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Oxidative Rearrangement of Indoles: A New Approach to the EFHG-Tetracyclic Core of Diazonamide A

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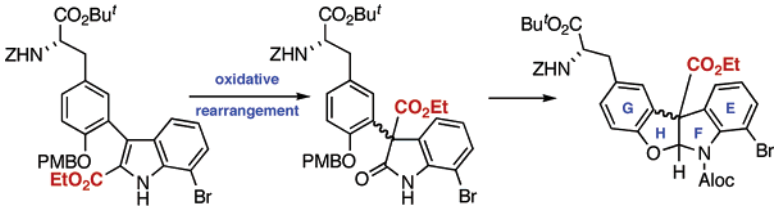

A new approach to the ring EFHG-tetracyclic core fragment of the marine secondary metabolite diazonamide A is described. The route is based on the oxidative rearrangement of 3-arylindole-2-carboxylates. Thus, a range of 3-arylindole-2-carboxylates (**3**, **8**) underwent rearrangement to the corresponding 3,3-disubstituted oxindoles (**4**, **9**) with migration of the ester group upon treatment with *tert*-butyl hypochlorite followed by acid. The oxindoles **9** with a 3-[2-(4-methoxybenzyloxy)]phenyl substituent underwent cyclization to the tetracyclic aminals **11** following N-protection, reduction, and treatment with methanesulfonic anhydride. The methodology was applied to the tyrosine-indole derivative **17** to give the EFHG-tetracyclic core of diazonamide A.

Introduction

The marine natural product diazonamide A, isolated from the colonial ascidian (sea squirt) *Diazona chinensis*, was assigned as structure **1** in 1991 on the basis of an X-ray crystallographic study of a derivative.[1] The combination of a unique and complex structure, and the reported potent biological activity against human tumor cell lines,[1,2] ensured that diazonamide A immediately captured the imagination of synthetic organic chemists. Hence, in the 15 years since the structure of diazonamide A was published, more than 10 research groups worldwide have reported approaches to this interesting natural product.[3−32] However, in 2001 when Harran and co-workers completed a total synthesis of structure **1**, they discovered that it was different

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(1) Lindquist, N.; Fenical, W.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.
(2) Cruz-Monserrate, Z.; Vervoort, H. C.; Bai, R. L.; Newman, D. J.; Howell, S. B.; Los, G.; Mullaney, J. T.; Williams, M. D.; Pettit, G. R.; Fenical, W.; Hamel, E. *Mol. Pharmacol.* **2003**, *63*, 1273.
(3) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Véliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609.
(4) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398.
(5) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223.
(6) Wipf, P.; Methot, J. L. *Org. Lett.* **2001**, *3*, 1261.
(7) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167.
(8) Booker, J. E. M.; Boto, A.; Churchill, G. H.; Green, C. P.; Ling, M.; Meek, G.; Prabhakaran, J.; Sinclair, D.; Blake, A. J.; Pattenden, G. *Org. Biomol. Chem.* **2006**, *4*, 4193.
(9) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640.
(10) Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 937.
(11) Li, J.; Chen, X.; Burgett, A. W. G.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2682.
(12) Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451.
(13) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831.
(14) Chan, F.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 835.
(15) Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2001**, *42*, 627.
(16) Magnus, P.; Lescop, C. *Tetrahedron Lett.* **2001**, *42*, 7193.
(17) Kreisberg, J. D.; Magnus, P.; Shinde, S. *Tetrahedron Lett.* **2002**, *43*, 7393.
(18) Magnus, P.; Venable, J. D.; Shen, L.; Lynch, V. *Tetrahedron Lett.* **2005**, *46*, 707.
(19) Magnus, P.; Turnbull, R. *Tetrahedron Lett.* **2006**, *47*, 6461.
(20) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031.
(21) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033.
(22) Vedejs, E.; Zajac, M. A. *Org. Lett.* **2001**, *3*, 2451.
(23) Zajac, M. A.; Vedejs, E. *Org. Lett.* **2004**, *6*, 237.
(24) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521.

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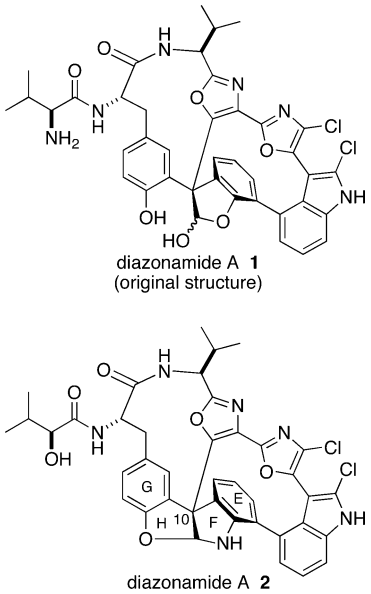


FIGURE 1. Original and revised structures for the marine secondary metabolite diazonamide A.

from the natural product.[33,34] After a re-examination of the original X-ray data, Harran proposed structure **2** for diazonamide A (Figure 1). Not only did this subsequently prove to be correct, but it also better fits a biosynthetic route in which the bicyclic core could be derived from modification of a Tyr-Val-Trp−Trp tetrapeptide. Final 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.[35,36] Subsequently, the Nicolaou group reported a second route to diazonamide A,[37,38] while Harran and co-workers completed their own total synthesis of the correct structure.[39]

Although Nicolaou's and Harran's endeavors have now solved the structural problem of diazonamide A, such is its attraction as a target for organic synthesis that it continues to hold the attention of a number of research groups. Of particular interest is the tetracyclic core of the molecule, comprising rings EFHG and the C-10 quaternary asymmetric center, and various approaches have been reported. Much of the early work was directed toward old diazonamide A and, for example, involved arylation or alkylation of benzofuranones,[3,24] DMAP catalyzed rearrangement of 2-acyloxybenzofurans to 3-acylbenzofuranones,[20,22] and intramolecular Heck reactions.[5,40] Unsurprisingly, some of these strategies have also been applied to the correct structure, substituting the relevant oxindole for a benzofuranone. Thus, arylation, alkylation, and acylation reactions of 3-substituted oxindoles have been employed,[23,35−38] as have intramolecular Heck reactions,[8] oxindole rearrangements,[41,42] rhodium carbene chemistry,[25] and intramolecular capture of a tyrosine-derived phenoxenium ion by an indole.[39]

Our own interest in diazonamide A started over a decade ago when we reported an approach to a benzofuranone related to the original structure using the DMAP-induced C-acylation reaction and an approach to 5-(3-indolyl)oxazoles using dirhodium(II) catalyzed reactions of diazocarbonyl compounds.[43,44] More recently, we have described further approaches to the tyrosine-derived unit using the Claisen rearrangement or an intramolecular Heck reaction[45,46] and a range of studies on the indole-oxazole fragments,[47−49] including a biomimetic route based on the oxidation of a Try-Val-Trp-Trp tetrapeptide.[50] We now report a new approach to the tetracyclic ring EFHG core of diazonamide A using the oxidative rearrangement of indoles as the key step.

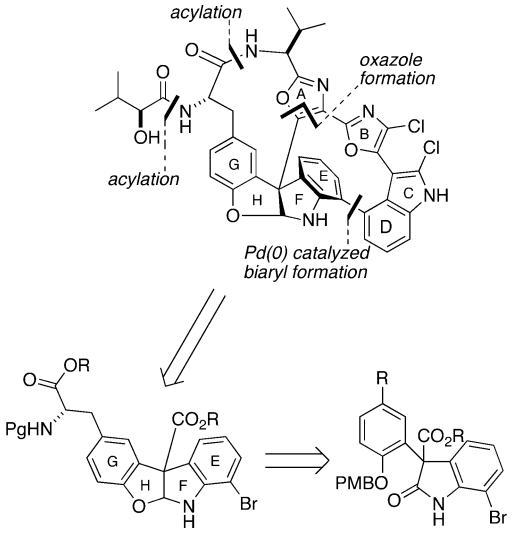
Results and Discussion

Our retrosynthetic analysis of diazonamide A **2** is based on the disconnection of one biaryl and two amide bonds, which together with formation of the ring A oxazole, leads directly back to the EFHG-tetracyclic core, that by analogy with the aforementioned published work, should be available from the 3,3-disubstituted oxindole shown in Scheme 1. The choice of a *p*-methoxybenzyl (PMB) protecting group for the phenolic oxygen is influenced by the work of Vedejs and Zajac who demonstrated its facile removal under conditions required to cyclize the H-ring.[23] The key to the whole strategy is therefore the synthesis of a suitable 3,3-disubstituted oxindole precursor, and hence, we sought to investigate the oxidative rearrangement of indoles as a potential route.

The oxidative rearrangement of indoles to oxindoles upon treatment with electrophilic halogenating agents has been known for several decades. Although the reaction has been investigated

(25) Sawada, T.; Fuerst, D. E.; Wood, J. L. *Tetrahedron Lett.* **2003**, *44*, 4919.
(26) Nicolaou, K. C.; Snyder, S. A.; Simonsen, K. B.; Koumbis, A. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 3473.
(27) Nicolaou, K. C.; Huang, X.; Giuseppone, N.; Rao, P. B.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4705.
(28) Nicolaou, K. C.; Snyder, S. A.; Huang, X. H.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.* **2004**, *126*, 10162.
(29) Nicolaou, K. C.; Snyder, S. A.; Giuseppone, N.; Huang, X. H.; Bella, M.; Reddy, M. V.; Rao, P. B.; Koumbis, A. E.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 10174.
(30) Radspieler, A.; Liebscher, J. *Synthesis* **2001**, 745.
(31) Schley, D.; Radspieler, A.; Christoph, G.; Liebscher, J. *Eur. J. Org. Chem.* **2002**, 369.
(32) Feldman, K. S.; Eastman, K. J.; Lessene, G. *Org. Lett.* **2002**, *4*, 3525.
(33) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765.
(34) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770.
(35) Nicolaou, K. C.; Bella, M.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495.
(36) Nicolaou, K. C.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888.
(37) Nicolaou, K. C.; Rao, P. B.; Hao, J. L.; Reddy, M. V.; Rassias, G.; Huang, X. H.; Chen, D. Y. K.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753.
(38) Nicolaou, K. C.; Hao, J. L.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X. H.; Chen, D. Y. K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897.
(39) Burgett, A. W. G.; Li, Q. Y.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961.
(40) Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E. M. *Synthesis* **1998**, 1501.
(41) Goldberg, F. W.; Magnus, P.; Turnbull, R. *Org. Lett.* **2005**, *7*, 4531.
(42) Magnus, P.; Turnbull, R. *Org. Lett.* **2006**, *8*, 3497.
(43) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107.
(44) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2413.
(45) Lach, F.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6893.
(46) Palmer, F. N.; Lach, F.; Poriel, C.; Pepper, A. G.; Bagley, M. C.; Slawin, A. M. Z.; Moody, C. J. *Org. Biomol. Chem.* **2005**, *3*, 3805.
(47) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897.
(48) Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901.
(49) Davies, J. R.; Kane, P. D.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 7305.
(50) Sperry, J.; Moody, C. J. *Chem. Commun.* **2006**, 2397.

