellow crystalline solid (1.3 g, 3.5 mmol, 71%), mp 70−72 °C; IR (KBr/cm^{-1}) 2134 (C=N_2), 1739 (C=O), 1696 (C=O); ^1H NMR (300 MHz; $CDCl_3$) δ 8.13 (1H, d, *J* = 8.4), 7.58 (1H, d, *J* = 7.8), 7.41−7.35 (2H, m), 6.80 (1H, s), 4.15 (2H, q, *J* = 7.1), 1.61 (9H, s), 1.11 (3H, t, *J* = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 180.5, 161.3, 149.6, 136.3, 135.9, 128.7, 126.6 (CH), 123.6 (CH), 122.3 (CH), 115.8 (CH), 111.4 (CH), 85.2, 62.0 (CH_2), 28.3 (Me), 14.5 (Me), diazo C not observed; *m/z* (CI) 358 (MH^+, 40%), 357 (13), 302 (100). Found: C, 60.4; H, 5.4; N, 11.7. $C_{18}H_{19}N_3O_5$ requires: C, 60.5; H, 5.4; N, 11.8.

(48) Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E.-M. *Synthesis* **1998**, 1501−1505.

(49) Kutschy, P.; Suchy, M.; Andreani, A.; Dzurilla, M.; Kovácik, V.; Alföldi, J.; Rossi, M.; Gramatová, M. *Tetrahedron* **2002**, *58*, 9029−9039.

(50) Gribble, G. W.; Jiang, J.; Liu, Y. *J. Org. Chem.* **2002**, *67*, 1001−1003.

(51) Carlier, P. R.; Lam, P. C.-H.; Wong, D. M. *J. Org. Chem.* **2002**, *67*, 6256−6259.

Ethyl 2-Diazo-3-(1-methylindol-3-yl)-3-oxopropanoate ,44. (a) To a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.9 mL, 9.0 mmol) in THF (25 mL) cooled to 0 °C was added *n*-butyllithium (1.6 M in hexanes; 5.6 mL, 9.0 mmol) and the resulting mixture was stirred for 30 min before being cooled to −78 °C. A solution of 3-acetyl-1-methyl indole **43**[52] (780 mg, 4.5 mmol) in THF (20 mL) was added to the reaction over 20 min. After stirring for a further 1 h, DMPU (0.54 mL, 4.5 mmol) and then ethyl cyanoformate (0.89 mL, 9.0 mmol) were added to the reaction mixture. The mixture was then stirred for a further 30 min before being quenched with water (60 mL) and extracted with ether (3 × 75 mL). The combined organic extractions were washed with brine, dried ($MgSO_4$), concentrated in vacuo, and then purified by column chromatography (ethyl acetate/light petroleum) to yield ethyl 3-(1-methylindol-3-yl)-3-oxopropanoate as a yellow crystalline solid (897 mg, 3.7 mmol, 82%), mp 72−74 °C (ethyl acetate/light petroleum); IR (KBr/cm^{-1}) 1736 (C=O), 1635 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.37−8.34 (1H, m), 7.73 (1H, s), 7.31−7.28 (3H, m), 4.20 (2H, q, J = 7.2), 3.83 (2H, s), 3.80 (3H, s), 1.26 (3H, t, J = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 186.6, 168.6, 137.9, 137.0 (CH), 126.7, 124.1 (CH), 123.3 (CH), 122.9 (CH), 116.2, 110.2 (CH), 61.8 (CH_2), 47.8 (CH_2), 34.0 (Me), 14.6 (Me); *m/z* (FI) 245 (M^+, 100%). Found: C, 68.4; H, 6.1; N, 5.6. $C_{14}H_{15}NO_3$ requires: C, 68.6; H, 6.2; N, 5.7.

(b) To a solution of the above β-ketoester (1.0 g, 4.1 mmol) and 4-acetamidobenzenesulfonyl azide[34] (4.5 mmol) in acetonitrile (30 mL) at 0 °C was added triethylamine (12 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 title compound as a yellow solid (1.05 g, 3.9 mmol, 94%), mp 125 °C dec; IR (KBr/cm^{-1}) 2136 (C=N$_2$), 1711 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.39−8.35 (1H, m), 8.29 (1H, s), 7.36−7.25 (3H, m), 4.30 (2H, q, J = 7.2), 3.81 (3H, s), 1.34 (3H, t, J = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 178.0, 162.5, 138.2 (CH), 137.2, 128.1, 123.7 (CH), 123.1 (CH), 122.9 (CH), 113.8, 110.0 (CH), 61.7 (CH_2), 34.1 (Me), 14.8 (Me), diazo C not observed; *m/z* (FI) 271 (M^+, 100%). Found: C, 61.6; H, 4.6; N, 15.4. $C_{14}H_{13}N_3O_3$ requires: C, 62.0; H, 4.8; N, 15.5.

Reaction of Ethyl (1-*tert*-Butoxycarbonylindol-3-yl)-2-diazo-3-oxopropanoate, 25, with Hexanamide. To a solution of hexanamide (500 mg, 4.3 mmol) and dirhodium tetraoctanoate (85 mg, 0.1 mmol) in dichloromethane (10 mL) heated under reflux was added diazo indole **25** (1.9 g, 5.3 mmol) in dichloromethane (10 mL) over 16 h. The reaction mixture was then 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-*tert*-butoxycarbonylindol-3-yl)-*N*-hexanoylmalonamate **27** as a pale yellow oily solid (1.1 g, 2.4 mmol, 55%); IR (KBr/cm^{-1}) 3269 (N−H), 1738 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.06, (1H, s), 8.14 (1H, d, J = 7.9), 7.71 (1H, s), 7.56 (1H, d, J = 7.9), 7.33 (1H, app. t, J = 7.2), 7.23 (1H, app. t, J = 7.2), 5.21 (1H, s), 4.25 (2H, m), 2.61 (2H, t, J = 5.6), 1.66 (9H, s), 1.59 (2H, app. t, J = 5.6), 1.27 (7H, m), 0.86 (3H, t, J = 5.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.6, 168.2, 167.3, 149.3, 135.4, 128.9, 125.4 (CH), 125.0 (CH), 123.0 (CH), 119.4 (CH), 115.4 (CH), 112.0, 84.2, 62.3 (CH_2), 51.5 (CH), 37.4 (CH_2), 31.1 (CH_2), 28.1 (Me), 23.8 (CH_2), 22.3 (CH_2), 14.0 (Me), 13.9 (Me); *m/z* (CI) 445 (MH^+, 10%), 444 (5), 116 (100). Found: MH^+, 445.2333. $C_{24}H_{33}N_2O_6$ requires: 445.2338). (ii) Ethyl 3-(1-*tert*-butoxycarbonylindol-3-yl)-2-hexanoylamino-3-oxopropanoate **26** as a colorless crystalline solid (749 mg, 1.7 mmol, 39%), mp 108−110 °C; IR (KBr/cm^{-1}) 3431 (N−H), 1745 (C=O), 1664 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.69 (1H, s), 8.33−8.30 (1H, m), 8.18 (1H, d, J = 7.6), 7.42−7.34 (2H, m), 6.96 (1H, d, J = 7.2), 5.94 (1H, d, J = 7.3), 4.24−4.17 (2H, m), 2.38−2.27 (2H, m), 1.71−1.66 (11H, m), 1.34−1.30 (4H, m), 1.23 (3H, t, J = 7.1), 0.88 (3H, t, J = 7.0); ^{13}C NMR (100 MHz; $CDCl_3$) δ 185.9, 173.0, 167.0, 148.6, 135.6, 135.3 (CH), 127.2, 126.0 (CH), 124.8 (CH), 122.4 (CH), 117.2, 115.1 (CH), 85.9, 62.5 (CH_2), 59.6 (CH), 36.2 (CH_2), 31.3 (CH_2), 28.1 (Me), 25.2 (CH_2), 22.4 (CH_2), 13.9 (2 × Me); *m/z* (CI) 445 (MH^+, 11%), 345 (100). Found: C, 64.7; H, 7.3; N, 6.0. $C_{24}H_{32}N_2O_6$ requires: C, 64.9; H, 7.3; N, 6.3.

