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Preparation of the Central Tryptophan Moiety of the Celogentin/ Moroidin Family of Anti-Mitotic Cyclic Peptides

Alexander K. L. Yuen,[A] *Katrina A. Jolliffe*,[A] *and Craig A. Hutton*[B,C]

[A] School of Chemistry, University of Sydney, Sydney NSW 2006, Australia.
[B] School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Melbourne VIC 3010, Australia.
[C] Corresponding author. Email: chutton@unimelb.edu.au

The central functionalized tryptophan core of the celogentin/moroidin family of cyclic peptides has been prepared. The strategy incorporates a novel preparation of 4-iodobenzaldehyde and employs a Larock annulation as the key step.

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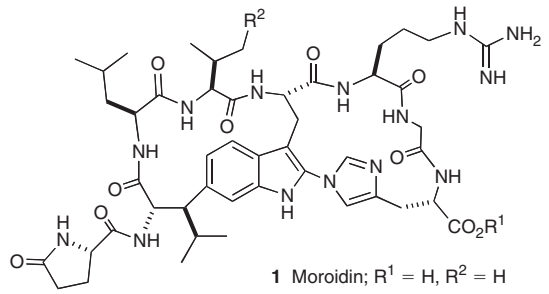
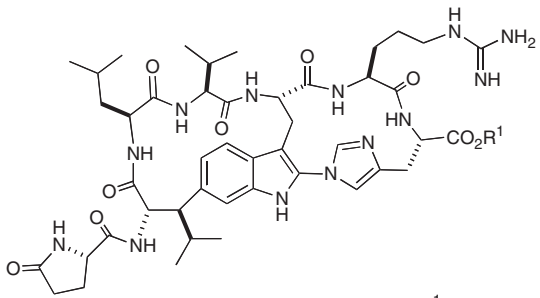
Introduction

Moroidin was first isolated in 1986 by Williams and co-workers,[1] who were interested in discovering the causative agent of biological activity in the extract of the leaves of the Australian rainforest bush *Laportea moroides*. Contact with the stinging hairs present on the leaves of *L. moroides* causes vasodilation, piloerection, local sweating, and intense long-lasting pain, which results in anxiety and severe distress, and as such the bush is regarded as a menace to humans and stock, particularly horses.[2]

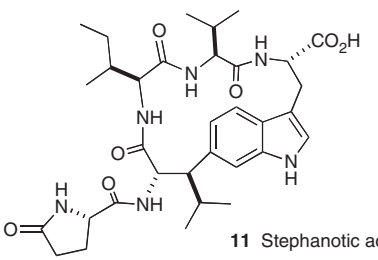
Moroidin (**1**, Fig. 1) is an octapeptide composed of two fused macrocycles. The 'left-hand' macrocycle contains a leucine–tryptophan cross-link while the 'right-hand' macrocycle contains a histidine–tryptophan cross-link. Extensive spectroscopic and chemical analysis and molecular modelling performed by Williams and co-workers[1,3] suggested



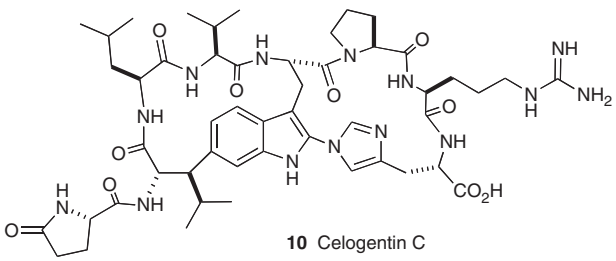
1 Moroidin; R^1 = H, R^2 = H
2 Celogentin E; R^1 = Asp, R^2 = H
3 Celogentin F; R^1 = Arg, R^2 = H
4 Celogentin G; R^1 = H, R^2 = Me
5 Celogentin H; R^1 = Asp, R^2 = Me
6 Celogentin J; R^1 = Arg, R^2 = Me



7 Celogentin A; R^1 = H
8 Celogentin B; R^1 = His
9 Celogentin D; R^1 = His-Lys



11 Stephanotic acid



10 Celogentin C

Fig. 1. Structures of moroidin, celogentins A–J, and stephanotic acid.

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that moroidin was composed entirely of L-amino acids, that the β-carbon of the leucine residue was appended to the tryptophan C6 and was of (*R*)-configuration, and that the *N*-1 of the histidine imidazole group was bonded to C2 of the central tryptohan residue. The structural assignment of moroidin was unambiguously confirmed by Kobayashi et al. in 2004 by X-ray crystallographic analysis.[4]