SCHEME 1. Retrosynthetic Analysis of Diazonamide A[a]

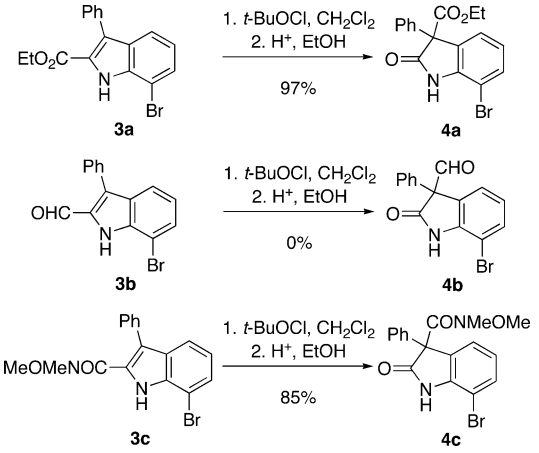


[a] Pg = protecting group.

in simple indoles,[51−54] and its mechanism studied in detail,[55,56] it has also found use in indole alkaloids[57,58] and has recently been elegantly exploited in a biogenetically patterned transformation of the *Corynanthe* skeleton into the *Strychnos* system.[59]

Our own work started with an extension of the seminal work by Walser et al.[54] Thus, ethyl 7-bromo-3-phenylindole-2-carboxylate **3a**, prepared from 2-bromoaniline and ethyl 2-benzyl-3-oxobutanoate in a Japp−Klingemann synthesis,[60] was treated with *tert*-butyl hypochlorite followed by ethanolic HCl to give, after chromatography, the 3,3-disubstituted oxindole **4a** in excellent yield (Scheme 2). The generally accepted mechanism involves conversion of the indole into a 3-haloindolenine, followed by protonation and attack of a nucleophile (water) and finally migration of the ester group, concomitant with loss of chloride, to form the oxindole. In an attempt to introduce other functionality at the oxindole 3-position, the corresponding aldehyde **3b** was investigated. Unfortunately, the aldehyde **3b**, prepared from the ester **3a** by reduction with lithium aluminum hydride followed by oxidation with manganese(IV) oxide, did not undergo oxidative rearrangement to give the desired oxindole **4b**. It was previously noted by Walser et al. that related 2-acetylindoles did not give the expected 3-acetyloxindoles upon oxidative rearrangement.[54] On the hand, the Weinreb amide **3c**, prepared by reaction of ester **3a** with *N*,*O*-dimethylhydroxylamine in the presence of dimethylaluminum chloride,[61] underwent smooth oxidative rearrangement to give the oxindole **4c** (85%) (Scheme 2). The structure of

SCHEME 2



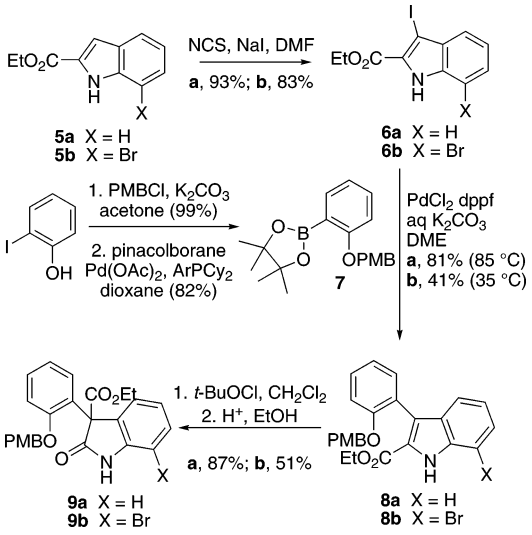
oxindole **4c** was confirmed by X-ray crystallography (see Supporting Information);[62] attempted reduction using diisobutylaluminum hydride, however, did not result in the formation of the desired oxindole **4b**.

To incorporate the essential functionality for formation of the ring EFHG-tetracycle, we next investigated 3-arylindole-2-carboxylate **8a**, prepared from ethyl indole-2-carboxylate **5a**, by iodination (93%) and palladium catalyzed cross coupling of the iodide **6a** with the PMB protected phenolic boronate ester **7**, available from 2-iodophenol by alkylation and boration. The boration using the standard Miyaura conditions[63] was low yielding, probably due to the steric hindrance of the aryl iodide. Baudoin reported a modification of Masuda's method for the conversion of *ortho*-substituted aryl bromides and iodides using $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl as a ligand, and pinacolborane as a boron source.[64,65] Under these conditions, the alkylated 2-iodophenol was efficiently converted into the corresponding boronate ester **7** as shown in Scheme 3. Upon treatment with *tert*-butyl hypochlorite followed by HCl in ethanol, the indole **8a** underwent oxidative rearrangement to the 3,3-disubstituted oxindole **9a** in excellent yield. Some care was necessary to avoid cleavage of the PMB protecting group under the acidic conditions. The reaction sequence was repeated starting from ethyl 7-bromoindole-2-carboxylate **5b**, prepared from 2-bromophenylhydrazine and ethyl pyruvate in a Fischer indole reaction. As expected, selective cross coupling with the iodide was possible, although the yield of the indole **8b** was modest, and the use of the $PdCl_2$(dppf) catalyst at 35 °C was essential to avoid over-reaction at the C-7 bromide. Oxidative rearrangement as before gave the oxindole **9b** (Scheme 3).

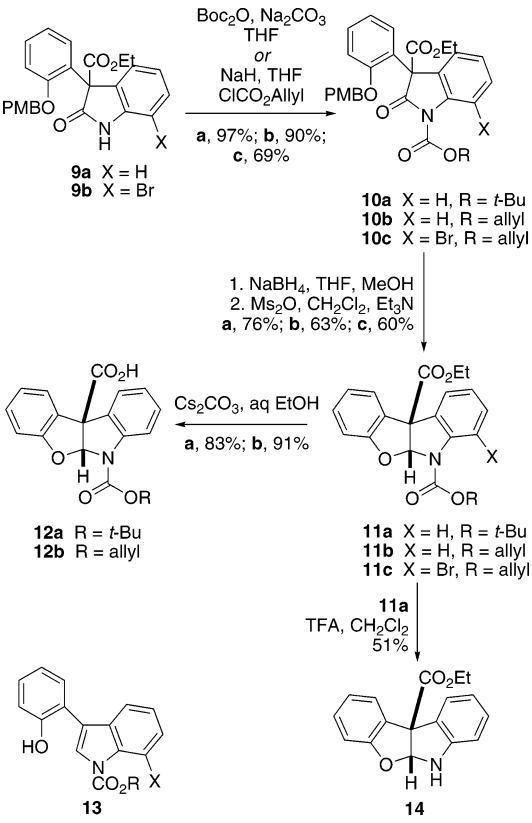
With a suitably substituted oxindole available, attention was turned to its conversion into the diazonamide tetracyclic core ring system. Therefore, the nitrogen in oxindole **9** was protected with either *tert*-butyl or allyl carbamate **10** (Scheme 4), the structure of the Boc-derivative **10a** being confirmed by X-ray crystallography (see Supporting Information).[62]

(51) Acheson, R. M.; Vernon, J. M.; Snaith, R. W. *J. Chem. Soc.* **1964**, 3229.
(52) Acheson, R. M.; Prince, R. J.; Procter, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 595.
(53) Muchowski, J. M. *Can. J. Chem.* **1970**, *48*, 422.
(54) Walser, A.; Blount, J. F.; Fryer, R. I. *J. Org. Chem.* **1973**, *38*, 3077.
(55) De Rosa, M.; Alonso, J. L. T. *J. Org. Chem.* **1978**, *43*, 2639.
(56) De Rosa, M.; Carbognani, L.; Febres, A. *J. Org. Chem.* **1981**, *46*, 2054.
(57) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871.
(58) Lichman, K. V. *J. Chem. Soc. C* **1971**, 2539.
(59) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003.
(60) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
(61) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.
(62) X-ray crystal data: these can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK; fax: 44-1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk.
(63) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
(64) Baudoin, O.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2000**, *65*, 9268.
(65) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458.

SCHEME 3

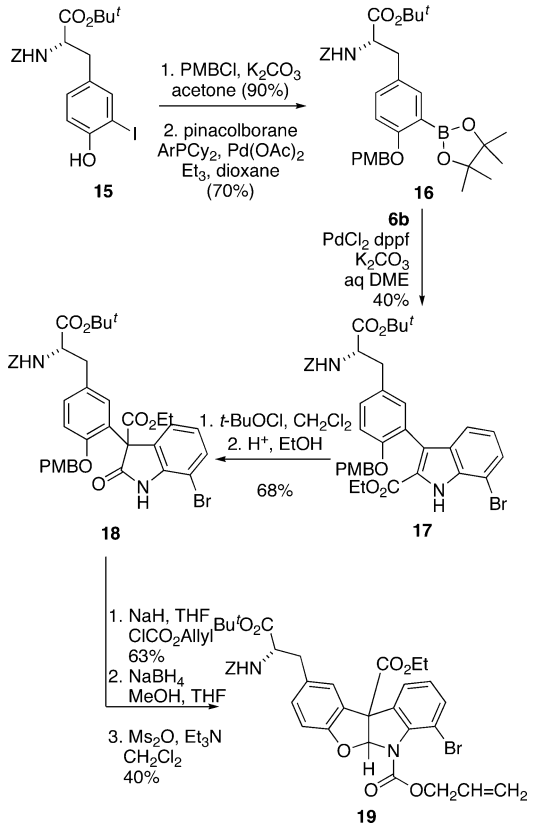


SCHEME 4



Thereafter, using the methodology established by Vedejs and Zajac,[22] sodium borohydride reduction of the oxindole carbonyl followed by treatment with methanesulfonic anhydride resulted in cyclization to the tetracyclic aminal **11** with concomitant removal of the PMB protecting group in good yield for all three substrates **10** (Scheme 4). The 5,5-system **11** was isolated as a single diastereoisomer. Initial attempts to hydrolyze the ester in compound **11** were unsuccessful and invariably led to loss of the ester, presumably by decarboxylation of the acid **12**, and formation of the indole **13** by an aromatization reaction with the phenolate acting as a good leaving group. However, under milder hydrolysis conditions, the acids **12a** and **12b** could be isolated in good yield. Heating the acid **12a** to about 95 °C

SCHEME 5



leads to decarboxylation and isolation of the indole **13** (X = H, R = *t*-Bu) in good yield. Finally, in this series of model compounds, the Boc protecting group was removed from tetracycle **11a** to give the crystalline NH compound **14** (Scheme 4), X-ray crystallographic analysis of which (see Supporting Information)[62] confirmed the cis-stereochemistry of the 5,5-system.