Ethyl 2-(1-*tert*-Butoxycarbonylindol-3-yl)-*N*-(4-bromobenzoyl)-malonamate, 28. To a solution of 4-bromobenzamide (500 mg, 2.5 mmol) and dirhodium tetraacetate (30 mg, 0.06 mmol) in 1,2-dichloroethane (22 mL), heated to reflux, was added a solution of the diazo indole **25** (1.2 g, 3.2 mmol) in the same solvent dropwise over 16 h. The reaction mixture was then heated for a further 2−4 h until complete by TLC and then evaporated in vacuo and purified on silica gel eluting with ethyl acetate−light petroleum (1:4) to yield the title compound as a colorless crystalline solid (75%), mp 156−158 °C (hexanes); IR (film/cm^{-1}) 3296 (N−H), 1730 (C=O), 1687 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.45 (1H, br s), 8.09 (1H, d, J = 8.4), 7.63 (2H, d, J = 8.5), 7.57 (1H, d, J = 7.9), 7.45 (2H, d, J = 8.6), 7.29 (1H, app. t, J = 7.2), 7.21−7.16 (2H, m), 5.56 (1H, s), 4.23−4.14 (2H, m), 5.56 (9H, s), 1.19 (3H, t, J = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 169.6, 168.9, 165.3, 149.8, 135.8, 132.5 (CH), 131.3, 129.9 (CH), 129.6, 129.0, 126.0 (CH), 125.3 (CH), 123.4 (CH), 120.2 (CH), 115.8 (CH), 112.8, 84.6, 62.7 (CH_2), 52.1 (CH), 28.6 (Me), 14.4 (Me); *m/z* (CI) 531/529 (MH^+, 2%), 200 (100). Found: MH^+, 529.0990. $C_{25}H_{26}{}^{79}BrN_2O_6$ requires: 529.0974.

Ethyl 2-Hexanoylamino-3-oxo-3-phenylpropanoate, 33. According to the above procedure, hexanamide (240 mg, 2.1 mmol) and diazoindole **32**[26] (545 mg, 2.5 mmol) in dichloromethane yielded the title compound as a colorless oil (561 mg, 1.8 mmol, 88%); IR (film/cm^{-1}) 3373 (N−H), 1751 (C=O), 1661 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.15−8.11 (2H, m), 7.67−7.61 (1H, m), 7.53−7.48 (2H, m), 6.90 (1H, d, J = 7.5), 6.22 (1H, d, J = 7.5), 4.17 (2H, q, J = 7.2), 2.31 (2H, t, J = 6.6), 1.71−1.61 (2H, m), 1.37−1.27 (4H, m), 1.15 (3H, t, J = 7.2), 0.88 (3H, t, J = 6.8); ^{13}C NMR (75 MHz; $CDCl_3$) δ 192.3, 173.4, 167.2, 134.8 (CH), 134.6, 130.0 (CH), 129.2 (CH), 62.9 (CH_2), 58.5 (CH), 36.6 (CH_2), 31.7 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 14.3 (Me), 14.2 (Me); *m/z* (FI^+) 305 (M^+, 83%), 105 (100). Found: M^+, 305.1620. $C_{17}H_{23}NO_4$ requires: 305.1627.

Reaction of Ethyl 3-(1-*tert*-Butoxycarbonyl-2-chloroindol-3-yl)-2-diazo-3-oxopropanoate, 36, with Hexanamide. To a solution of hexanamide (200 mg, 1.7 mmol) and dirhodium tetraoctanoate (90 mg, 0.1 mmol) in dichloromethane (45 mL) heated under reflux was added diazo indole **36** (816 mg, 2.1 mmol) in dichloromethane (15 mL) over 16 h. The reaction mixture was then 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-*tert*-butoxycarbonyl-2-chloroindol-3-yl)-*N*-hexanoylmalonamate **48** as a colorless crystalline solid (315 mg, 0.7 mmol, 38%), mp 98−101 °C; IR (KBr/cm^{-1}) 3252 (N−H), 1737 (C=O), 1701 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.83 (1H, s), 8.10 (1H, d, J = 8.3), 7.52 (1H, dd, J = 0.8, 7.9), 7.34−7.23 (2H, m), 5.40 (1H, s), 4.26−4.18 (2H, m), 2.61 (2H, t, J = 7.4), 1.69 (9H, s), 1.68−1.59 (2H, m), 1.33−1.26 (4H, m), 1.22 (3H, t, J = 7.1), 0.87 (3H, t, J = 6.8); ^{13}C NMR (75 MHz; $CDCl_3$) δ 175.0, 168.3, 167.9, 149.4, 136.1, 127.3, 125.7 (CH), 125.6, 124.2 (CH), 120.1 (CH), 116.0 (CH), 112.1, 86.2, 63.1 (CH_2), 51.6 (CH), 38.2 (CH_2), 31.9 (CH_2), 28.9 (Me), 24.6 (CH_2), 23.1 (CH_2), 14.8 (Me), 14.6 (Me); *m/z* (CI) 481/479 (MH^+, 29/58%), 379 (100). Found: MH^+, 479.1945. $C_{24}H_{32}{}^{35}ClN_2O_6$ requires: 479.1949. (ii) Ethyl 3-(1-*tert*-butoxycarbonyl-2-chloroindol-3-yl)-2-hexanoylamino-3-oxopropanoate **47** as an orange oil (394 mg, 0.8 mmol, 47%); IR (film/cm^{-1}) 3256 (N−H), 1753 (C=O),

(52) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1968**, *24*, 1145−1162.