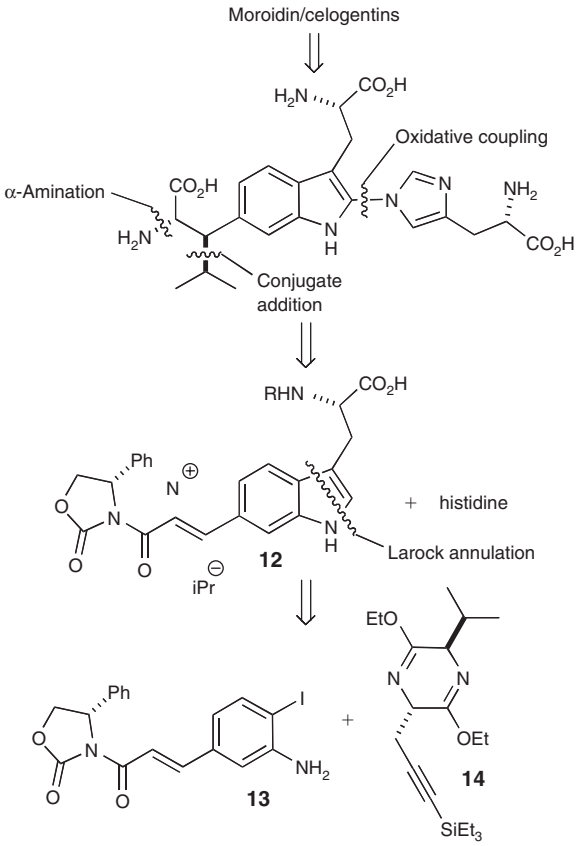
In recent years the Kobayashi group has reported the isolation and characterization of many more members of this family of natural products, derived from the seeds of *Celosia argentea*, along with moroidin itself (Fig. 1).[4–6] These bicyclic peptides have very closely related structures. The same 'left-hand' macrocycle is present in all members of the family with the exception that celogentins G, H, and J (**4**–**6**) have an isoleucine residue in place of the valine residue. All other variation between the family members occurs in the size and composition of the 'right-hand' macrocycle. All family members (except celogentin K) contain both tryptophan C2–histidine *N*-1 and tryptophan C6–leucine Cβ crosslinks. Stephanotic acid (**11**) has also recently been isolated and is closely related to the 'left-hand' ring of the celogentin/moroidin family.[7]

The celogentins (**2**–**10**) and moroidin (**1**) have been shown to possess potent anti-tubulin activity.[8] The anti-mitotic activity of the most potent member of the family, celogentin C (IC_{50} 0.8×10^{-6} M), is more potent than the vinca alkaloid, vinblastine (IC_{50} 3.0×10^{-6} M), which is the same as that of moroidin (IC_{50} 3.0×10^{-6} M). The combination of the remarkable biological activity yet very low natural abundance (2×10^{-5}–3×10^{-3} wt.-%) of these compounds has led to significant interest in the development of methods toward their total synthesis.[9–14]

Moody and co-workers[9,10] have reported a method for the generation of the Trp–His cross-link in the 'right-hand' macrocycle of the celogentin/moroidin family. The key steps include a nucleophilic aromatic substitution of 2-chloro-3-formylindole[9] and catalytic asymmetric hydrogenation of the subsequently prepared dehydrotryptophan derivative.[10,11] More recently, Moody and co-workers[12] prepared the 'left hand' ring in the form of stephanotic acid (**11**) using a combination of their previous asymmetric hydrogenation methodology and a non-stereoselective preparation of the Leu–Trp linkage.

Castle and Srikanth have reported progress towards celogentin C (**10**), which employs a Larock annulation to generate the indole moiety of the central tryptophan residue.[13] Castle and co-workers have also developed a novel route to the Trp–His linkage using an oxidative coupling, and has employed this methodology in the preparation of the 'right-hand' macrocycle of celogentin C.[14]

Our retrosynthetic analysis of the celogentin/moroidin family suggested that Castle's oxidative coupling was the most efficient route to the Trp–His cross-link, and that a conjugate addition approach ought to furnish the Leu–Trp structure (Scheme 1). Hruby and co-workers[15] have reported the preparation of β,β-disubstituted α-amino acids using a conjugate addition–azidation strategy, which employs Evans' oxazolidinone auxiliary to control the configuration



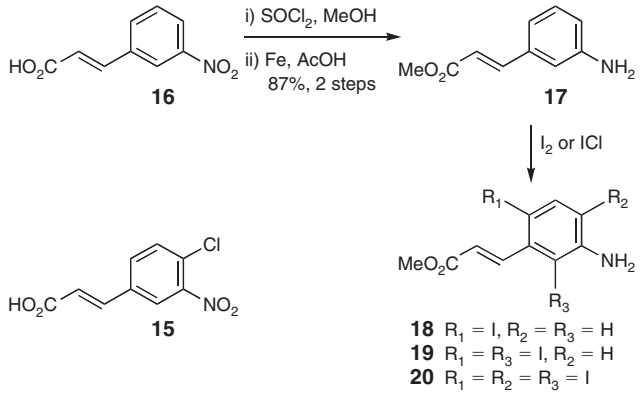
Scheme 1. Retrosynthesis of moroidin/celogentins.

at both stereocentres. Accordingly, our approach to the celogentin/moroidin bicyclic peptides required the preparation of oxazolidinone-appended C6-substituted L-tryptophan derivative **12**, which in turn is to be assembled by the Larock annulation of iodoaniline **13** with propargylglycine derivative **14** according to the method of Cook and co-workers.[16]

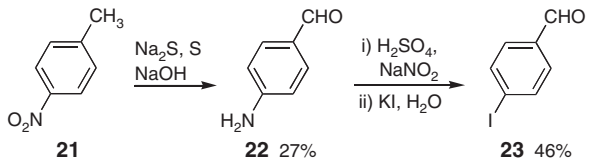
Results and Discussion

Cook and co-workers have generated D-tryptophan derivatives through Larock annulation of D-propargylglycine derivative *ent*-**14**.[16] Accordingly, we chose to employ the corresponding (*R*)-Schollkopf auxiliary-derived L-propargylglycine derivative **14** as one of the key intermediates for our synthesis. Our approach, therefore, required 3-amino-4-iodocinnamic acid **13** as the Larock annulation coupling partner to generate the central tryptophan core of the moroidin/celogentin family.