Having established methodology for the formation of 3,3-disubstituted oxindoles and their subsequent conversion into tetracyclic compounds, we embarked on the synthesis of the complete tetracyclic aminal core of diazonamide incorporating the correct tyrosine side chain. The starting material was the protected iodotyrosine **15**, previously prepared in our earlier studies on diazonamide.[46] Protection of the phenol as its PMB ether was followed by a palladium catalyzed reaction with pinacolborane to give the tyrosine boronate **16** (Scheme 5). A second palladium catalyzed reaction under Suzuki conditions then combined the indole **6b** and tyrosine **16** fragments to give the 3-arylindole-2-carboxylate **17**. The key oxidative rearrangement then proceeded as planned to provide the oxindole **18** in an acceptable yield of 68%, albeit as an inseparable mixture of diastereoisomers. Finally, protection of the oxindole NH as its allyl carbamate, followed by application of the Vedejs protocol, delivered the tetracyclic aminal core **19** of diazonamide A, again as an inseparable mixture of diastereoisomers (Scheme 5). The diastereoisomers of tetracycle **19** both have a cis-fused 5−5 system but are diastereomeric with respect to the tyrosine-derived stereocenter.

Hence, we have shown that the long known oxidative rearrangement of indoles to oxindoles upon treatment with an electrophilic chlorinating reagent can be used to access 3,3-disubstituted oxindoles appropriately substituted for conversion into the EFHG-tetracyclic aminal core of diazonamide A. In

parallel work,[66] we have recently shown that use of a 2-methoxymethylpyrrolidine chiral auxiliary in place of the ethyl ester results in a diastereoselective rearrangement to give, after crystallization, optically pure oxindoles. This methodology, combined with that described herein, is under investigation as a route to diazonamide A.

Experimental Section

For general experimental details and the preparation of starting indoles **3a**, **3b**, **3c**, **5b**, **6a**, and **6b**, see the Supporting Information.

Ethyl 7-Bromo-2-oxo-3-phenylindole-3-carboxylate 4a. To a solution of *tert*-butyl hypochlorite (400 mg, 3.6 mmol) in dichloromethane (3 mL) was added ethyl 7-bromo-3-phenylindole-2-carboxylate **3a** (400 mg, 1.2 mmol) in dichloromethane (3 mL), and the mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in a mixture of dichloromethane (9.5 mL), ethanol (6.5 mL), and a solution of HCl in ethanol (5%, 1.5 mL) and stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography to yield the title product as a colorless crystalline solid (406 mg, 97%); mp 95 − 97 °C; IR (KBr/cm^{-1}) 3237, 3088, 3001, 2981, 2925, 2853, 1737, 1721, 1614, 1470, 1450, 1224; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.94 (1 H, s), 7.49−7.46 (1 H, m), 7.39−7.30 (6 H, m), 7.03 (1 H, t, *J* 7.9), 4.34−4.16 (2 H, m), 1.22 (3 H, t, *J* 7.1); ^{13}C NMR (75 MHz; $CDCl_3$) δ 173.3 (C), 168.8 (C), 141.3 (C), 135.6 (C), 132.7 (CH), 129.1 (CH), 128.9 (CH), 128.1 (CH), 125.6 (CH), 124.5 (CH), 103.6 (C), 66.0(C), 63.1 (CH_2), 14.3 (Me); MS (CI) 362/360 (MH^+, 100/95%), 359 (5), 317 (4), 316 (8), 289 (8), 288 (30), 282 (48), 281 (5), 266 (1), 236 (4), 222 (2), 210 (5), 208 (10); Found: MH^+, 360.0244. $C_{17}H_{14}{}^{79}BrNO_3$ + H requires: 360.0236. Found: C, 56.48; H, 3.77; N, 3.65. $C_{17}H_{14}BrNO_3$ requires: C, 56.69; H, 3.92; N, 3.89%.

***N*-Methoxy-*N*-methyl 7-Bromo-2-oxo-3-phenylindole-3-carboxamide 4c.** To a solution of *N*-methoxy-*N*-methyl 7-bromo-3-phenyl-1H-indole-2-carboxamide (50 mg, 0.14 mmol) **3c** in dichloromethane (5 mL) was added *tert*-butyl hypochlorite (23 μL, 0.20 mmol), and the reaction mixture was stirred for 5 h protected from the light. The reaction mixture was concentrated in vacuo, and the residue was dissolved in a mixture of dichloromethane (3 mL) and ethanol (1.5 mL). A solution of HCl in ethanol (5%, 0.5 mL) was added, and the solution was stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with ethyl acetate and light petroleum (3:7) to give the title compound as a colorless crystalline solid (45 mg, 86%); mp 209−210 °C (from light petroleum/ethyl acetate); IR ($CHCl_3$/cm^{-1}) 3427, 2941, 1736, 1668, 1619, 1455, 1374, 1306, 1128, 997; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.68 (1 H, s), 7.48 (1 H, d, *J* 8.4), 7.36−7.31 (6 H, m), 7.05 (1 H, t, *J* 7.8), 3.21 (3 H, s), 3.20 (3 H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.7 (C), 169.3 (C), 141.2 (C), 135.6 (C), 131.9 (CH), 128.8 (C), 128.5 (CH), 128.23 (CH), 128.17 (CH), 124.7 (CH), 123.7 (CH), 102.9 (C), 64.9 (C), 59.8 (Me), 33.5 (Me); MS (ES) 399:397 (M + Na^+, 100:99%), 377:375 (MH^+, 70:75); Found: MH^+, 375.0330. $C_{17}H_{15}{}^{79}BrN_2O_3$ + H requires: 375.0339.

2-[2-(4-Methoxybenzyloxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 7. (a) To a suspension of 2-iodophenol (2.23 g, 10 mmol), potassium carbonate (1.65 g, 12 mmol), tetra-*n*-butylammonium iodide (184 mg, 0.5 mmol), and 18-crown-6 (176 mg, 0.66 mmol) in acetone (50 mL) was added 4-methoxybenzyl chloride (1.49 mL, 11 mmol). The resulting suspension was stirred rapidly at reflux overnight. The solvent was removed in vacuo, and the residue was partitioned between water and ethyl acetate (2 × 100 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was recrystallized from light petroleum/acetate to afford 2-(4-methoxybenzyloxy)iodobenzene as a colorless solid (3.15 g, 99%); mp 101−102 °C; IR (KBr/cm^{-1}) 3008, 2955, 2932, 2833, 1610, 1580, 1567, 1515, 1478, 1465, 1438, 1375, 1303, 1281, 1241, 1178, 1164, 1115, 1052, 1030, 1016, 992, 868, 754; ^{1}H NMR (270 MHz; $CDCl_3$) δ 7.80 (1 H, dd, *J* 7.8, 1.5), 7.43 (2 H, d, *J* 8.7), 7.28 (1 H, ddd, *J* 8.2, 7.4, 1.5), 6.94 (2 H, d, *J* 8.7), 6.88 (1 H, dd, *J* 1.2, 8.2), 6.73 (1 H, ddd, *J* 7.6, 7.4, 1.2), 5.09 (2 H, s), 3.83 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 159.7 (C), 157.7 (C), 139.9 (CH), 129.9 (CH), 129.2 (CH), 129 (C), 123.3 (CH), 114.4 (CH), 113.3 (CH), 87.4 (C), 71.1 (CH_2), 55.7 (Me), MS (CI) 341 (MH^+, 16%), 232 (39), 213 (14), 121 (100); Found: MH^+, 341.0038. $C_{14}H_{13}IO_2$ + H requires: 341.0033. Found: C, 49.27; H, 3.82. $C_{14}H_{13}IO_2$ requires: C, 49.43; H, 3.85%.

(b) Triethylamine (2.76 mL, 10 mmol) was added to a degassed solution of 2-(4-methoxybenzyloxy)iodobenzene (1.70 g, 5 mmol), palladium acetate (11 mg, 0.05 mmol), and 2-(dicyclohexylphosphino)biphenyl (70 mg, 0.20 mmol) in anhydrous dioxane (23 mL) under argon. The resulting solution was degassed again before the slow addition of pinacolborane (2.24 mL, 15 mmol). The resulting dark-green solution was heated to 85 °C for 10 min and was then cooled to 0 °C. Saturated aqueous ammonium chloride (30 mL) was added carefully, and the reaction mixture was extracted with ether (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (17:3) and recrystallized from light petroleum. The title compound was obtained as a colorless solid (1.36 g, 82%); mp 79−81 °C; IR (KBr/cm^{-1}) 2976, 2935, 2885, 1613, 1600, 1575, 1516, 1490, 1448, 1354, 1271, 1249, 1141, 1073, 1049, 1035; 835, 826, 762; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.69 (1 H, dd, *J* 7.2, 1.7), 7.51 (2 H, d, *J* 8.6), 7.39 (1 H, ddd, *J* 8.3, 7.4, 1.7), 6.96 (1 H, d, *J* 7.3), 6.94 − 6.89 (3 H, m), 5.05 (2 H, s), 3.82 (3 H, s), 1.36 (12 H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 163.3 (C), 158.9 (C), 136.6 (CH), 132.4 (CH), 129.8 (C), 128.3 (CH), 120.6 (CH), 113.5 (CH), 112.3 (CH), 83.4 (C), 69.9 (CH_2), 55.3 (Me), 24.9 (Me); C−B carbon not observed; Found: M^+, 340.1837. $C_{20}H_{25}{}^{11}BO_4$ requires: 340.1846. Found: C, 70.58; H, 7.63. $C_{20}H_{25}BO_4$ requires: C, 70.40; H, 7.68%.