1653 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.19−8.15 (1H, m), 7.99−7.96 (1H, m), 7.35−7.30 (2H, m), 6.86 (1H, d, J = 7.7), 6.57 (1H, d, J = 7.7), 4.15 (2H, q, J = 7.1), 2.33−2.28 (2H, t, J = 7.3), 1.69−1.63 (11H, m), 1.32−1.27 (4H, m), 1.12 (3H, t, J = 7.1), 0.86 (3H, t, J = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 188.5, 173.4, 167.2, 148.4, 135.3, 130.9, 126.4, 126.1 (CH), 125.1 (CH), 121.7 (CH), 116.9, 114.7 (CH), 87.3, 62.7 (CH_2), 60.1 (CH), 36.5 (CH_2), 31.7 (CH_2), 28.4 (Me), 25.5 (CH_2), 22.7 (CH_2), 14.3 (Me), 14.2 (Me); *m/z* (CI) 481/479 (MH^+, 24/66%), 289 (100). Found: MH^+, 479.1946. $C_{24}H_{32}{}^{35}ClN_2O_6$ requires: 479.1949.

Reaction of Ethyl 3-(1-Benzenesulfonylindol-3-yl)-2-diazo-3-oxopropanoate, 38, with Hexanamide. To a solution of hexanamide (250 mg, 2.2 mmol) and dirhodium tetraoctanoate (43 mg, 0.06 mmol) in dichloromethane (45 mL) heated under reflux was added diazo indole **38** (1.5 g, 53.8 mmol) in dichloromethane (20 mL) over 16 h. The reaction mixture was then 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*-hexanoylmalonamate **50** as a colorless solid (240 mg, 0.5 mmol, 23%), mp 153−155 °C; IR (KBr/cm^{-1}) 3257 (N−H), 1737 (C=O), 1726 (C=O), 1685 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.62 (1H, s, NH), 7.98 (1H, d, J = 8.2), 7.91−7.88 (2H, m), 7.75 (1H, s), 7.56−7.53 (2H, m), 7.47−7.43 (2H, m), 7.36−7.32 (1H, m), 7.27−7.23 (1H, m), 5.20 (1H, s), 4.28−4.19 (2H, m), 2.58 (2H, t, J = 7.4), 1.65−1.55 (2H, m), 1.33−1.22 (7H, m, 2 × CH_2 + OCH_2*Me*), 0.87 (3H, t, J = 6.8); ^{13}C NMR (75 MHz; $CDCl_3$) δ 174.5, 168.3, 167.1, 138.3, 134.4 (CH), 129.8 (CH), 129.7, 127.2 (CH), 126.2 (CH), 125.7 (CH), 124.1 (CH), 120.5 (CH), 112.4, 114.0 (CH), 62.8 (CH_2), 51.7 (CH), 37.9 (CH_2), 31.5 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 14.4 (Me), 14.3 (Me), one C not observed; *m/z* (CI) 485 (MH^+, 10%), 116 (100). Found: MH^+, 485.1739. $C_{25}H_{29}N_2O_6S$ requires: 485.1746. (ii) Ethyl 3-(1-benzenesulfonylindol-3-yl)-2-hexanoylamino-3-oxopropanoate **49** as a colorless oil (550 mg, 1.1 mmol, 52%); IR (film/cm^{-1}) 3384 (N−H), 1744 (C=O), 1663 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.76 (1H, s), 8.27−8.25 (1H, dd, J = 1.2, 7.0), 8.02−7.95 (3H, m), 7.61−7.56 (1H, m), 7.51−7.46 (2H, m), 7.41−7.29 (2H, m), 7.02 (1H, d, J = 7.4), 6.00 (1H, d, J = 7.4), 4.23−4.15 (2H, m), 2.34−2.28 (2H, m), 1.70−1.60 (2H, m), 1.30−1.26 (4H, m), 1.21 (3H, t, J = 7.2), 0.85 (3H, t, J = 6.8); ^{13}C NMR (75 MHz; $CDCl_3$) δ 186.4, 173.4, 167.3, 137.7, 135.7 (CH), 135.2 (CH), 135.1, 130.1 (CH), 127.8, 127.7 (CH), 126.6 (CH), 125.6 (CH), 123.3 (CH), 118.6, 113.6 (CH), 63.0 (CH_2), 60.0 (CH), 36.6 (CH_2), 31.7 (CH_2), 25.6 (CH_2), 22.8 (CH_2), 14.32 (Me), 14.30 (Me); *m/z* (CI) 485 (MH^+, 27%), 255 (100). Found: MH^+, 485.1750. $C_{25}H_{29}N_2O_6S$ requires: 485.1746.

Reaction of Ethyl 2-Diazo-3-[1-(2-nitrobenzenesulfonyl)indol-3-yl]-3-oxopropanoate, 40, with Hexanamide. According to general procedure used for compound **33**, hexanamide (100 mg, 0.9 mmol) and diazoindole **40** (480 mg, 1.1 mmol) were reacted in the presence of catalytic dirhodium tetraoctanoate to yield ethyl 2-hexanoylamino-3-[1-(2-nitrobenzenesulfonyl)indol-3-yl]-3-oxopropanoate **51** as an oily solid (240 mg, 0.45 mmol, 52%); IR (KBr/cm^{-1}) 3293 (N−H), 1721 (C=O), 1685 (C=O), 1655 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.73 (1H, s), 8.35 (1H, dd, J = 3.1, 6.2), 8.19 (1H, dd, J = 1.6, 6.7), 7.84−7.78 (4H, m), 7.42−7.39 (2H, m), 6.91 (1H, d, J = 7.1), 5.97 (1H, d, J = 7.1), 4.32−4.20 (2H, m), 2.34 (2H, t, J = 7.3), 1.71−1.64 (2H, m), 1.36−1.29 (4H, m), 1.26 (3H, t, J = 7.1), 0.89 (3H, t, J = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 186.7, 173.4, 167.1, 148.4, 136.5 (CH), 136.3 (CH), 134.9, 133.3 (CH), 131.6 (CH), 131.1, 127.9, 126.7 (CH), 126.0 (CH), 125.9 (CH), 123.7 (CH), 118.5, 113.3 (CH), 63.3 (CH_2), 60.3 (CH), 36.6 (CH_2), 31.7 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 14.3 (Me), 14.2 (Me); *m/z* (CI) 530 (M^+, 36%), 345 (100). Found: MH^+, 530.1600. $C_{25}H_{28}N_3O_5S$ requires: 530.1597.