Initially, we attempted to prepare 3-amino-4-iodocinnamic acid from commercially available nitrocinnamates **15** and **16**. However, conversion of 4-chloro-3-nitrocinnamate **15** to the corresponding 4-iodo compound, using the halogen displacement method reported by Burnett and Conner[17] for substitution of 2,4-dinitrochlorobenzene, was not effective. Esterification of 3-nitrocinnamic acid **16** and chemoselective reduction[18] of the nitro-group was then pursued to afford methyl 3-aminocinnamate **17** in good yield (Scheme 2). However, iodination of **17** under various conditions led to



Scheme 2.



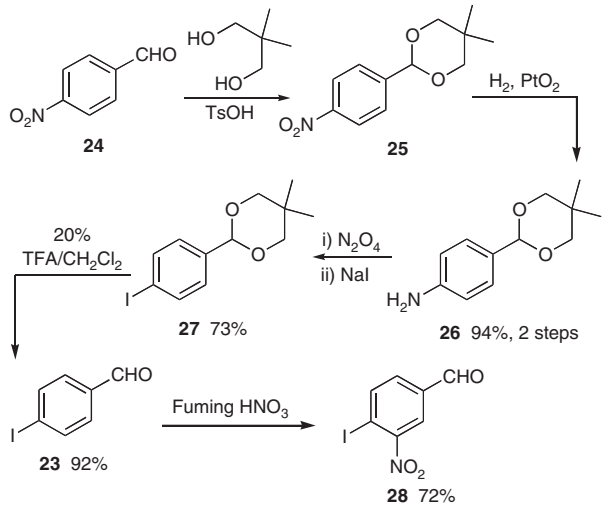
Scheme 3.

a complicated mixture of products from which the 6′-iodo- (**18**), 2′,6′-diiodo- (**19**), and 2′,4′,6′-triiodo- (**20**) compounds were isolated in varying amounts.

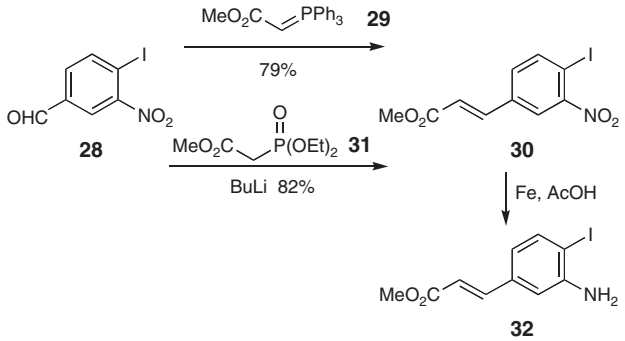
Preparation of the required functionalized cinnamate by olefination of the corresponding benzaldehyde was therefore investigated. This approach required 4-iodobenzaldehyde (**23**) as the starting material, which is commercially available but prohibitively expensive. In order to gain access to multi-gram amounts of 4-iodobenzaldehyde **23**, a concise preparation from inexpensive starting materials was required. A route from 4-nitrotoluene **21** via 4-aminobenzaldehyde **22**[19] was initially investigated (Scheme 3), but the best isolated yield of 4-iodobenzaldehyde **23** from this two-step procedure was 12%, the main problem being the inherent propensity for self-polymerization of **22** into intractable tars.

An alternative route to **23** was then developed starting from 4-nitrobenzaldehyde (**24**). To avoid self-polymerization, the aldehyde functionality was protected as a cyclic acetal. Hydrogenation of the aromatic nitro-group of acetal **25** was achieved in quantitative yield in the presence of platinum(IV) oxide catalyst, to give the desired aniline **26** in excellent yield (Scheme 4).[20] Conversion of aniline **26** to the iodide **27** by a diazo-displacement required non-acidic conditions in order that the acetal functionality remained intact. A suitable method was found using liquid N_2O_4 at low temperature under anhydrous conditions,[21] which yielded the desired iodoacetal **27** in high yield. This material was then deprotected under anhydrous acidic conditions to afford 4-iodobenzaldehyde **23**. This high-yielding, four-step procedure was found to be an effective means for the preparation of multi-gram amounts of 4-iodobenzaldehyde **23** from inexpensive starting materials.

Regioselective nitration of **23** was achieved using the procedure described by Miller et al.[22] to give **28**. Wittig reaction of aldehyde **28** with commercially available ylide **29** resulted



Scheme 4.



Scheme 5.

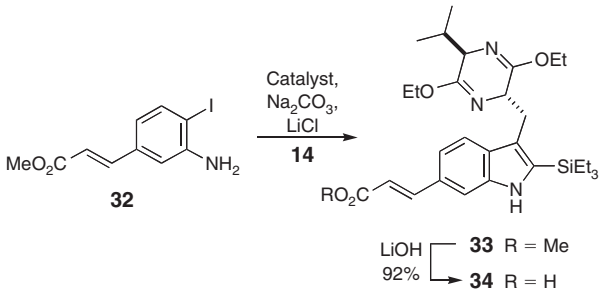
in quantitative conversion to the desired methyl cinnamate as a 5:1 mixture of (*E*)- and (*Z*)-isomers, from which the desired (*E*)-isomer **30** was obtained in 76% yield after recrystallization. Alternatively, Horner–Wadsworth–Emmons reaction of **28** using methyl diethylphosphonoacetate **31** was completely selective for the (*E*)-isomer, providing **30** in 82% yield (Scheme 5). Though the Horner–Wadsworth–Emmons reaction provided a slightly higher yield of **30**, it was not as operationally simple as the Wittig reaction on a large scale. Selective reduction of the nitro group of **30** using iron in acetic acid/ethanol gave the aniline **32** in high yield.