Ethyl 3-[2-(4-Methoxybenzyloxy)phenyl]indole-2-carboxylate 8a. To a degassed solution of ethyl 3-iodoindole-2-carboxylate **6a** (945 mg, 3 mmol) and 2-[2-(4-methoxybenzyloxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (1.22 g, 3.6 mmol) in DME (28 mL) was added $PdCl_2(dppf)\cdot CH_2Cl_2$ (122 mg, 0.15 mmol). Then, potassium carbonate (1.65 g, 12 mmol) in water (4 mL) was added slowly. The resulting red solution was stirred at 85 °C overnight. The mixture was allowed to cool to room temperature, water (50 mL) was added, and the solution was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The dark residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (17:3) to give the title product as a colorless solid (974 mg, 81%); mp 39−40 °C (from light petroleum); IR (neat/cm^{-1}) 3320, 1676, 1513, 1329, 1240, 1173, 1108, 1025, 1007; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.16 (1 H, s), 7.54 (1 H, d, *J* 8.0), 7.45−7.40 (2 H, m), 7.39−7.33 (2 H, m), 7.15−7.12 (1 H, m), 7.10−7.05 (4 H, m), 6.74 (2 H, d, *J* 8.8), 4.95 (2 H, s), 4.23 (2 H, q, *J* 7.2), 3.73 (3 H, s), 1.14 (3 H, t, *J* 7.2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 162.1 (C), 158.9 (C), 156.7 (C), 135.7 (C), 132.1 (CH), 129.3 (C), 128.7 (CH), 128.4 (CH), 128.2 (C), 125.3 (CH), 124.0 (C), 123.7 (C), 122.0 (CH), 120.5 (CH), 120.4 (CH), 120.0 (C), 113.6 (CH), 113.0 (CH), 111.6 (CH), 70.1 (CH_2), 60.6 (CH_2), 55.1 (Me), 13.9 (Me); MS (ESI) 424 (M + Na^+, 100%), 402 (MH^+, 51%); Found: MH^+, 402.1677. $C_{25}H_{23}NO_4$ + H requires: 402.1705. Found: C, 74.48; H, 5.80; N, 3.40. $C_{25}H_{23}NO_4$ requires: C, 74.79; H, 5.77; N, 3.49%.

Ethyl 7-Bromo-3-[2-(4-methoxybenzyloxy)phenyl]indole-2-carboxylate 8b. To a degassed solution of ethyl 7-bromo-3-iodoindole-2-carboxylate **6b** (300 mg, 0.76 mmol) and $PdCl_2$(dppf)

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·CH_2Cl_2 (117 mg, 0.16 mmol) in DME (10.5 mL) was added under nitrogen 2-[2-(4-methoxybenzyloxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (130 mg, 0.38 mmol), followed by a solution of potassium carbonate (525 mg, 3.81 mmol) in water (1.5 mL). The resulting mixture was degassed and heated to 30 °C for 2 h, and more borolane (260 mg, 0.76 mmol) was then gradually added over 3 h. The reaction mixture was stirred for 20 h and poured into saturated aqueous ammonium chloride (7 mL). Dichloromethane (20 mL) and water (20 mL) were added, and the residual aqueous solution was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography on silica, eluting with ethyl acetate/light petroleum (1:9) to give the title compound as a colorless oil (150 mg, 41%); IR (CH_2Cl_2/cm^{-1}) 3434, 2938, 1724, 1698, 1515, 1313, 1230, 1033, 720; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.95 (1 H, s), 7.42−7.22 (4 H, m), 7.03−6.89 (5 H, m), 6.67 (2 H, d, *J* 8.6), 4.86 (2 H, s), 4.14 (2 H, m), 3.68 (3 H, s), 1.04 (3 H, t, *J* 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 162.0 (C), 159.4 (C), 157.0 (C), 134.9 (C), 132.4 (CH), 129.6 (C), 129.5 (C), 129.4 (CH), 128.9 (CH), 128.0 (CH), 125.1 (C), 123.6 (C), 122.0 (CH), 121.7 (CH), 121.4 (C), 120.9 (CH), 114.0 (CH), 113.4 (CH), 105.4 (C), 70.5 (CH_2), 61.3 (CH_2), 55.6 (Me), 14.4 (Me); MS (FI) 481: 479 (M^+, 100:96%), 338 (5), 337 (20), 121 (4); Found: M^+, 479.0725. $C_{25}H_{22}{}^{79}BrNO_4$ requires: 479.0732.

Ethyl 3-[2-(4-Methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate 9a. To a solution of ethyl 3-[2-(4-methoxybenzyloxy)-phenyl]indole-2-carboxylate **8a** (401 mg, 1.0 mmol) in dichloromethane (30 mL) protected from the light was added *tert*-butyl hypochlorite (183 mg, 1.5 mmol). The solution was stirred at room temperature for 4 h before the solvents were removed in vacuo. The residue was dissolved in dichloromethane (30 mL) and ethanol (20 mL), and a solution of HCl in diethyl ether (1 M; 1.0 mL) was added. The solution was stirred overnight. The solvents were removed in vacuo, and the residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (4:1) to give the title compound as a colorless solid (360 mg, 87%); mp 160−161 °C (from light petroleum); IR ($CHCl_3$/cm^{-1}) 3435, 2936, 2838, 1747, 1614, 1453, 1317, 1310, 1095, 1038, 1002; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.89 (1 H, s), 7.35−7.26 (4 H, m), 7.23 (1 H, dt, *J* 1.2, 7.8), 7.06−6.99 (3 H, m), 6.92−6.88 (3 H, m), 6.77 (1 H, d, *J* 7.8), 4.98 (2 H, s), 4.04−3.85 (2 H, m), 3.79 (3 H, s), 1.03 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 175.0 (C), 168.4 (C), 159.2 (C), 157.0 (C), 141.4 (C), 129.5 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.6 (C), 126.0 (C), 125.8 (CH), 122.5 (CH), 120.8 (CH), 113.7 (CH), 113.1 (CH), 109.9 (CH), 70.5 (CH_2), 63.0 (C), 61.9 (CH_2), 55.2 (Me), 13.7 (Me); one C unobserved; MS (ESI) 440 (MH^+, 100%), 287 (9%); Found: MH^+, 440.1457. $C_{25}H_{23}NO_5$ + H requires: 440.1468. Found: C, 71.87; H, 5.64; N, 3.28. $C_{25}H_{23}NO_5$ requires: C, 71.93; H, 5.55; N, 3.36%.

Ethyl 7-Bromo-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate 9b. To a solution of ethyl 7-bromo-3-[2-(4-methoxybenzyloxy)phenyl]indole-2-carboxylate **8b** (78 mg, 0.16 mmol) protected from light in dichloromethane (3 mL) was added a solution of *tert*-butyl hypochlorite (35 mg, 0.32 mmol) in dichloromethane (3 mL). The solution was stirred at room temperature for 2 h. Further *tert*-butyl hypochlorite (26 mg, 0.24 mmol) was added, and the reaction mixture was stirred for a further 3 h. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane (4 mL) and ethanol (2 mL). A total of 500 μL of a solution of acetyl chloride (0.5 mL) in ethanol (9.5 mL) was added, and the resulting mixture was stirred overnight, protected from light. The solvent was removed in vacuo, and the residue was purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a colorless solid (40 mg, 51%); mp 144−146 °C (light petroleum); IR (CH_2Cl_2/cm^{-1}) 3413, 2938, 1757, 1614, 1516, 1492, 1474, 1454, 1304, 1229, 1112, 1035; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.32−6.80 (12 H, m), 4.85 (2 H, s), 4.04−3.90 (2 H, m), 3.75 (3 H, s), 1.05 (3 H, t, *J* 7.0); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.9 (C), 167.8 (C), 159.4 (C), 156.7 (C), 140.4 (C), 131.4 (CH), 130.1 (C), 129.8 (CH), 129.5 (CH), 128.7 (CH), 128 (C), 125.2 (C), 124.7 (CH), 123.7 (CH), 120.8 (CH), 113.9 (CH), 112.9 (CH), 102.5 (C), 70.5 (CH_2), 64.3 (C), 62.3 (CH_2), 55.2 (Me), 13.8 (Me); MS (EI) 497:495 (M^+, 27: 54%), 338 (30), 337 (100), 330:328 (18:12), 206:204 (12:29), 121 (17), 106 (40), 83 (39); Found: M^+, 495.0699. $C_{25}H_{22}{}^{79}BrNO_5$ requires: 495.0681.

Ethyl 1-(*tert*-Butoxycarbonyl)-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate 10a. A suspension of ethyl 3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate **9a** (270 mg, 0.64 mmol), sodium carbonate (342 mg, 3.23 mmol), and di-*tert*-butyl dicarbonate (352 mg, 1.61 mmol) in anhydrous THF (15 mL) was stirred at reflux for 3 h. Water (20 mL) was added, and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (8:2) to give the title compound as a colorless solid (320 mg, 97%); mp 142−144 °C (from light petroleum/chloroform); IR ($CHCl_3$/cm^{-1}) 2982, 2937, 2838, 1799, 1795, 1731, 1613, 1586, 1465, 1454, 1370, 1346, 1303, 1148, 1090, 1037, 1003; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.78 (1 H, d, *J* 7.9), 7.36−7.32 (2 H, m), 7.27 (1 H, ddd, *J* 8.2, 7.5, 1.7), 7.24−7.21 (2 H, m), 7.15 (1 H, ddd, *J* 7.5, 7.3, 1.0), 7.01 (1 H, dd, *J* 7.8, 1.6), 6.98 (1 H, dd, *J* 8.2, 0.8), 6.90−6.84 (3 H, m), 4.96 (2 H, d, *J* 2.9), 4.04−3.90 (2 H, m), 3.81 (3 H, s), 1.61 (9 H, s), 1.08 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; CD_2Cl_2) δ 170.2 (C), 168.3 (C), 159.2 (C), 156.8 (C), 149.1 (C), 140.1 (C), 129.8 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.4 (C), 127.0 (C), 125.9 (C), 125.4 (CH), 124.4 (CH), 120.6 (CH), 114.9 (CH), 113.7 (CH), 113.2 (CH), 84.1 (C), 70.5 (CH_2), 62.7 (C), 62.1 (CH_2), 55.2 (Me), 28.0 (Me), 13.7 (Me); MS (ESI) 540 (M + Na^+, 100%), 518 (MH^+, 2%), 418 (17%); Found: MH^+, 518.2168. $C_{30}H_{31}NO_7$ + H requires: 518.2173.