Reaction of Ethyl 3-(Benzothien-3-yl)-2-diazo-3-oxopropanoate, 42, with Hexanamide. To a solution of hexanamide (520 mg, 4.5 mmol) and dirhodium tetraoctanoate (90 mg, 0.1 mmol) in dichloromethane (45 mL) heated under reflux was added diazo indole **42** (1.5 g, 5.5 mmol) in dichloromethane (15 mL) over 16 h. The reaction mixture was then 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-(benzothien-3-yl)-*N*-hexanoylmalonamate **54** as a pale green oily solid (497 mg, 1.4 mmol, 30%); IR (KBr/cm^{-1}) 3257 (N−H), 1737 (C=O), 1685 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.13 (1H, s), 7.88−7.81 (2H, m), 7.53 (1H, s), 7.40−7.36 (2H, m), 5.41 (1H, s), 4.29−4.20 (2H, m), 2.61 (2H, t, J = 7.4), 1.61−1.56 (2H, m), 1.32−1.15 (7H, m), 0.87 (3H, t, J = 6.7); ^{13}C NMR (75 MHz; $CDCl_3$) δ 174.9, 168.4, 167.0, 140.6, 138.0, 126.9, 126.7 (CH), 125.3 (CH), 125.0 (CH), 123.4 (CH), 122.3 (CH), 62.8 (CH_2), 54.2 (CH), 37.9 (CH_2), 31.5 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 14.4 (Me), 14.3 (Me); *m/z* (CI) 362 (MH^+, 100%). Found: MH^+, 362.1418. $C_{19}H_{24}NO_4S$ requires: 362.1426. (ii) Ethyl 3-(benzothien-3-yl)-2-hexanoylamino-3-oxopropanoate **53** as an oily yellow solid (630 mg, 1.7 mmol, 38%); IR (KBr/cm^{-1}) 3242 (N−H), 1753 (C=O), 1672 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.89 (1H, s), 8.71−8.68 (1H, m), 7.88 (1H, dd, J = 1.2, 7.6), 7.54−7.42 (2H, m), 6.93 (1H, d, J = 7.6), 6.14 (1H, d, J = 7.6), 4.21 (2H, q, J = 7.1), 2.32 (2H, t, J = 7.6), 1.72−1.64 (2H, m), 1.35−1.25 (4H, m), 1.20 (3H, t, J = 7.1), 0.87 (3H, t, J = 6.8); ^{13}C NMR (75 MHz; $CDCl_3$) δ 186.0, 173.4, 167.5, 142.1 (CH), 140.0, 136.9, 132.3, 126.6 (CH), 126.3 (CH), 125.7 (CH), 122.8 (CH), 63.0 (CH_2), 59.8 (CH), 36.6 (CH_2), 31.7 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 14.4 (Me), 14.3 (Me); *m/z* (CI) 362 (MH^+, 100%). Found: MH^+, 362.1431. $C_{19}H_{24}NO_4S$ requires: 362.1426.

Reaction of Ethyl 2-Diazo-3-(1-methylindol-3-yl)-3-oxopropanoate, 44, with Hexanamide. According to general procedure used for compound **33**, using hexanamide (300 mg, 2.6 mmol), diazoindole **44** (848 mg, 3.1 mmol), dirhodium tetraoctanoate (51 mg, 0.07 mmol), and dichloromethane (50 mL), ethyl 2-(1-methylindol-3-yl)-*N*-hexanoylmalonamate **52** was isolated as a colorless oil (758 mg, 2.1 mmol, 81%); IR (KBr/cm^{-1}) 3292 (N−H), 1730 (C=O), 1695 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.85 (1H, s), 7.63 (1H, d, J = 7.9), 7.33−7.23 (2H, m), 7.19 (1H, s), 7.17−7.12 (1H, m), 5.11 (1H, s), 4.29−4.18 (2H, m), 3.75 (3H, s), 2.68 (2H, t, J = 7.5), 1.63 (2H, m), 1.30−1.24 (7H, m), 0.86 (3H, t, J = 6.6); ^{13}C NMR (75 MHz; $CDCl_3$) δ 175.4, 169.6, 168.2, 137.4, 128.9 (CH), 127.1, 122.9 (CH), 120.5 (CH), 119.5 (CH), 110.1 (CH), 105.8, 62.5 (CH_2), 52.4 (CH), 37.8 (CH_2), 33.4 (Me), 31.6 (CH_2), 24.2 (CH_2), 22.8 (CH_2), 14.5 (Me), 14.3 (Me); *m/z* (FI) 358 (M^+, 85%). Found: M^+, 358.1892. $C_{20}H_{26}N_2O_4$ requires: 358.1893.

Ethyl 1-Hydroxy-4-oxo-(1,3)-oxazino[3,4-*a*]indole-2-carboxylate, 55. To a solution of hexanamide (100 mg, 0.87 mmol) and dirhodium tetraoctanoate (17 mg, 0.02 mmol) in dichloromethane (5 mL) heated under reflux was added diazo indole **46** (372 mg, 1.0 mmol) in dichloromethane (5 mL) over 16 h. The reaction mixture was then heated for a further 30 min, allowed to cool, evaporated in vacuo, and purified by flash chromatography (ethyl acetate−light petroleum) to yield the title compound as a colorless crystalline solid (160 mg, 0.58 mmol, 56%), mp 172−174 °C; IR (KBr/cm^{-1}) 1767 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 10.60 (1H, s), 8.70 (1H, dd, J = 0.8, 7.5), 7.95 (1H, dd, J = 1.0, 7.6), 7.75−7.46 (2H, m), 7.40 (1H, s), 4.67 (2H, q, J = 7.1), 1.65 (3H, t, J = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 165.5, 145.4, 143.0, 135.2, 130.1, 128.2, 127.0 (CH), 125.7 (CH), 122.2 (CH), 122.0, 116.3 (CH), 106.6 (CH), 62.9 (CH_2), 14.6 (Me); *m/z* (CI) 274 (MH^+, 100%). Found: MH^+, 274.0708. $C_{14}H_{12}NO_5$ requires: 274.0715.

Reaction of Ethyl (1-*tert*-Butoxycarbonylindol-3-yl)-2-diazo-3-oxopropanoate, 25, with Methanol. To a solution of methanol (0.11 mL, 5.6 mmol) and dirhodium tetraoctanoate (12 mg, 0.02 mmol) in dichloromethane (5 mL) heated under reflux was added diazo indole **25** (200 mg, 0.6 mmol) in dichloromethane (7 mL) over 16 h. The reaction mixture was then 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 methyl 2-(1-*tert*-butoxycarbonylindol-3-yl)malonate **57** as a colorless oil (51 mg, 0.14 mmol, 25%); IR (film/cm^{-1}) 1737 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.09 (1H, d, J = 8.1), 7.69 (1H, s), 7.50 (1H, d, J = 7.5), 7.28−7.14 (2H, m), 4.81 (1H, s), 4.20−4.13 (2H, m), 3.69 (3H, s), 1.58 (9H, s), 1.19 (3H, t, J = 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 167.3, 166.6, 148.4, 134.3, 128.1, 124.4 (CH), 123.6 (CH), 121.7 (CH), 118.3 (CH), 114.3 (CH), 111.1, 82.9, 61.0 (CH_2), 51.9 (CH), 48.4 (Me), 27.1 (Me), 13.0 (Me); *m/z* (CI) 362 (MH^+, 35%), 306 (100). Found: MH^+, 362.1591. $C_{19}H_{24}NO_6$ requires: 362.1604. (ii) Ethyl 3-(1-*tert*-butoxycarbonylindol-3-yl)-2-methoxy-3-oxopropanoate **56** as a colorless oil (120 mg, 0.33 mmol, 60%); IR (film/cm^{-1}) 1747 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.66 (1H, s), 8.39−8.36 (1H, m), 8.13−8.10 (1H, m), 7.38−7.34 (2H, m), 4.75 (1H, s), 4.28−4.20 (2H, m), 3.54 (3H, s), 1.70 (9H, s), 1.25 (3H, t, J = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 188.8, 167.7, 149.1, 135.2, 135.1 (CH), 127.9, 125.9 (CH), 124.8 (CH), 122.8 (CH), 116.5, 115.1 (CH), 87.0 (CH), 85.8, 62.2 (CH_2), 58.6 (Me), 28.2 (Me), 14.3 (Me); *m/z* (CI) 362 (MH^+, 18%), 306 (100). Found: MH^+, 362.1591. $C_{19}H_{24}NO_6$ requires: 362.1604).