With the required 3-amino-4-iodocinnamic acid **32** in hand, Larock annulation with propargylglycine derivative **14** was then investigated. Use of Cook's conditions[16] (Table 1, entry 1) gave the tryptophan derivative **33** in 42% yield (Scheme 6). Increasing the amount of palladium acetate from 5 to 10 mol-% improved the yield slightly (entry 2). Variation of the palladium catalyst led to the marginally improved yield of 53% with palladium bis(diphenylphoshinoferrocene) catalyst (entry 4).

Hydrolysis of the methyl ester of tryptophan derivative **33** was effective, providing acid **34** in 92% yield (Scheme 6). However, subsequent coupling of acid **34** to the Evans oxazolidinone auxiliary **38** under various conditions was unsuccessful, possibly because of the presence

of the unprotected indole. Preparation of the corresponding Boc-protected indole **36** was, therefore, undertaken, and for optimum convergency it was decided to generate **36** by Larock annulation of the Boc-protected aniline **35**.

Kelly and McNeil[23] reported that simple anilines can be mono-Boc-protected using two equivalents of sodium hexamethyldisilazide (NaHMDS) to form the anilide anion, followed by addition of di-*tert*-butyl dicarbonate. The second equivalent of base is required to deprotonate the resultant carbamate, thereby preventing further reaction with the anilide anion, which would otherwise lead to formation of a symmetrical urea. However, treatment of **32** with two equivalents of NaHMDS at room temperature led to polymerization of the starting material, presumably as a result of intermolecular addition of the anilide anion to the methyl ester. Modification of the literature procedure through inclusion of the di-*tert*-butyl dicarbonate in the initial reaction mixture and performing the reaction at −78°C resulted in production of the desired carbamate **35** in good yield (Scheme 7).



Scheme 6.

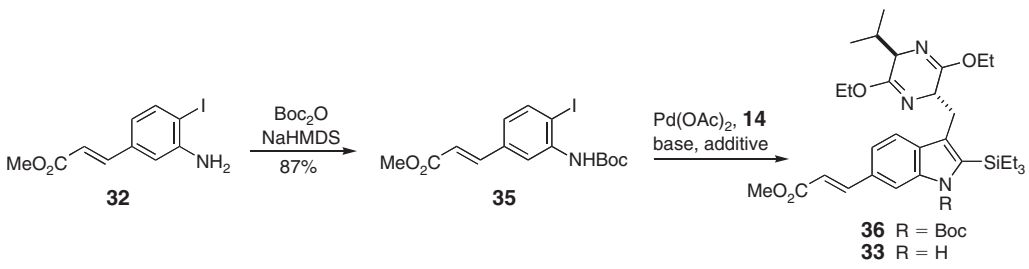
Table 1. Larock annulations of iodoaniline 32

Entry	Catalyst	Catalyst conc. [mol-%]	Time [h]	Yield [%]
1	$Pd(OAc)_2$	5	48	42
2	$Pd(OAc)_2$	10	48	50
3	$Pd(OAc)_2(PPh_3)_2$	20	48	38
4	$Pd(dppf)Cl_2$	5	36	53

Application of Cook and co-workers'[16] conditions for the Larock annulation of **35** led to the formation of Boc-protected tryptophan derivative **36** in only 27% yield, accompanied by tryptophan derivative **33** lacking the Boc-group, in 21% yield (Table 2, entry 1). Conducting the reaction at a lower temperature in order to suppress thermolysis of the Boc group was only partially effective, with less deprotected compound **33** formed but no improvement in the yield of Boc-indole derivative **36**. Gathergood and Scammells[24] have reported the preparation of 4-hydroxytryptamines, under modified Larock annulation conditions, using a Boc-protected iodoaniline. Their procedure employs 20 mol-% palladium acetate and 40 mol-% triphenylphosphine ligand. However, application of Gathergood and Scammells' procedure yielded only 8% of Boc-indole **36** with significant amounts of indole **33** formed and starting material **35** recovered. After significant experimentation, a hybrid procedure that employed 20 mol-% palladium acetate and 40 mol-% triphenylphosphine (as per Scammells and Gathergood's procedure) in the presence of sodium carbonate and lithium chloride (as per Cook's procedure) was developed that yielded 52% of the desired tryptophan derivative **36**, with only trace amounts of **33** observed (entry 4).

In order to append the oxazolidinone auxiliary, removal of the methyl ester was required. However, hydrolysis of **36** was not effective as competitive hydrolysis of the carbamate group occurred to yield a mixture of *N*-protected and unprotected indoles.

With the attachment of the oxazolidinone auxiliary to Larock adducts **33** and **36** proving problematic, direct preparation of tryptophan fragment **12** through Larock annulation of oxazolidinone-appended cinnamate **13** was investigated. Ester hydrolysis of methyl cinnamate **35** and subsequent coupling to the oxazolidinone **38** were achieved under standard conditions, to yield functionalized cinnamate **39** in 69% yield



Scheme 7.