10-*tert*-Butyl 4b-Ethyl 9a,10-Dihydro-10-aza-9-oxaindeno[1,2-*a*]indene-4b,10-dicarboxylate 11a. To a solution of ethyl 1-(*tert*-butoxycarbonyl)-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate **10a** (270 mg, 0.52 mmol) in anhydrous THF (6 mL) was added slowly at 0 °C a solution of sodium borohydride (38 mg, 1.04 mmol) in MeOH (4 mL). The solution was stirred at 0 °C for 30 min before the careful addition of a solution of sulfuric acid (0.5 M, 1.5 mL). Water (20 mL) was added, and the reaction mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was taken up in dry dichloromethane (10 mL), triethylamine (215 μL, 1.56 mmol) was added under nitrogen, and the solution was cooled to 0 °C. Then, methanesulfonic anhydride (135 mg, 0.78 mmol) was added portion-wise over 15 min. A saturated solution of sodium hydrogen carbonate (20 mL) was added at 0 °C, and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (24:1) to afford the title compound as a colorless oil (141 mg, 76%); IR ($CHCl_3$/cm^{-1}) 2982, 2932, 1733, 1713, 1603, 1484, 1387, 1370, 1358, 1303, 1154, 1101, 1057, 1024, 907; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.79 (1 H, br), 7.67 (1 H, dd, *J* 7.62, 1.1), 7.63 (1 H, dd, *J* 7.7, 0.9), 7.26 (1 H, ddd, *J* 8.2, 7.9, 1.3), 7.19 (1 H, ddd, *J* 8.1, 7.6, 1.4), 7.14 (1 H, br), 7.05 (1 H, ddd, *J* 7.6, 7.6, 1.0), 6.95 (1 H, ddd, *J* 7.5, 7.5, 1.0), 6.84 (1 H, d, *J* 8.0), 4.28 (2 H, q, *J* 7.1), 1.64 (9 H, s), 1.33 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.9 (C), 158.1 (C), 151.9 (C), 140.8 (C), 129.6 (CH), 128.3 (CH), 126.5 (C), 124.1 (2 × CH), 123.4 (CH), 121.4 (CH), 115.3 (CH), 113.8 (C), 110.2 (CH), 98.3 (CH), 82.5 (C), 63.4 (C), 62.3 (CH_2), 28.3 (Me), 14.0 (Me); MS (ESI) 404 (M + Na^+, 49%), 382 (MH^+, 11%), 326 (75%), 282 (100%), 236 (55%); Found: MH^+, 382.1668. $C_{22}H_{23}NO_5$ + H requires: 382.1654. Found: C, 69.52; H, 6.15; N, 3.64. $C_{22}H_{23}NO_5$ requires C, 69.28; H, 6.08; N, 3.67%.

Ethyl 1-Allyloxycarbonyl-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate 10b. To a suspension of sodium hydride (60% dispersion in mineral oil; 50 mg, 1.25 mmol) in dry THF (15 mL) was added slowly at 0 °C under nitrogen a solution of ethyl 3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate **9a** (180 mg, 0.42 mmol) in THF (5 mL). The suspension was stirred for 5 min at 0 °C and then for 10 min at room temperature. Allyl chloroformate (78 μL, 0.71 mmol) in dichloromethane (1 mL) was added dropwise to the suspension at 0 °C. The solution was stirred for 10 min at room temperature before the slow addition of 4-dimethylaminopyridine (30 mg, 0.25 mmol) in dichloromethane (1 mL). After stirring for 5 min at room temperature, the reaction mixture was cooled down again to 0 °C, and water (15 mL) was added dropwise. The reaction mixture was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (4:1) to give the title compound as a colorless oil (191 mg, 90%); IR ($CHCl_3$/cm^{-1}) 2930, 1782, 1731, 1613, 1465, 1368, 1342, 1302, 1156, 1091, 1038, 908; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.83 (1 H, d, *J* 8.1), 7.35 (1 H, ddd *J* 8.3, 8.2, 1.3), 7.31−7.27 (2 H, m), 7.20−7.15 (3 H, m), 7.07, (1 H, d, *J* 7.0), 6.97 (1 H, d, *J* 7.8), 6.91 (1 H, ddd, *J* 7.7, 7.6, 0.9), 6.87−6.83 (2 H, m), 6.02 (1 H, dddd, *J* 17.0, 10.4, 5.6, 5.6), 5.52 (1 H, d, *J* 17.0), 5.33 (1 H, d, 10.4), 4.90 (2 H, s), 4.81 (2 H, d, *J* 5.4), 4.11−3.93 (2 H, m), 3.82 (3 H, s), 1.10 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.0 (C), 167.7 (C), 159.3 (C), 156.6 (C), 150.5 (C), 139.6 (C), 131.1 (CH), 129.0 (CH), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.1 (C), 127.1 (C), 125.6 (C), 125.4 (CH), 124.7 (CH), 120.6 (CH), 119.0 (CH_2), 115.0 (CH), 113.7 (CH), 112.9 (CH), 70.4 (CH_2), 67.4 (CH_2), 62.7 (C), 62.3 (CH_2), 55.2 (Me), 13.7 (Me); MS (ESI) 524 (M + Na$^+$, 100%); Found: M + Na$^+$, 524.1660. $C_{29}H_{27}NO_7$ + Na requires: 524.1685.

10-Allyl 4b-Ethyl 9a,10-Dihydro-10-aza-9-oxaindeno[1,2-*a*]indene-4b,10-dicarboxylate 11b. To a solution of ethyl 1-allyloxycarbonyl-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate **10b** (190 mg, 0.38 mmol) in anhydrous THF (5 mL) was added slowly at 0 °C a solution of sodium borohydride (29 mg, 0.76 mmol) in MeOH (3.5 mL). The solution was stirred at 0 °C for 30 min before the careful addition of a solution of sulfuric acid (0.5 M, 1 mL). Water (20 mL) was added, and the reaction mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo. The residue was taken up with dry dichloromethane (5 mL), triethylamine (157 μL, 1.14 mmol) was added under nitrogen, and the solution was cooled to 0 °C. Then, methanesulfonic anhydride (99 mg, 0.57 mmol) was added portion-wise over 15 min. Saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (19:1) to afford the title compound as a colorless oil (87 mg, 63%); IR ($CHCl_3$/cm^{-1}) 2983, 1731, 1603, 1485, 1395, 1347, 1298, 1153, 1102, 1058, 1030, 993, 945; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.85 (1 H, br), 7.69 (1 H, dd, *J* 7.6, 1.2), 7.66 (1 H, ddd, *J* 7.6, 1.3, 0.5), 7.29 (1 H, ddd, *J* 8.2, 7.8, 1.3), 7.21 (1 H, s), 7.20 (1 H, ddd, *J* 8.0, 7.5, 1.3), 7.08 (1 H, ddd, *J* 7.6, 7.5, 1.0), 6.96 (1 H, ddd, *J* 7.6, 7.5, 1.0), 6.85 (1 H, d, *J* 8.0), 6.10 (1 H, dddd, *J* 17.2, 10.6, 5.5, 5.5), 5.50 (1 H, d, *J* 17.2), 5.34 (1 H, ddd, *J* 10.5, 2.6, 1.3), 4.87 (2 H, m), 4.29 (2 H, q, *J* 7.1), 1.33 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.3 (C), 158.5 (C), 152.8 (C), 141.3 (C), 132.7 (CH), 130.5 (CH), 130.1 (CH), 127.1 (C), 124.97 (CH), 124.88 (CH), 124.5 (CH), 122.3 (CH), 118.8 (CH_2), 115.9 (CH), 110.7 (CH), 98.8 (CH), 67.4 (CH_2), 64.0 (C), 63.2 (CH_2), 14.5 (Me); one C unobserved; MS (ESI) 388 (M + Na$^+$, 20%), 366 (MH$^+$, 100), 320 (25); Found: M + Na$^+$, 366.1336. $C_{21}H_{19}NO_5$ + Na requires: 366.1342. Found: C, 68.76; H, 5.27; N, 3.77. $C_{21}H_{19}NO_5$ requires: C, 69.03; H, 5.24; N, 3.83%.

Ethyl 1-Allyloxycarbonyl-7-bromo-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate 10c. To a solution of ethyl 7-bromo 3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate **9b** (20 mg, 0.04 mmol) in THF (3 mL) was added at 0 °C sodium hydride (60% dispersion in mineral oil, 6 mg, 0.15 mmol) in one portion under nitrogen. The suspension was stirred for 5 min at 0 °C and then warmed to room temperature, stirred for 10 min, and then cooled to 0 °C. Allyl chloroformate (8 mg, 0.07 mmol) in dichloromethane (2 mL), was added dropwise over 5 min. The suspension was warmed to room temperature and stirred for 10 min, and a solution of 4-dimethylaminopyridine (4 mg, 0.03 mmol) in dichloromethane (1 mL) was added dropwise over 5 min. The reaction mixture was stirred for a further 45 min and then quenched with acetic acid (1 mL) at 0 °C. The mixture was poured into a saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with diethyl ether (4 × 20 mL). The organic layers were then washed sequentially with sulfuric acid (1 M), a saturated solution of sodium hydrogen carbonate water, dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a colorless oil (16 mg, 69%); IR (CH_2Cl_2/cm^{-1}) 2938, 1799, 1742, 1612, 1515, 1490, 1463, 1446, 1363, 1285, 1222, 1176, 1159, 1110, 1026, 941; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.43 (1 H, d, *J* 8.1), 7.23−6.75 (10 H, m), 5.92 (1 H, ddt, *J* 17.1, 10.5, 5.8), 5.36 (1 H, dd, *J* 17.3, 1.3), 5.24 (1 H, dd, *J* 10.3, 1), 4.88 (2 H, s), 4.80 (2 H, d, *J* 5.9), 4.01−3.81 (2 H, m), 3.72 (3 H, s), 1.03 (3 H, t, *J* 7.0); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.4 (C), 167.1 (C), 159.1 (C), 156.3 (C), 149.3 (C), 138.7 (C), 133.8 (CH), 130.7 (C), 130.6 (CH), 129.9 (CH), 129.0 (CH), 128.8 (CH), 128.2 (C), 125.6 (CH), 124.8 (C), 124.5 (CH), 120.6 (CH), 119.6 (CH_2), 113.7 (CH), 113.0 (CH), 106.7 (C), 70.2 (CH_2), 68.7 (CH_2), 64.3 (C), 62.5 (CH_2), 55.1 (Me), 13.5 (Me); MS (FI) 581/579 (M$^+$, 94: 100%), 106 (25); Found: M$^+$, 579.0908. $C_{29}H_{26}{}^{79}BrNO_7$ requires: 579.0893.