Synthesis of 5-(Indol-3-yl)oxazoles and Related Compounds. To a solution of triphenylphosphine (0.20 mmol) and iodine (0.20 mmol) in dry dichloromethane (10 mL) was added triethylamine (0.41 mmol) and then a solution of the keto amide substrate (0.10 mmol) in dry dichloromethane (3 mL). The reaction mixture was then stirred for 16 h and then evaporated in vacuo and purified on silica gel eluting with ethyl acetate−light petroleum to yield the desired product.

Ethyl 2-Pentyl-5-phenyloxazole-4-carboxylate, 34. According to the above general procedure, ketoamide **33** (300 mg, 0.98 mmol) was cyclodehydrated to give the title compound as a colorless oil (193 mg, 0.68 mmol, 69%); IR (film/cm^{-1}) 1720 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.06−8.02 (2H, m), 7.50−7.40 (3H, m), 4.42 (2H, q, J = 7.0), 2.85 (2H, t, J = 7.5), 1.88−1.78 (2H, m), 1.46−1.31 (7H, m), 0.91 (3H, t, J = 6.8); ^{13}C NMR (100 MHz; $CDCl_3$) δ 163.9, 162.7, 155.4, 130.4 (CH), 128.7 (2 × CH), 127.6, 127.3, 61.7 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 27.2 (CH_2), 22.6 (CH_2), 14.7 (Me), 14.3 (Me); *m/z* (FI^+) 287 (M^+, 87%), 192 (100). Found: M^+, 287.1505. $C_{17}H_{21}NO_3$ requires: 287.1521.

Ethyl 5-(1-*tert*-Butoxycarbonylindol-3-yl)-2-pentyloxazole-4-carboxylate, 58. According to the above general procedure, the title compound was isolated from **24** (350 mg, 0.79 mmol) as a colorless crystalline solid (263 mg, 0.61 mmol, 78%), mp 35−37 °C; IR (KBr/cm^{-1}) 1741 (C=O), 1709 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.95 (1H, s), 8.24 (1H, d, J = 7.7), 8.07−8.85 (1H, m), 7.40−7.34 (2H, m), 4.45 (2H, q, J = 7.1), 2.92 (2H, t, J = 7.6), 1.88 (2H, m), 1.71 (9H, s), 1.46−1.37 (7H, m), 0.92 (3H, t, J = 6.9); ^{13}C NMR (100 MHz; $CDCl_3$) δ 162.7, 162.3, 151.7, 149.3, 135.2, 129.4 (CH), 127.7, 126.0, 125.1 (CH), 123.6 (CH), 121.3 (CH), 115.4 (CH), 107.9, 84.7, 61.1 (CH_2), 31.4 (CH_2), 28.1 (Me + CH_2), 26.8 (CH_2), 22.3 (CH_2), 14.5 (Me), 13.9 (Me); *m/z* (CI) 427 (MH^+, 74%), 371 (100). Found: C, 67.6; H, 7.2; N, 6.3. $C_{24}H_{30}N_2O_5$ requires: C, 67.6; H, 7.1; N, 6.6.

Ethyl 5-(1-*tert*-Butoxycarbonyl-2-chloroindol-3-yl)-2-pentyloxazole-4-carboxylate, 59. According to the above general procedure, the title compound was isolated from **47** (390 mg, 0.81 mmol) as a pale orange solid (300 mg, 0.65 mmol, 80%), mp 77−79 °C; IR (KBr/cm^{-1}) 1747 (C=O), 1639 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.13 (1H, d, J = 8.1), 7.39−7.27 (3H, m), 4.31 (2H, q, J = 7.1), 2.89 (2H, t, J = 7.6), 1.88−1.83 (2H, m), 1.71 (9H, s), 1.43−1.37 (4H, m), 1.22 (3H, t, J = 7.1), 0.94−0.89 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 165.8, 161.8, 148.9, 147.7, 135.4, 130.9, 126.9, 126.5, 125.5 (CH), 124.0 (CH), 119.7 (CH), 115.7 (CH), 108.9, 86.2, 61.5 (CH_2), 31.7 (CH_2), 28.6 (CH_2), 28.5 (Me), 27.1 (CH_2), 22.6 (CH_2), 14.5 (Me), 14.3 (Me); *m/z* (CI) 463/461 (MH^+, 7/17%), 361 (100). Found: MH^+, 461.1826. $C_{24}H_{30}{}^{35}ClN_2O_5$ requires: 461.1843.

Ethyl 5-(1-Benzenesulfonylindol-3-yl)-2-pentyloxazole-4-carboxylate, 60. According to the above general procedure, the title compound was isolated from **49** (550 mg, 1.1 mmol) as a colorless crystalline solid (345 mg, 0.72 mmol, 65%), mp 123−125 °C; IR (KBr/cm^{-1}) 1706 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.02 (1H, s), 8.07−8.03 (2H, m), 8.00−7.97 (2H, m), 7.59−7.54 (1H, m), 7.49−7.45 (2H, m), 7.42−7.33 (2H, m), 4.48 (2H, q, J = 7.2), 2.90 (2H, t, J = 7.6), 1.88−1.84 (2H, m), 1.46 (3H, t, J = 7.2), 1.42−1.36 (4H, m), 0.90 (3H, t, J = 7.0); ^{13}C NMR (75 MHz; $CDCl_3$) δ 163.0, 162.2, 150.9, 137.8, 134.6, 134.2 (CH), 129.5 (CH), 129.4 (CH), 127.9, 127.0 (CH), 126.6, 125.5 (CH), 124.2 (CH), 121.8 (CH), 113.6 (CH), 109.5, 61.4 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 26.8 (CH_2), 22.3 (CH_2), 14.5 (Me), 13.9 (Me); *m/z* (CI) 467 (MH^+, 8%). Found: C, 64.3; H, 5.6; N, 5.8. $C_{25}H_{26}N_2O_5S$ requires: C, 64.4; H, 5.6; N, 6.0.