Table 2. Larock annulations of *N*-Boc iodoaniline 35

Entry	$Pd(OAc)_2$ [mol-%]	PPh_3 [mol-%]	Base (3 equiv)	Additive	Temp. [°C]	Time [h]	Yield **36** [%]	Yield **33** [%]
1	5	–	Na_2CO_3	LiCl	100	48	27	21
2	5	–	Na_2CO_3	LiCl	80	78	23	12
3	20	40	NEt_3	Bu_4NCl	80	48	8	47
4	20	40	Na_2CO_3	LiCl	80	48	52	<5

over two steps (Scheme 8). Removal of the Boc protecting group was then effected upon treatment with 10% sulfuric acid in 1,4-dioxan to give the aniline **13**.

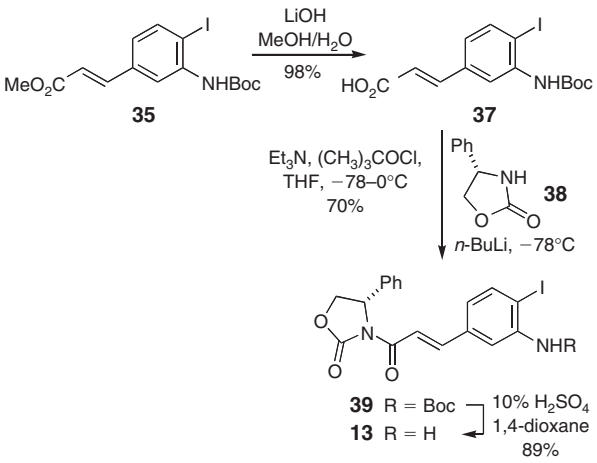
With the oxazolidinone-appended iodoaniline **13** in hand, we returned to Cook's optimized conditions for the Larock annulation with propargylglycine **14**, which proceeded in reasonable yield to provide the desired functionalized tryptophan derivative **40** (Scheme 9).

In conclusion, a novel, inexpensive preparation of 4-iodobenzaldehyde **23** has been developed that enabled an efficient preparation of *ortho*-iodoaniline **13**, which was coupled with propargylglycine **14** using Cook's modification of the Larock annulation to provide 2,6-disubstituted tryptophan derivative **40**. Elaboration of **40** to provide the Leu–Trp fragment of the celogentin/moroidin family of cyclic peptides is currently underway.

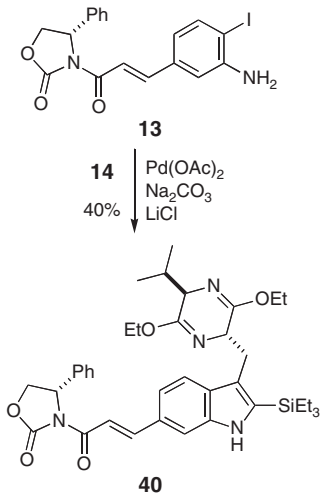
Experimental

*Methyl (*E*)-3′-Aminocinnamate **17***

To a suspension of (*E*)-3′-nitrocinnamic acid **16** (4.8 g, 25.0 mmol) in methanol (50 mL) at 0°C was added thionyl chloride (2.0 mL, 27.5 mmol). The reaction was stirred under nitrogen at room temperature for 4 h, and then concentrated under vacuum. The crude material was dissolved in absolute ethanol (200 mL) and acetic acid (20 mL). Iron powder (4.82 g, 86.4 mmol) was added and the suspension was heated at reflux under nitrogen overnight. The mixture was allowed to cool to room temperature, and was then concentrated under vacuum and the residue partitioned between ethyl acetate (150 mL) and saturated $NaHCO_3$(aq.) (150 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL) and the combined organic phases were washed with saturated $NaHCO_3$(aq.) (50 mL), dried over sodium sulfate, and concentrated under vacuum to give a brown solid. Purification by chromatography on silica afforded the title compound **17** (3.80 g, 87%) as a white solid; mp 81–84°C. ν_{max} (CH_2Cl_2)/cm^{-1} 3487, 3398, 3153, 2986, 2951, 2901, 2253, 1817, 1794, 1705, 1636, 1620, 1605. δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 16.0, *H*CCH), 7.16 (1H, m, ArH), 6.92 (1H, d, *J* 7.7, ArH), 6.82 (1H, m, ArH), 6.70 (1H, dd, *J* 1.5, 7.7, ArH), 6.37 (1H, d, *J* 16.0, HCC*H*), 3.79 (3H, s, OCH_3), 3.63 (2H, br s, NH_2). δ_C (100 MHz, $CDCl_3$) 167.5, 146.8, 145.2, 135.4, 129.8, 118.7, 117.6, 117.1, 114.1, 51.6. *m/z* (ESI, positive ion) 178 ([M + Na]$^+$, 100%). HRMS (ESI, positive ion) $C_{10}H_{11}NO_2Na$ requires *m/z* 200.0682, found [M + Na]$^+$ 200.0686.



Scheme 8.



Scheme 9.