10-Allyl 4b-Ethyl 9a,10-Dihydro-10-aza-9-oxa-1-bromoindeno[1,2-*a*]indene-4b,10-dicarboxylate 11c. To a solution of ethyl 1-allyloxycarbonyl-7-bromo-3-[2-(4-methoxybenzyloxy)phenyl]-2-oxoindole-3-carboxylate **10c** (20 mg, 34 μmol) in THF (3 mL) was added at 0 °C under a nitrogen atmosphere a solution of sodium borohydride (6 mg, 158 μmol) dissolved at 0 °C in methanol. The reaction mixture was stirred for a further 45 min, poured into a stirred solution of sulfuric acid (1 M, 5 mL), and extracted with ether (4 × 20 mL). The organic layers were washed with saturated aqueous sodium hydrogen carbonate, water, dried ($MgSO_4$), and evaporated in vacuo. The residue was taken up in dichloromethane (3 mL), and triethylamine (40 μL, 285 μmol) was added, followed by methanesulfonic anhydride (72 mg, 414 μmol) in one portion. The resulting mixture was stirred for 24 h and was poured into a solution of sodium hydrogen carbonate (10%, 5 mL) and extracted with dichloromethane (3 × 20 mL). The organic layers were washed with water, dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a colorless oil (9 mg, 60%); IR (CH_2Cl_2/cm^{-1}) 2962, 2930, 1738, 1600, 1477, 1465, 1446, 1381, 1369, 1297, 1217, 1098, 1028; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.60 (1 H, dd, *J* 7.5, 1.3), 7.42 (2 H, td, *J* 7.7, 1.0), 7.13 (1 H, td, *J* 7.5, 1.0), 7.11 (1 H, s), 6.94 (1 H, t, *J* 7.7), 6.88 (1 H, td, *J* 7.5, 1.0), 6.77 (1 H, d, *J* 7.5), 5.99 (1 H, ddt, *J* 17.1, 10.3, 5.8), 5.36 (1 H, ddt, *J* 17.3, 1.5, 1.3), 5.24 (1 H, ddt, *J* 10.3, 1.5, 1.3), 4.82 (1 H, ddt, *J* 13, 5.8, 1.3), 4.76 (1 H, ddt, *J* 13, 5.8, 1.3), 4.21 (2 H, q, *J* 7.2), 1.26 (3 H, t, *J* 7.2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.9 (C), 157.9 (C), 152.2 (C), 139.7 (C), 134.6 (C), 134.2 (CH), 131.5 (CH), 129.8 (CH), 126.7 (CH), 125.4 (C), 124.1 (CH), 123.1 (CH), 121.6 (CH), 118.9 (CH_2), 112.1 (C), 110.0 (CH), 100.4 (CH), 67.5 (CH_2), 64.0 (C), 62.4 (CH_2), 13.8 (Me); MS (FI) 445:443 (M$^+$, 100%), 337 (70), 338 (25); Found: M$^+$, 443.0353. $C_{21}H_{18}{}^{79}BrNO_5$ requires: 443.0368.

10-*tert*-Butoxycarbonyl-9a,10-dihydro-10-aza-9-oxaindeno-[1,2-*a*]indene-4b-carboxylic Acid 12a. To a solution 10-*tert*-butyl 4b-ethyl 10-aza-9-oxaindeno[1,2-*a*]indene-4b,10-dicarboxylate **11a** (72 mg, 0.188 mmol) in ethanol (2.5 mL) was added a solution of cesium carbonate (66 mg, 0.20 mmol) in water (4 mL). The milky suspension was stirred at room temperature for 48 h. The clear reaction mixture was concentrated in vacuo, water was added (4 mL), and the pH was adjusted to 1 using hydrochloric acid (2 M). The precipitate was filtered, washed with cold water, and dried in vacuo. The title compound was obtained as a powder (55 mg, 83%); mp 98−100 °C (light petroleum/chloroform); IR ($CHCl_3$/cm^{-1}) 3198, 2981, 1754, 1715, 1603, 1484, 1387, 1370, 1358, 1303, 1154, 1102, 1057, 1021, 967, 945, 866; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.82 (1 H, br), 7.66 (1 H, d, *J* 7.5), 7.62 (1 H, d, *J* 7.5), 7.26 (1 H, t, *J* 7.7), 7.20−7.15 (2 H, m), 7.03 (1 H, t, *J* 7.5), 6.93 (1 H, t, *J* 7.5), 6.86 (1 H, d, *J* 8.0), 1.65 (9 H, s); OH not observed; ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.5 (C), 158.0 (C), 140.8 (C, br), 129.9 (CH), 129.6 (CH), 128.8 (C, br), 125.8 (C), 124.3 (CH), 123.5 (CH), 121.6 (CH), 115.4 (CH), 110.3 (CH), 98.1 (CH), 82.9 (C, br), 63.6 (C, br), 28.3 (Me); MS (FI) 376 (M + Na^+, 100%), 320 (23%), 254 (15%); Found: M + Na^+, 376.1153. $C_{20}H_{19}NO_5$ + Na requires: 376.1160.

10-Allyloxycarbonyl-9a,10-dihydro-10-aza-9-oxaindeno[1,2-*a*]indene-4b-carboxylic Acid 12b. To a solution of 10-allyl 4b-ethyl 10-aza-9-oxaindeno[1,2-*a*]indene-4b,10-dicarboxylate **11b** (25 mg, 0.068 mmol) in ethanol (2.5 mL) was added a solution of cesium carbonate (66 mg, 0.20 mmol) in water (4 mL). The milky suspension was stirred at room temperature for 48 h. The clear reaction mixture was concentrated in vacuo, and water was added (4 mL). The pH was adjusted to 1 using hydrochloric acid (2 M), and the precipitate was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting powder was recrystallized from light petroleum and chloroform to give the title compound as a colorless solid (21 mg, 91%); mp 164−166 °C (light petroleum/chloroform); IR ($CHCl_3$/cm^{-1}) 2891, 1715, 1603, 1485, 1466, 1396, 1347, 1297, 1153, 1103, 1057, 1022, 975, 946; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.89 (1 H, br), 7.68 (1 H, dd, *J* 0.8, 7.6), 7.64 (1 H, d, *J* 7.6), 7.28 (1 H, t, *J* 7.2), 7.22−7.18 (2 H, m), 7.07 (1 H, ddd, *J* 7.6, 0.8), 6.96 (1 H, td, *J* 7.6, 0.8), 6.87 (1 H, d, *J* 8.4), 6.08 (1 H, dddd, *J* 17.2, 10.5, 5.6, 5.4). 5.49 (1 H, d, *J* 17.2), 5.34 (1 H, dd, *J* 1.2, 10.4), 4.89 (2 H, d, *J* 5.6); OH not observed; ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.1 (C), 157.9 (C), 140.0 (C), 131.9 (C), 130.1 (CH), 129.8 (CH), 128.7 (C), 125.5 (C), 124.3 (CH), 124.0 (CH), 121.8 (C), 118.6 (CH_2), 115.5 (CH), 110.4 (CH), 97.8 (CH), 66.9 (CH_2), 63.7 (C); MS (FI) 445/443 (M^+, 100%), 337 (70), 338 (25); Found: MH^+, 338.1014. $C_{19}H_{15}NO_5$ + H requires: 338.1023.

2-(Indol-3-yl)-phenol 13. 10-*tert*-Butoxycarbonyl-9a,10-dihydro-10-aza-9-oxaindeno[1,2-*a*]indene-4b-car boxylic acid **12a** (10 mg, 28 μmol) was heated to 100 °C until the gas emission ceased. The residue was purified by flash chromatography eluting with light petroleum and ethyl acetate (8:2) to give the title compound as a colorless oil (5.0 mg, 84%); (lit.,[67] mp 135 °C); IR ($CHCl_3$/cm^{-1}) 3530, 3473, 1482, 1456, 1347, 1094; ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.42 (1 H, s), 7.63 (1 H, dd, *J* 8.0, 1.0), 7.49 (1 H, dt, *J* 8.0, 7.0), 7.41 (1 H, dd, *J* 7.5, 1.5), 7.38 (1 H, d, *J* 2.8), 7.32−7.29 (2 H, m), 7.20 (1 H, ddd, *J* 8.0, 7.5, 1.0), 7.07 (1 H, dd, *J* 8.0, 1.0), 7.02 (1 H, dd, *J* 7.5, 1.5), 5.41 (1 H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 153.4 (C), 136.4 (C), 130.8 (CH), 128.6 (CH), 126.3 (C), 123.1 (CH), 123.0 (CH), 120.8 (C), 120.6 (CH), 120.5 (CH), 119.8 (CH), 115.3 (CH), 112.0 (C), 111.5 (CH); MS (ES) 222 (M + Na^+, 74%), 210 (MH^+, 100%); Found: MH^+, 210.0911. $C_{14}H_{11}NO_3$ + H requires: 210.0919.