Ethyl 5-[1-(2-Nitrobenzenesulfonyl)indol-3-yl]-2-pentyloxazole-4-carboxylate, 61. According to the above general procedure, ketoamide **51** (280 mg, 0.53 mmol) was cyclodehydrated to give the title compound as a yellow crystalline solid (230 mg, 0.45 mmol, 85%), mp 165−167 °C (ethyl acetate/light petroleum); IR (KBr/cm^{-1}) 1708 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.00 (1H, s), 8.10 (1H, app. t, J = 4.9), 7.92−7.89 (2H, m), 7.78−7.68 (3H, m), 7.43−7.40 (2H, m), 4.49 (2H, q, J = 7.1), 2.93 (2H, t, J = 7.7), 1.94−1.84 (2H, m), 1.47−1.40 (7H), 0.92 (3H, t, J = 7.2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 175.5, 163.3, 162.1, 150.3, 148.0, 135.2 (CH), 134.5, 132.6 (CH), 131.5, 130.1 (CH), 130.0 (CH), 127.8, 125.7 (CH), 125.2 (CH), 124.6 (CH), 122.1 (CH), 113.6 (CH), 109.5, 61.5 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 26.8 (CH_2), 22.3 (CH_2), 14.4 (Me), 13.9 (Me); *m/z* (CI) 512 (MH^+, 7%), 327 (100). Found: MH^+, 512.1491. $C_{25}H_{26}N_3O_7S$ requires: 512.1491.

Ethyl 5-(Benzothien-3-yl)-2-pentyloxazole-4-carboxylate, 62. According to the above general procedure, the title compound was isolated from **53** (630 mg, 1.7 mmol) as an oily orange solid (450 mg, 1.3 mmol, 75%); IR (KBr/cm^{-1}) 1716 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.66 (1H, s), 8.15−8.12 (1H, m), 7.91−7.88 (1H, m), 7.48−7.40 (2H, m), 4.40 (2H, q, J = 7.1), 2.92 (2H, t, J = 7.5), 2.03−1.83 (2H, m), 1.46−1.33 (7H, m), 0.92 (3H, t, J = 7.3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 163.5, 162.7, 151.9, 140.0, 137.3, 132.2 (CH), 128.0, 125.4 (CH), 125.3 (CH), 124.0 (CH), 123.2 (CH), 122.7, 61.7 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.7 (Me), 14.3 (Me); *m/z* (CI) 344 (MH^+, 100%). Found: MH^+, 344.1318. $C_{19}H_{22}NO_3S$ requires: 344.1320.

Ethyl 5-(Indol-3-yl)-2-pentyloxazole-4-carboxylate, 63. To a solution of nosylindole **61** (100 mg, 0.20 mmol) in DMF (4 mL) was added lithium hydroxide (33 mg, 0.80 mmol) and then mercaptoacetic acid (27 μL, 0.40 mmol) and the resulting mixture was stirred overnight. The solution was then partition with ether (30 mL) and saturated sodium hydrogen carbonate (30 mL) and the aqueous layer was extracted with ether (10 mL). The combined organic layers were then washed with brine, dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography to yield the title compound as a yellow solid (55 mg, 0.17 mmol, 86%), mp 83−85 °C (ethyl acetate/light petroleum); IR (KBr/cm^{-1}) 3146 (N−H), 1702 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.07 (1H, s), 8.81 (1H, d, J = 2.9), 8.19−8.15 (1H, m), 7.47−7.43 (1H, m), 7.33−7.25 (2H, m), 4.45 (2H, q, J = 7.1), 2.92 (2H, t, J = 7.7), 1.95−1.85 (2H, m), 1.49−1.32 (7H, m), 0.92 (3H, t, J = 7.0); ^{13}C NMR (75 MHz; $CDCl_3$) δ 163.5, 161.9, 154.9, 136.2, 129.7 (CH), 125.6, 123.6, 123.5 (CH), 121.8 (CH), 121.7 (CH), 112.1 (CH), 104.7, 61.4 (CH_2), 31.8 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 22.7 (CH_2), 14.9 (Me), 14.4 (Me); *m/z* (CI) 327 (MH^+, 100%). Found: MH^+, 327.1703. $C_{19}H_{23}N_2O_3$ requires: 327.1709.

Methyl (*S*)-2-*tert*-Butoxycarbonylamino-4-methylhex-2-enoate, 65. To a solution of trimethyl 2-(*tert*-butoxycarbonylamino)phosphonoacetate[53] (1.0 g, 3.5 mmol) in dichloromethane (1 mL) was added TMG (0.40 mL, 3.2 mmol) and

(53) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60.

the mixture was then stirred for 10 min. The reaction was then cooled to 0 °C, (*S*)-2-methylbutanal **64** (250 mg, 2.9 mmol) was added dropwise, and the mixture was then allowed to warm to ambient temperature overnight. The reaction was then diluted with ethyl acetate and washed with potassium hydrogen sulfate (1 M; 20 mL) and brine (2 × 20 mL). The combined aqueous layers were then back extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was then purified by flash chromatography to yield the title compound as a colorless solid (656 mg, 2.6 mmol, 88%), mp 45−47 °C, $[\alpha]^{33}$ 26.0 (*c* 0.96, $CHCl_3$); IR (KBr/cm^{-1}) 3437 (N−H), 1731 (C=O), 1706 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.35 (1H, br), 5.87 (1H, s), 3.77 (3H, s), 2.55−2.43 (1H, m), 1.46 (9H, s), 1.42−1.36 (2H, m), 1.04 (3H, d, J = 6.7), 0.87 (3H, t, J = 7.4); ^{13}C NMR (75 MHz; $CDCl_3$) δ 165.7, 153.8, 143.2 (CH), 125.1, 80.4, 52.2 (CH_2), 34.2 (CH), 29.2 (CH_2), 28.2 (Me), 19.2 (Me), 11.8 (Me); *m/z* (CI) 258 (M^+, 12%), 202 (100). Found: C, 60.9; H, 9.0; N, 5.4. $C_{13}H_{23}NO_4$ requires: C, 60.7; H, 9.0; N, 5.4.