*5,5-Dimethyl-2-(4-nitrophenyl)-[1,3]dioxan **25***

A solution of 4-nitrobenzaldehyde **24** (92.0 g, 0.61 mol), 2,2-dimethylpropane-1,3-diol (69.0 g, 0.67 mol), and toluenesulfonic acid (10.5 g, 0.06 mol) in toluene (1.0 L) was refluxed under Dean–Stark conditions until no more water was observed to form. The reaction was allowed to cool, and washed with saturated $NaHCO_3$(aq.) (3 × 400 mL), water (200 mL), and brine (100 mL). The organic phase was stirred over sodium sulfate and activated charcoal overnight, filtered, and concentrated. The crude solid was recrystallized from methanol/water to afford the title compound **25** as off-white crystals (136.5 g, 94%), mp 87–88°C (lit.[25] 83–85°C). δ_H (200 MHz, $CDCl_3$) 8.22 (2H, d, *J* 8.7, 3′H/5′H), 7.68 (2H, d, *J* 8.7, 2′H/6′H), 5.46 (1H, s, CH), 3.80 (2H, d, *J* 11.1, 2 × OC*H*H′), 3.67 (2H, d, *J* 11.1, 2 × OCH*H*′), 1.27 (3H, s, CH_3), 0.82 (3H, s, CH_3); ^{1}H NMR data is in accordance with literature values.[20]

*2-(4-Aminophenyl)-5,5-dimethyl-[1,3]dioxan **26***

5,5-Dimethyl-2-(4′-nitrophenyl)-[1,3]dioxan **25** (40.5 g, 170.7 mmol) was dissolved in ethyl acetate (480 mL), and platinum(IV) oxide (774 mg, 3.41 mmol) was added. The resulting suspension was stirred under an atmosphere of hydrogen for 4.5 h. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to afford the title compound **26** as a white solid (35.4 g, 100%), mp 105–106°C (lit.[25] 102–104°C). δ_H (200 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.4, 2′H/6′H), 6.65 (2H, d, *J* 8.4, 3′H/5′H), 5.29 (1H, s, CH), 3.74 (2H, d, *J* 11.0, 2 × OC*H*H′), 3.61 (2H, d, *J* 11.0, 2 × OCH*H*′), 1.29 (3H, s, CH_3), 0.78 (3H, s, CH_3); ^{1}H NMR data in is accordance with literature values.[20]

*2-(4-Iodophenyl)-5,5-dimethyl-[1,3]dioxan **27***

A solution of 2-(4-aminophenyl)-5,5-dimethyl-[1,3]dioxan **26** (20.7 g, 100 mmol) in acetonitrile (500 mL) was cooled to −20°C, and then ice-cooled nitrogen dioxide/dinitrogen tetroxide (7.00 mL, 220 mmol) was added by a cannula. The resulting brown slurry was stirred under nitrogen at −20°C for 1.25 h and then sodium iodide (22.5 g, 150 mmol) was added. Upon completion of gas evolution, the reaction was allowed to warm to room temperature, and ethyl acetate (500 mL) and water (500 mL) were then added. The aqueous phase was extracted with ethyl acetate (250 mL) and the combined organic phases were washed with saturated $Na_2S_2O_3$(aq.) (5 × 100 mL) and hydrochloric acid (1 M, 100 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was passed through a short column of silica and the crude product recrystallized from methanol/water to afford the title compound **27** as lustrous white flakes (23.2 g, 73%), mp 75–76°C. Found C 45.5, H 4.8. $C_{12}H_{15}O_2I$ requires C 45.3, H 4.8%. ν_{max} (CH_2Cl_2)/cm^{-1} 2952, 2853 (C–H), 2367. δ_H (300 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.5, ArH), 7.24 (2H, d, *J* 8.5, ArH), 5.33 (1H, s, CH), 3.75 (2H, d, *J* 10.8, 2 × OC*H*H′), 3.62 (2H, d, *J* 10.8, 2 × OCH*H*′), 1.27 (3H, s, CH_3), 0.79 (3H, s, CH_3). δ_C (75 MHz, $CDCl_3$) 138.2, 137.3, 128.1, 101.0, 94.7, 30.2, 23.0, 21.8. *m/z* (EI) 318 ($M^{+\bullet}$,

40%), 317 (100), 232 (33), 231 (100), 232 (38). HRMS (EI) $C_{12}H_{15}IO_2$ requires *m/z* 318.0117, found 318.0112.

4-Iodobenzaldehyde ***23***

Trifluoroacetic acid (50 mL) was added to a solution of 2-(4′-iodophenyl)-5,5-dimethyl-[1,3]dioxane **27** (23.2 g, 73.0 mmol) in dichloromethane (250 mL). The reaction mixture was stirred at room temperature for 23 h, during which time the reaction mixture turned green. Water (250 mL) was added and $NaHCO_3$ was added slowly until the pH of the aqueous phase was approx. 8.0. The aqueous phase was extracted with dichloromethane (40 mL) and the combined organic phases were dried over sodium sulfate, concentrated under vacuum, and recrystallized from hexanes (200 mL) to afford the title compound **23** as white crystals (15.5 g, 92%), mp 76–81°C (lit.[22] 79–80°C). δ_H (200 MHz, $CDCl_3$) 9.96 (1H, s, CHO), 7.92 (2H, d, *J* 8.4, C-2H/C-5H), 7.59 (2H, d, *J* 8.4, C-3H/C-4H).

4-Iodo-3-nitrobenzaldehyde ***28***

Fuming nitric acid (9.40 mL, 223 mmol) was cooled to 0°C and then added to 4-iodobenzaldehyde **23** (8.62 g, 37.1 mmol). The resulting brown solution was stirred at 0°C for 3.5 h. Ice-water was then added and the canary yellow precipitate was filtered off, washed with water, and dried under vacuum over phosphorous pentoxide. The crude product was recrystallized from a minimal amount of chloroform/hexanes to afford the title compound **28** as yellow crystals (7.44 g, 72%), mp 147–148°C (lit.[22] 141°C). δ_H (200 MHz, $CDCl_3$) 10.03 (1H, s, CHO), 8.31 (1H, d, *J* 2.0, C-2H), 8.27 (1H, d, *J* 8.1, C-5H), 7.75 (1H, dd, *J* 2.0, 8.1, C-6H).