Ethyl 9a,10-Dihydro-10-aza-9-oxaindeno[1,2-*a*]indene-4b-carboxylate 14. To a solution of 10-*tert*-butyl 4b-ethyl 10-aza-9-oxaindeno[1,2-*a*]indene-4b,10-dicarboxylate **11a** (95 mg, 0.25 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.40 mL). The solution was stirred overnight at room temperature, and a saturated solution of sodium hydrogen carbonate (10 mL) was carefully added. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with light petroleum/ethyl acetate (9:1) to give the title compound as a colorless solid (36 mg, 51%); mp 115−117 °C (from light petroleum); IR ($CHCl_3$/cm^{-1}) 3450, 1731, 1609, 1485, 1319, 1051; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.67 (1 H, ddd, *J* 7.6, 1.4, 0.4), 7.58 (1 H, ddd, *J* 7.6, 1.3, 0.5), 7.18 (1 H, ddd, *J* 8.0, 7.5, 1.4), 7.13 (1 H, ddd, *J* 7.8, 7.7, 1.3), 6.93 (1 H, ddd, *J* 7.5, 7.5, 1.0), 6.89 (1 H, d, *J* 2.7), 6.85−6.81 (2 H, m), 6.69 (1 H, d, *J* 7.9), 5.10 (1 H, br), 4.30 (2 H, q, *J* 7.1), 1.36 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.6 (C), 158.2 (C), 147.2 (C), 129.4 (CH), 129.3 (CH), 127.5 (C), 126.9 (C), 124.4 (CH), 124.2 (CH), 121.1 (CH), 119.9 (CH), 110.1 (CH), 109.7 (CH), 99.9 (CH), 65.8 (C), 62.1 (CH_2), 14.1 (Me); MS (ES) 304 (M + Na^+, 100%), 282 (MH^+, 67%), 236 (52%); Found: MH^+, 282.1116. $C_{17}H_{15}NO_3$ + H requires: 282.1125. Found: C, 72.29; H, 5.50; N, 4.83. $C_{17}H_{15}NO_3$ requires: C, 72.58; H, 5.37; N, 4.98%.

(*S*)-*N*-Benzyloxycarbonyl-*O*-(4-methoxybenzyl)-3-iodotyrosine *tert*-Butyl Ester. To a suspension of *N*-benzyloxycarbonyl-3-iodotyrosine *tert*-butyl ester **15**[46] (468 mg, 0.94 mmol), potassium carbonate (156 mg, 1.13 mmol), 18-crown-6 (16.6 mg, 0.06 mmol), and tetra-*n*-butylammonium iodide (17 mg, 0.05 mmol) in acetone (50 mL) was added 4-methoxybenzyl chloride (141 μL, 1.04 mmol). The resulting mixture was heated to reflux for 12 h. The solvent was removed in vacuo, and the residue was taken up in dichloromethane, washed with water (2 × 50 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography eluting with dichloromethane/ether (100:0 to 97:3) to give the title compound as a colorless oil (520 mg, 90%); $[\alpha]_D^{35}$ +49 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2/cm^{-1}) 3424, 2981, 2938, 1720, 1613, 1514, 1488, 1353, 1276, 1245, 1175, 1154, 1040, 1005, 717; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.50 (1 H, d, *J* 1.9), 7.36−7.20 (7 H, m), 6.97 (1 H, d, *J* 8.1), 6.84 (2 H, d, *J* 8.8), 6.67 (1 H, d, *J* 8.4), 5.20 (1 H, d, *J* 8.0), 5.02 (2 H, m), 4.97 (2 H, s), 4.40 (1 H, td, *J* 7.9, 6.0), 3.74 (3 H, s), 2.91 (2 H, br d, *J* 5.7), 1.33 (9 H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.3 (C), 159.3 (C), 156.3 (C), 155.5 (C), 140.3 (CH), 136.3 (C), 130.5 (C), 130.4 (CH), 128.7 (CH), 128.6 (CH), 128.5 (C), 128.2 (CH), 128.1 (CH), 113.9 (CH), 112.6 (CH), 86.8 (C), 82.6 (C), 70.8 (CH_2), 66.9 (CH_2), 55.3 (Me), 55.2 (CH), 37.0 (CH_2), 28.0 (Me); MS (CI) 618 (MH^+, 25%), 518 (46), 390 (17), 211 (20), 121 (100); Found: MH^+, 618.1348. $C_{29}H_{32}INO_6$ + H requires: 618.1352.

(*S*)-*N*-Benzyloxycarbonyl-*O*-(4-methoxybenzyl)-3-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl] Tyrosine *tert*-Butyl Ester 16. To a solution of *N*-benzyloxycarbonyl-*O*-(4-methoxybenzyl)-3-iodotyrosine *tert*-butyl ester (683 mg, 1.11 mmol) and 2-(dicyclohexylphosphino)biphenyl (78 mg, 0.22 mmol) in dry and degassed dioxane (6 mL) was added nitrogen palladium(II) acetate (14 mg, 0.06 mmol) and triethylamine (617 μL, 4.43 mmol). The resulting mixture was degassed. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (481 μL, 3.31 mmol) was then added dropwise over 15 min, and the resulting green−black mixture was heated to 85 °C for 30 min. The reaction mixture was poured into saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (4 × 20 mL). The combined extracts were washed with water (10 mL), dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography eluting with ethyl acetate/light petroleum (1:9 to 3:7) to give the title compound as a yellow oil (480 mg, 70%); $[\alpha]_D^{26}$ +40 (*c* 0.74, CH_2Cl_2); IR (CH_2Cl_2/cm^{-1}) 3426, 2982, 2935, 1720, 1608, 1514, 1496, 1372, 348, 1243, 1241, 1175, 1146, 1071, 1035, 910; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.42 (2 H, d, *J* 8.5), 7.31−7.22 (6 H, m), 7.09 (1 H, d, *J* 8.3), 6.83 (2 H, d, *J* 8.5), 6.75 (1 H, d, *J* 8.5), 5.17 (1 H, d, *J* 7.9), 5.02 (2 H, s), 4.95 (2 H, s), 4.43 (1 H,

(67) Saleha, S.; Khan, N. H.; Siddiqui, A. A.; Kidwai, M. M. *Indian J. Chem., Sect. B* **1978**, *16*, 1122.

td, *J* 8, 6.2), 3.74 (3 H, s), 2.96 (2 H, br d, *J* 5.8), 1.33 (9 H, s), 1.26 (12 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 170.5 (C), 162.4 (C), 158.8 (C), 155.5 (C), 137.8 (CH), 136.3 (C), 133.5 (CH), 130.5 (CH), 129.6 (C), 129.2 (CH), 128.4 (CH), 128.2 (CH), 128.02 (CH), 127.98 (CH), 127.7 (C), 114.7 (CH), 113.9 (CH), 113.4 (CH), 112.3 (CH), 83.3 (C), 82.2 (C), 69.8 (CH_2), 66.7 (CH_2), 55.2 (Me + CH), 37.3 (CH_2), 27.9 (Me), 24.95 (Me), 24.88 (Me); one ArC not observed (C−B); MS (EI) 617 (M^+, 10%), 466 (7), 121 (100), 91 (36); Found: M^+, 617.3166. $C_{35}H_{44}{}^{11}BNO_8$ requires: 617.3160.

(*S*)-Ethyl 3-[5-(2-Benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-(4-methoxybenzyloxy)]phenyl-7-bromoindole-2-carboxylate 17. To a solution of ethyl 7-bromo-3-iodoindole-2-carboxylate **6b** (465 mg, 1.18 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (136 mg, 0.19 mmol) in degassed DME (15.5 mL) was added *N*-benzyloxycarbonyl-*O*-(4-methoxybenzyl)-3-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]tyrosine *tert*-butyl ester **16** (364 mg, 0.59 mmol), followed by potassium carbonate (856 mg, 6.22 mmol) dissolved in water (2.2 mL). The resulting mixture was degassed and heated to 35 °C for 2 h, and more of the borolane (728 mg, 1.18 mmol) was then gradually added over 3 h. The reaction mixture was stirred for 40 h at 35 °C, cooled to room temperature, and poured into saturated aqueous ammonium chloride (10 mL). Dichloromethane (25 mL) and water (25 mL) were added, and the residual aqueous solution was extracted with dichloromethane (4 × 25 mL). The combined extracts were dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a yellow solid (350 mg, 40%); mp 60−68 °C (dec) (light petroleum); $[\alpha]_D{}^{32}$ + 28.4 (*c* 0.74, CH_2Cl_2); IR (film/cm^{-1}) 3430, 2981, 1722, 1637, 1514, 1309, 1231, 1174, 1155, 1033; ^{1}H NMR (300 MHz; toluene-*d*; 100 °C) δ 8.77 (1 H, s), 7.40 (1 H, t, *J* 8.1), 7.24−6.95 (8 H, m), 6.84 (3 H, t, *J* 7.9), 6.70 (1 H, t, *J* 7.9), 6.66 (2 H, d, *J* 8.9), 5.09 (1 H, br d, *J* 8.1), 4.96 (2 H, m), 4.66 (2 H, s), 4.56 (1 H, td, *J* 6.2, 8.1), 4.02 (2 H, q, *J* 7.1), 3.32 (3 H, s), 3.03 (1 H, dd, *J* 6.1, 14.1), 2.99 (1 H, dd, *J* 6.1, 14.1), 1.27 (9 H, s), 0.87 (3 H, t, *J* 7.1); ^{13}C NMR (100 MHz; DMSO-*d*; 60 °C) δ 170.5 (C), 160.6 (C), 158.4 (C), 154.6 (C), 136.6 (C), 134.3 (C), 131.9 (CH), 128.9 (CH), 128.8 (C), 128.75 (C), 128.7 (C), 128.6 (C), 128.3 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 125.7 (C), 122.3 (C), 120.9 (CH), 120.2 (CH), 119.1 (C), 113.2 (CH), 112.5 (CH), 104.3 (C), 80.3 (C), 69.2 (CH_2), 65.1 (CH_2), 59.8 (CH_2), 56.0 (CH), 54.7 (Me), 35.7 (CH_2), 27.2 (Me), 13.3 (Me); MS (ES) 781/779 (M + Na^+, 99/87%), 759:757 (MH^+, 30/28), 725:723 (13:20), 703:701 (34:32), 659:657 (42:44), 640 (12), 530 (20), 518 (12); Found: MH^+, 757.2122. $C_{40}H_{41}{}^{79}BrN_2O_8$ + H requires: 757.2119.