(*S*,*S*)-*N*-(*tert*-Butoxycarbonyl)homoisoleucine Methyl Ester, 66. The alkene **65** (400 mg, 1.6 mmol) and (+)-1,2-bis-((2*S*,5*S*)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)-rhodium(I) trifluoromethanesulfonate (4 mg) were placed in the reaction vessel and then the system was evacuated and purged with nitrogen (× 5); the vessel was then charged with methanol (2 mL) and evacuated and purged with nitrogen (× 5) and then with hydrogen (× 5), pressurized with hydrogen to 90 psi, and stirred for 3 days under pressure. The reaction mixture was then concentrated in vacuo and purified by column chromatography to yield the title compound as a colorless oil (360 mg, 1.4 mmol, 89%) (lit.[54] data not given), $[\alpha]^{32}$ 5.5 (*c* 1.02, $CHCl_3$); IR (KBr/cm^{-1}) 3366 N−H), 1747 (C=O), 1718 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 4.95 (1H, d, J = 7.7), 4.37−4.32 (1H, m), 3.73 (3H, s), 1.75−1.65 (1H, m), 1.55−1.37 (11H, m), 1.26−1.11 (2H, m), 0.92 (3H, d, J = 6.0), 0.87 (3H, t, J = 7.0); ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.0, 155.3, 79.8, 52.2 (Me), 52.1 + 51.9 (CH, diast.), 39.8 + 39.6 (CH_2, diast.), 30.94 + 30.87 (CH, diast.), 28.6 + 28.7 (CH_2, diast.), 28.3 (Me), 19.2 + 18.5 (Me, diast.), 10.9 + 11.2 (Me, diast.); *m/z* (CI) 260 (M^+, 100%). Found: MH^+, 260.1861. $C_{13}H_{26}NO_4$ requires: 260.1862.

(*S*,*S*)-Ethyl 2-(1-*tert*-Butoxycarbonylamino-2-methylbutyl)-5-[1-(2-nitrobenzenesulfonyl)indol-3-yl]oxazole-4-carboxylate, 70. To a stirred solution of (*S*)-*N*-*tert*-butyloxycarbonylisoleucinamide **67**[55] (300 mg, 1.3 mmol) and dirhodium tetraoctanoate (25 mg, 0.03 mmol) in dichloromethane (15 mL) heated under reflux conditions was added a solution of nosyl diazoindole **40** (692 mg, 1.6 mmol) in dichloromethane (15 mL) over 16 h. The resulting mixture was then concentrated in vacuo and purified by column chromatography (ethyl acetate/light petroleum 4:6) to yield an inseparable mixture of products **68** (ca. 33%) and **69** (ca. 11%) (yields were based on analysis of the ^{1}H NMR spectrum of the mixture). To a solution of triphenylphosphine (244 mg, 0.93 mmol) and iodine (118 mg, 0.93 mmol) in dichloromethane (5 mL) was added triethylamine (0.27 mL, 1.9 mmol) and then a mixture of **68/69** in dichloromethane (5 mL). The resulting mixture was stirred overnight and concentrated in vacuo, and the resulant oil was purified by column chromatography to yield the title compound as a yellow oil (271 mg, 0.43 mmol, 33%, over two steps), $[\alpha]^{31}$ −9.0 (*c* 0.52, $CHCl_3$); IR ($CDCl_3$)/cm^{-1}) 3440 (N−H), 1713 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.96 (1H, s), 8.10−8.07 (1H, m), 7.94−7.88 (2H, m), 7.81−7.77 (2H, m), 7.74−7.67 (1H, m), 7.45−7.38 (2H, m), 5.39 (1H, d, J = 9.1), 4.99 (1H, dd, J = 6.2, 9.1), 4.51 (2H, q, J = 7.2), 2.09−2.05 (1H, m), 1.66−1.42 (13H, m), 1.33−1.21 (1H, m), 0.97 (3H, d, J = 7.7), 0.96 (3H, t, J = 7.5); ^{13}C NMR (75 MHz; $CDCl_3$) δ 162.6, 162.3, 155.8, 150.7, 148.4, 135.7 (CH), 134.9, 133.1 (CH), 131.8, 130.7 (CH), 130.6 (CH), 128.2, 127.7, 126.2 (CH), 125.7 (CH), 125.2 (CH), 122.5 (CH), 113.9 (CH), 109.6, 80.5, 62.1 (CH_2), 53.9 (CH), 39.8 (CH), 29.7 (Me), 25.5 (CH_2), 15.8 (Me), 14.8 (Me), 11.9 (Me); *m/z* (FI^+) 626 (M^+, 15%), 123 (100). Found: M^+, 626.2049. $C_{30}H_{34}N_4O_9S$ requires: 626.2047.

(*S*,*S*)-Ethyl 2-(1-*tert*-Butoxycarbonylamino-2-methylbutyl)-5-(indol-3-yl)oxazole-4-carboxylate, 71. To a solution of nosylindoleoxazole **70** (180 mg, 0.29 mmol) in DMF (6 mL) was added lithium hydroxide (48 mg, 1.1 mmol) and then mercaptoacetic acid (40 μL, 0.57 mmol) and the resulting solution was stirred at ambient temperature overnight. The reaction was then partitioned with ether (40 mL) and sodium hydrogen carbonate solution (40 mL). The aqueous layer was then extracted with ether (20 mL) and the combined organic extractions were washed with brine, dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography to yield the title compound as a colorless foam (112 mg, 0.26 mmol, 88%), $[\alpha]^{31}$ −53.7 (*c* 1.03, $CHCl_3$); IR ($CDCl_3$)/cm^{-1}) 3468 (N−H), 1711 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.11 (1H, s), 8.71 (1H, s), 8.10−8.07 (1H, m), 7.45−7.43 (1H, m), 7.30 − 7.22 (2H, m), 5.42 (1H, d, J = 9.0), 4.99 (1H, dd, J = 6.0, 9.0), 4.44 (2H, q, J = 6.8), 2.08 (1H, m), 1.58−1.45 (10H, m), 1.41 (3H, t, J = 6.8), 1.31−1.26 (1H, m), 0.98 (3H, d, J = 6.4), 0.93 (3H, t, J = 7.3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 163.3, 160.5, 155.9, 154.9, 136.2, 130.0 (CH), 125.5, 123.7, 123.6 (CH), 121.9 (CH), 121.6 (CH), 112.1 (CH), 104.4, 80.5, 61.4 (CH_2), 54.0 (CH), 39.9 (CH), 28.8 (Me), 25.5 (CH_2), 15.9 (Me), 14.9 (Me), 11.9 (Me); *m/z* (FI^+) 441 (M^+, 100%). Found: M^+, 441.2260. $C_{24}H_{31}N_3O_5$ requires: 441.2264.