*Methyl (*E*)-3′-Nitro-4′-iodocinnamate* ***30***

Method 1

4-Iodo-3-nitrobenzaldehyde **28** (9.41 g, 34.0 mmol) and methyl (triphenylphosphoranyl)acetate **29** (13.7 g, 41.0 mmol) were dissolved in dichloromethane (200 mL) and stirred overnight under nitrogen at room temperature. The resulting yellow solution was concentrated under vacuum, and the residue purified by chromatography on silica to give the product as a yellow solid (11.1, 98%, 5:1 *E*:*Z*). Recrystallization from dichloromethane/hexanes afforded the (*E*)-isomer **30** as a yellow crystalline solid (8.99 g, 79%), mp 156–157°C. Found C 36.1, H 2.3, N 4.1. $C_{10}H_8INO_4$ requires C 36.1, H 2.4, N 4.2%. ν_{max} (CH_2Cl_2)/cm^{-1} 3942, 3757, 3691, 3051, 2987, 2927, 2852, 2685, 2521, 2409, 2305, 2154, 2125, 2054, 1720, 1647, 1597, 1553, 1533, 1421. δ_H (200 MHz, $CDCl_3$) 8.06 (1H, d, *J* 8.3, 5′H), 7.97 (1H, d, *J* 2.1, 2′H), 7.61 (1H, d, *J* 16.0, ArC*H*CH), 7.38 (1H, dd, *J* 2.1, 8.3, 6′H), 6.53 (1H, d, *J* 16.0, ArCHC*H*), 3.82 (3H, s, OCH_3). δ_C (50 MHz, $CDCl_3$) 166.3, 153.5, 142.5, 140.9, 135.9, 131.8, 124.2, 121.4, 87.6, 52.1. *m/z* (EI) 333 ($M^{+\bullet}$, 100%), 302 (67). HRMS (EI) $C_{10}H_8INO_4$ requires *m/z* 332.9498, found 332.9506.

Method 2

To a solution of methyl diethylphosphonoacetate **31** (6.83 g, 33.0 mmol), in tetrahydrofuran (125 mL), was added *n*-butyllithium (21 mL, 1.6 M), dropwise at −78°C. The reaction mixture was stirred under nitrogen at −78°C for 1 h and then a cooled solution of 4-iodo-3-nitrobenzaldehyde **28** (6.87 g, 25.0 mmol) in tetrahydrofuran (125 mL) was added using a cannula. The reaction mixture was allowed to warm to 0°C and was stirred for a further 2 h. Saturated NH_4Cl(aq.) (100 mL) was then added. The resulting precipitate was removed by filtration, the filtrate was extracted with ethyl acetate (30 mL), dried over sodium sulfate, and concentrated under vacuum to give a yellow solid. Purification by chromatography on silica afforded a mixture of starting material **28** and product **30**. Recrystallization from a minimal amount of dichloromethane/hexanes afforded the title compound **30** (6.75 g, 82%).

*Methyl (*E*)-3′-Amino-4′-iodocinnamate* ***32***

Methyl (*E*)-3′-nitro-4′-iodocinnamate **30** (8.9 g, 26.9 mmol) and iron powder (10.5 g, 188 mmol) were suspended in absolute ethanol (250 mL) and glacial acetic acid (21.5 mL). The mixture was heated at reflux under nitrogen for 4.5 h, during which time the reaction mixture darkened. The mixture was allowed to cool to room temperature and concentrated under vacuum. The dark brown residue was diluted with ethyl acetate (250 mL), and saturated $NaHCO_3$(aq.) was used to adjust the pH to approx. 8. The organic phase was separated, the aqueous phase was extracted with ethyl acetate (100 mL), and the combined extracts were dried over sodium sulfate and concentrated under vacuum. Purification by chromatography on silica afforded the title compound **32** as a pale yellow crystalline solid (6.91 g, 85%), mp 121–123°C. ν_{max} (CH_2Cl_2)/cm^{-1} 3942, 3757, 3692, 3474, 3379, 3049, 2986, 2953, 2831, 2685, 2521, 2409, 2305, 2154, 2125, 2054, 1705, 1636, 1612, 1558. δ_H (200 MHz, $CDCl_3$) 7.63 (1H, d, *J* 8.2, 5′H), 7.53 (1H, d, *J* 16.0, ArC*H*CH), 6.84 (1H, d, *J* 1.9, 2′H), 6.63 (1H, dd, *J* 2.0, 8.2, 6′H), 6.34 (1H, d, *J* 16.0, ArCHC*H*), 4.18 (2H, br s, NH_2), 3.79 (3H, s, OCH_3). δ_C (50 MHz, $CDCl_3$) 167.8, 147.8, 144.7, 140.0, 136.2, 119.7, 118.8, 114.2, 86.7, 52.3. HRMS (EI) $C_{10}H_{10}INO_2$ requires *m/z* 302.9756, found 302.9761.