Ethyl 3-[5-(2-Benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-(4-methoxybenzyloxy)]phenyl-7-bromo-2-oxoindole-3-carboxylate 18. To a stirred solution of ethyl 3-[5-(2-benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-(4-methoxybenzyloxy)]-phenyl-7-bromoindole-2 carboxylate **17** (140 mg, 0.18 mmol) in dichloromethane (3 mL) protected from light was added *tert*-butyl hypochlorite (42 mg, 0.39 mmol). The reaction was stirred under nitrogen at room temperature for 2 h. *tert*-Butyl hypochlorite (42 mg, 0.39 mmol) was added again, and the reaction mixture was stirred for a further 6 h. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane (14 mL) and ethanol (7 mL). A total of 570 μL of a solution of acetyl chloride (0.5 mL) in ethanol (9.5 mL) was added, and the resulting mixture was stirred overnight, protected from light. The solvent was removed in vacuo, and the residue was purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a yellow solid (95 mg, 68%) as an inseparable mixture of diastereoisomers; mp 88−93 °C (dec) (light petroleum); IR (CH_2Cl_2/cm^{-1}) 3419, 2934, 1728 (shoulder at 1758), 1614, 1515, 1499, 1468, 1369, 1304, 1212, 1156, 1036; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.28−6.74 (16 H, m), 5.17 (1 H, d, *J* 7.7), 5.01 (2 H, br s), 4.87−4.82 (2 H, m), 4.41−4.34 (1 H, m), 3.99−3.80 (2 H, m), 3.75 (3 H, s), 2.90 (2 H, br d, *J* 5.7), 1.26:1.24 (9 H, 2 × s), 1.02: 0.98 (3 H, 2 × t, *J* 7.0); diastereomeric ratio 1:1.4, determined from the CMe_3 group signal; ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.5 (C), 170.4 (C), 167.6 (C), 159.4 (C), 155.8 (C), 155.6 (C), 140.3 (C), 136.3 (C), 131.4 (CH), 130.8 (CH), 130.5 (CH), 129.9 (CH), 129.5 (CH), 128.9 (C), 128.5 (CH), 128.4 (C), 128.1 (CH), 128.0 (C), 125.3 (C), 124.7 (CH), 123.9 (CH), 113.8 (CH), 112.8 (CH), 102.5 (C), 82.3 (C), 70.7 (CH_2), 66.9 (CH_2), 64.1 (C), 62.3 (CH_2), 55.3 (Me), 54.9 (CH), 37.4 (CH_2), 27.8 (Me), 13.7 (Me); several of the carbon signals are doubled due to the presence of diastereoisomers; MS (ES) 797:795 (M + Na^+, 100%), 792:790 (M + NH_4^+, 36:34), 725:723 (13:20), 741:739 (17:14), 719:717 (19:16), 675:673 (29:20); Found: M + NH_4^+, 790.2330. $C_{40}H_{41}{}^{79}BrN_2O_9$ + NH_4 requires: 790.2334.

Ethyl 1-Allyloxycarbonyl-3-[5-(2-benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-(4-methoxybenzyloxy)]phenyl-7-bromo-2-oxoindole-3-carboxylate. To a solution of ethyl 3-[5-(2-benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-(4-methoxybenzyloxy)]phenyl-7-bromo-2-oxoindole-3 carboxylate **18** (20 mg, 26 μmol) in THF (5 mL) cooled at 0 °C was added sodium hydride (8 mg of 60% dispersion in mineral oil, 207 μmol) in one portion under nitrogen. The suspension was stirred for 5 min at 0 °C and then warmed to room temperature, stirred for 15 min, and then cooled down to 0 °C. A solution of allyl chloroformate (13 mg, 108 μmol) in dichloromethane (2 mL) was added dropwise over 5 min. The suspension was then warmed to room temperature and stirred for 10 min, and a solution of 4-dimethylaminopyridine (7 mg, 57 μmol) in dichloromethane (2 mL) was added dropwise over 5 min. The reaction mixture was stirred for a further 2 h and then quenched with acetic acid (1 mL) at 0 °C. The mixture was poured into a saturated solution of sodium hydrogen carbonate (10 mL) and extracted with diethyl ether (5 × 20 mL). The organic layers were then washed sequentially with sulfuric acid (1 M), saturated aqueous sodium hydrogen carbonate, water, dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a yellow oil (14 mg, 63%) as an inseparable mixture of diastereoisomers; IR (CH_2Cl_2/cm^{-1}) 2934, 1770, 1713 (shoulder at 1740), 1612, 1515, 1497, 1460, 1369, 1359, 1232, 1212, 1170, 1151, 1110, 1027, 947; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.48−6.74 (15 H, m), 5.92:5.91 (1 H, 2 × ddt, *J* 17.1, 10.4, 5.9), 5.35 (1 H, dd, *J* 17.3, 1.5), 5.21 (1 H, dd, *J* 10.3, 1.1), 5.14 (1 H, d, *J* 8.0), 5.02 (2 H, br s), 4.88−4.82 (2 H, m), 4.79 (2 H, d, *J* 5.9), 4.41−4.34 (1 H, m), 4.02−3.79 (2 H, m), 3.75 (3 H, s), 2.90 (2 H, m, *J* 5.7), 1.26:1.24 (9 H, s), 1.02:0.98 (3 H, 2 × t, *J* 6.9); diastereomeric ratio 1:1.4, determined from the CMe_3 group signal; ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.0 (C), 169.6 (C), 167.7 (C), 159.1 (C), 155.2 (C), 149.3 (C), 138.8 (C), 136.3 (C), 131.5 (CH), 131.3 (CH), 130.0 (CH), 130.5 (CH), 129.8 (CH), 129.0 (CH), 128.5 (CH), 128.5 (C), 128.7 (C), 128.0 (CH), 127.9 (C), 124.7 (C), 125.6 (CH), 125.7 (CH), 119.8 (CH_2), 113.6 (CH), 113.2 (CH), 110.1 (C), 106.7 (C), 82.3 (C), 70.4 (CH_2), 68.5 (CH_2), 66.9 (CH_2), 64.1 (C), 62.5 (CH_2), 55.2 (Me), 54.9 (CH), 37.4 (CH_2), 27.8 (Me), 13.4 (Me); several of the carbon signals are doubled due to the presence of diastereoisomers; MS (ES) 881:879 (M + Na^+, 100%), 876:874 (M + NH_4^+, 36:34), 759/:757 (36:32), 741:739 (17:14), 723:721 (20:14); Found: M + NH_4^+, 874.2541. $C_{44}H_{45}{}^{79}BrN_2O_{11}$ + NH_4 requires: 874.2545.

10-Allyl, 4b-Ethyl 6-(2-Benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-1-bromo-9a,10-dihydro-10-aza-9-oxaindeno-[1,2-*a*]indene-4b,10-dicarboxylate 19. Sodium borohydride (7 mg, 184 μmol) was dissolved in methanol (1 mL) at 0 °C and added at 0 °C to a solution of ethyl 1-allyloxycarbonyl-3-[5-(2-benzyloxycarbonylamino-2-*tert*-butoxycarbonylethyl)-2-(4-methoxybenzyloxy)]phenyl-7-bromo-2-oxoindole-3-carboxylate (30 mg, 35 μmol) in THF (7 mL) under nitrogen. The reaction mixture was stirred for a further 30 min, poured into a stirred solution of sulfuric acid (1 M), and extracted with ether (5 × 20 mL). The organic layers were washed with saturated aqueous sodium hydrogen carbonate, water, dried ($MgSO_4$), and evaporated in vacuo. The

residue was taken up in dichloromethane (3 mL) and triethylamine (50 μL, 360 μmol) was added, followed by methanesulfonic anhydride (90 mg, 517 μmol), in one portion. The resulting mixture was stirred for 52 h. The mixture was then poured into aqueous sodium hydrogen carbonate (10%, 5 mL) and extracted with dichloromethane (3 × 20 mL). The organic layers were washed with water, dried ($MgSO_4$), evaporated in vacuo, and purified by column chromatography eluting with ethyl acetate/light petroleum (3:7) to give the title compound as a colorless oil (10 mg, 40%) as an inseparable mixture of diastereoisomers; IR (CH_2Cl_2/cm^{-1}) 3426, 2982, 2935, 1735, 1606, 1507, 1489, 1446, 1370, 1340, 1231, 1156, 1123, 1060, 1029, 967; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.41−7.21 (7 H, m), 7.09 (1 H, s), 6.93−6.86 (2 H, m), 6.73 (1 H, t, *J* 7.9), 6.65 (1 H, d, *J* 8.3), 5.97 (1 H, ddt, *J* 17.1, 10.5, 5.6), 5.36 (1 H, br dd, *J* 17.3, 1.1), 5.29 (1 H, br dd, *J* 10.3, 1.1), 5.17 (1 H, m), 5.02 (2 H, m), 4.78 (2 H, dd, *J* 13, 5.8), 4.49−4.38 (1 H, m), 4.22−4.10 (2 H, m), 2.97 (2 H, br d, *J* 5.8), 1.30, (9 H, s), 1.22 (3 H, t, *J* 7.2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.5 (C), 168.0 (C), 157.1 (C), 155.5 (C), 152.4 (C), 139.8 (C), 136.2 (C), 134.6 (C), 134.4 (CH), 132.4 (CH), 131.6 (CH), 131.1 (CH), 130.0 (CH), 129.5 (C), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 125.7 (C), 125.2 (CH), 123.3 (CH), 119.1 (CH_2), 112.2 (C), 110.0 (CH), 100.8 (CH), 82.4 (C), 67.7 (CH_2), 66.9 (CH_2), 64.1 (C), 62.6 (CH_2), 55.0 (CH), 37.7 (CH_2), 27.9 (Me), 14.0 (Me); several of the carbon signals are doubled due to the presence of diastereoisomers; MS (ES) 745:743 (M + Na^+, 69:61%), 740:738 (M + NH_4^+, 29:24), 689:687 (42:35), 667:665 (33:29), 623:621 (100:93), 579 (33), 577 (56), 575 (33), 533/531 (30/37); Found: M + NH_4, 738.2019. $C_{36}H_{37}{}^{79}BrN_2O_9$ + NH_4 requires: 738.2021.

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Supporting Information Available: General experimental details and the preparation of starting indoles **3a**, **3b**, **3c**, **5b**, **6a**, and **6b**; X-ray crystal data for compounds **4c**, **10a**, and **14**; and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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