(*S*,*S*)-*N*-(*tert*-Butoxycarbonyl)homoisoleucinamide, 23. To a solution of (*S*,*S*)-*N*-(*tert*-butoxycarbonyl)homoisoleucine methyl ester **66** (480 mg, 1.9 mmol) in methanol (20 mL) cooled to 0 °C was added a solution of lithium hydroxide (1 M; 10 mL). The mixture was allowed to warm to ambient temperature over 3 h and then concentrated in vacuo. The residue was then partitioned between ethyl acetate and water (25 mL each) and the aqueous layer was then acidified with 2 M HCl and extracted with ethyl acetate (3 × 25 mL). The combined organic extractions were then dried ($MgSO_4$) and concentrated to yield the free acid. The free acid was then dissolved in THF (10 mL) to which was added triethylamine (0.28 mL, 1.9 mmol) and the resulting mixture was cooled to 0 °C. Ethyl chloroformate (0.19 mL, 1.9 mmol) was added and the mixture was stirred for 30 min at 0 °C. The reaction was then quenched with concentrated ammonia (3 mL) and THF (2 mL) and stirred for 30 min. The mixture was then partitioned with ethyl acetate/water (15 mL each) and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were then washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and concentrated in vacuo to yield the title compound as a colorless solid (366 mg, 1.5 mmol, 81%), mp 138−140 °C, $[\alpha]^{32}$ −24.9 (*c* 1.07, $CHCl_3$); IR (KBr/cm^{-1}) 3429 (N−H), 3362 (N−H), 3305 (N−H), 1666 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.23 (1H, s), 5.56 (1H, s), 4.94 (1H, d, J = 7.7), 4.22−4.15 (1H, m), 1.86−1.77 (1H, m), 1.45−1.31 (11H, m), 1.29−1.10 (2H, m), 094−9.85 (6H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 175.7 + 176.1 (diast.), 156.2, 80.5, 52.8 (CH), 39.8 (CH_2), 31.4 (CH), 29.1 + 30.3 (CH_2, diast.), 28.7 (Me), 19.7 + 19.0 (Me, diast.), 11.4 + 11.7 (Me, diast.); *m/z* (FI^+) 244 (M^+, 100%). Found: M^+, 244.1776. $C_{12}H_{24}N_2O_3$ requires: 244.1787.

(*S*,*S*)-Ethyl 2-(1-*tert*-Butoxycarbonylamino-3-methylpentyl)-5-[1-(2-nitrobenzenesulfonyl)indol-3-yl]oxazole-4-carboxylate, 74. To a stirred solution of (*S*,*S*)-*N*-*tert*-butyloxycarbonylhomoisoleucinamide **23** (250 mg, 1.0 mmol) and dirhodium tetraoctanoate (20 mg, 0.03 mmol) in dichloromethane (10 mL) heated under reflux conditions was added a solution of nosyl diazoindole **40** (543 mg, 1.2 mmol) in dichloromethane (15 mL) over 16 h. The resulting mixture was then concentrated in vacuo and purified by column chromatography to yield an inseparable mixture of products **72** (ca. 56%) and **73** (ca. 4%) (yields were based on analysis of the ^{1}H

(54) Papageorgiou, C.; Florineth, A.; Mikol, V. *J. Med. Chem.* **1994**, *37*, 3674−3676.
(55) Nozaki, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2647−2648.

NMR spectrum of the mixture). To a solution of triphenylphosphine (300 mg, 1.1 mmol) and iodine (145 mg, 1.1 mmol) in dichloromethane (5 mL) was added triethylamine (0.33 mL, 2.3 mmol) and then a mixture of **72/73** in dichloromethane (5 mL). The resulting mixture was stirred overnight and concentrated in vacuo and the resulting oil was purified by column chromatography to yield the title compound as a yellow oil (334 mg, 0.52 mmol, 51%, over two steps), $[\alpha]^{33}$ −11.0 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$)/cm^{-1}) 3440 (N−H), 1713 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.98 (1H, s), 8.14−8.11 (1H, m), 7.92−7.89 (2H, m), 7.83−7.66 (3H, m), 7.44−7.37 (2H, m), 5.16−5.11 (2H, m), 4.53 (2H, q, J = 7.0), 2.05−2.00 (1H, m), 1.79−1.70 (1H, m), 1.52−1.42 (13H, m), 1.33−1.16 (2H, m), 0.99 (3H, d, J = 6.4), 0.88 (3H, t, J = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 161.0, 159.9, 148.4, 145.9, 133.2 (CH), 132.5, 130.6 (CH), 129.4, 128.3 (CH), 128.1 (CH), 125.7, 125.2, 123.8 (CH), 123.6, 123.2 (CH), 122.7 (CH), 120.2 (CH), 111.5 (CH), 107.2, 78.1, 59.7 (CH_2), 45.2 (CH), 39.2 (CH_2), 28.9 (CH), 26.7 (CH_2), 26.3 (Me), 17.2 (Me), 12.4 (Me), 9.0 + 9.3 (Me, diast.); *m/z* (FI^+) 640 (M^+, 10%), 355 (100). Found: M^+, 640.2209. $C_{31}H_{36}N_4O_9S$ requires: 640.2203.

(*S*,*S*)-Ethyl 2-(1-*tert*-Butoxycarbonylamino-3-methylpentyl)-5-(indol-3-yl)oxazole-4-carboxylate, 75. To a solution of nosylindoleoxazole **74** (250 mg, 0.39 mmol) in DMF (8 mL) was added lithium hydroxide (65 mg, 1.6 mmol) and then mercaptoacetic acid (54 μL, 0.78 mmol) and the resulting solution was stirred at ambient temperature overnight. The reaction was then partitioned with ether (40 mL) and sodium hydrogen carbonate solution (40 mL). The aqueous layer was then extracted with ether (20 mL) and the combined organic extractions were washed with brine, dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography to yield the title compound as a colorless crystalline solid (157 mg, 0.34 mmol, 88%), mp 197−199 °C (ethyl acetate−light petroleum), $[\alpha]^{33}$ −34.0 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$/cm^{-1}) 3468 (N−H), 1710 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.06 (1H, s), 9.71 (1H, s), 8.11 (1H, d, J = 7.5), 7.43 (1H, d, J = 7.5), 7.29−7.22 (2H, m), 5.28 (1H, d, J = 6.8), 5.14−5.12 (1H, br), 4.43 (2H, q, J = 7.0), 2.04−2.01 (1H, m), 1.77−1.73 (1H, m), 1.51−1.46 (10H, m), 1.41 (3H, t, J = 7.1), 1.26−1.19 (2H, m), 0.99 (3H, d, J = 6.5), 0.87 (3H, t, J = 7.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 162.5, 160.9, 155.1, 154.4, 135.6, 129.5 (CH), 125.0, 123.0 (CH), 121.4 (CH), 121.1 (CH), 111.4 (CH), 103.8, 80.0, 60.9 (CH_2), 47.2 (CH), 41.2 + 41.0 (CH_2, diast.), 30.8 (CH), 28.7 + 29.5 (CH_2, diast.), 28.2 (Me), 19.0 (Me), 14.3 (Me), 10.9 + 11.1 (Me, diast.), 1 ArC unobserved; *m/z* (FI^+) 455 (M^+, 100%). Found: C, 65.9; H, 7.5; N, 9.0. $C_{25}H_{33}N_3O_5$ requires: C, 65.9; H, 7.3; N, 9.2.

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Supporting Information Available: Experimental details for preparation of compounds **24**, **35**, **37**, **39**, **43**, **45**, **64**, and **67**; X-ray crystal structures of compounds **26**, **28**, and **58**; copies of ^{1}H and ^{13}C NMR spectra of compounds **23**, **25**−**28**, **33**, **34**, **36**, **38**, **40**, **42**, **44**, **46**-**63**, **65**, **66**, **70**, **71**, **74**, and **75**. This material is available free of charge via the Internet at http://pubs.acs.org.

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