*Methyl (*E*)-3′-*tert*-Butoxycarbonylamino-4′-iodocinnamate* ***35***

Methyl (*E*)-3′-amino-4′-iodocinnamate **32** (2.67 g, 8.80 mmol) and di-*tert*-butyl dicarbonate (1.92 g, 8.80 mmol) were dissolved in tetrahydrofuran (45 mL), cooled to −78°C, and sodium hexamethyldisilazide (17.6 mL, 1.0 M in THF) was added dropwise at a rate that kept the internal temperature below −60°C. Upon completion of the addition, the reaction mixture remained blood-red. The reaction mixture was stirred for 3 h, quenched with methanol, and the mixture was allowed to warm to room temperature. The solvent was removed and the residue partitioned between saturated NH_4Cl (aq.) (150 mL) and dichloromethane (150 mL), the organic phase was separated, and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic extracts were dried over sodium sulfate and concentrated under vacuum to give a pale yellow oil. Purification by chromatography on silica afforded the title compound **35** as a white solid (3.09 g, 87%), mp 125–127°C. ν_{max} (CH_2Cl_2)/cm^{-1} 3393, 3153, 2984, 2900, 2358, 2253, 1817, 1718, 1639, 1568. δ_H (200 MHz, $CDCl_3$) 8.29 (1H, d, *J* 2.1, 2′H), 7.75 (1H, d, *J* 8.2, 5′H), 7.62 (1H, d, *J* 15.9, ArC*H*CH), 6.91 (1H, dd, *J* 2.1, 8.2, 6′H), 6.86 (1H, br s, NH), 6.49 (1H, d, *J* 15.9, ArCHC*H*), 3.80 (3H, s, OCH_3), 1.55 (9H, s, $C(CH_3)_3$). δ_C (50 MHz, $CDCl_3$) 167.1, 152.4, 143.8, 139.5, 139.2, 135.7, 123.8, 119.1, 118.8, 90.2, 81.4, 51.7, 28.3. *m/z* (EI) 403 ($M^{+\bullet}$, 7%), 347 (39), 303 (100), 220 (78). HRMS (EI) $C_{15}H_{18}INO_4$ requires *m/z* 403.0281, found 403.0280.

*(*E*)-3′-*tert*-Butoxycarbonylamino-4′-iodocinnamic Acid* ***37***

To a suspension of methyl (*E*)-3′-*tert*-butoxycarbonylamino-4′-iodocinnamate **35** (3.09 g, 7.66 mmol) in methanol (60 mL) was added a solution of lithium hydroxide (552 mg, 23.0 mmol) in water (20 mL). The white slurry was stirred at room temperature under nitrogen for 36 h, concentrated under vacuum, and the residue partitioned between hydrochloric acid (50 mL, 1 M) and 3/1 chloroform/isopropyl alcohol (250 mL). The organic extract was dried over sodium sulfate, and concentrated under vacuum to afford the title compound **37** as a white solid (2.95 g, 98%) that was used directly in the following reaction. δ_H (200 MHz, D_2O + NaOD) 7.88 (1H, d, *J* 8.2, 5′H), 7.55 (1H, br s, 2′H), 7.27 (1H, d, *J* 16.0, ArC*H*CH), 7.13 (1H, br d, *J* 8.2, 6′H), 6.50 (1H, d, *J* 16.0, ArCHC*H*), 1.51 (9H, s, $C(CH_3)_3$). δ_C (50 MHz, D_2O + NaOD) 175.7, 156.4, 140.1, 139.5, 136.4, 126.7, 125.9, 125.0, 96.4, 90.2, 82.5, 28.1. *m/z* (ESI, negative ion) 388 ($[M-H]^-$, 100%).

*(*S*)-3-[3′-*tert*-Butoxycarbonylamino-4′-iodo-(*E*)-cinnamoyl]-4-phenyloxazolidin-2-one* ***39***

A solution of *n*-butyllithium in hexanes (655 μL, 1.53 M) was added to a solution of (*S*)-4-phenyl-2-oxazolidinone **38** (164 mg, 1.00 mmol) in tetrahydrofuran (5 mL) at −78°C and the mixture was stirred at −78°C for 15 min. In a separate flask a suspension of (*E*)-3′-*tert*-butoxycarbonylamino-4′-iodocinnamic acid **37** (389 mg, 1.00 mmol) in tetrahydrofuran (5 mL) was cooled to −78°C, and then triethylamine

(140 μL, 1.0 mmol) and trimethylacetyl chloride (125 μL, 1.00 mmol) were added. The resulting slurry was stirred at −78°C for 15 min and then at 0°C for 1 h. The mixture was re-cooled to −78°C and then was transferred into the oxazolidinone anion solution through a cannula. The resulting mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with saturated NH_4Cl (aq.) (30 mL), and then was extracted with ethyl acetate (2 × 30 mL). The combined extracts were dried over sodium sulfate and concentrated under vacuum to give a yellow solid. Purification by chromatography on silica afforded the title compound **39** as a pale yellow oil (368 mg, 70%). ν_{max} (CH_2Cl_2)/cm^{-1} 3393, 3390, 3096, 2978, 2930, 2363, 2253, 1817, 1778, 1724, 1684, 1620. δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 1.9, 2′H), 7.81 (1H, d, *J* 15.8, ArC*H*CH), 7.61 (1H, d, *J* 8.2, 5′H), 7.56 (1H, d, *J* 15.8, ArCHC*H*), 7.27–7.18 (5H, m, Ph), 6.89 (1H, dd, *J* 1.9, 8.2, 6′H), 6.73 (1H, br s, NH), 5.41 (1H, dd, *J* 3.9, 8.8, OC*H*CH′), 4.59 (1H, t, *J* 8.8, OCHC*H*′), 4.15 (1H, dd, *J* 3.9, 8.8, PhC*H*), 1.43 (9H, s, $C(CH_3)_3$). δ_C (100 MHz, $CDCl_3$) 164.1, 153.5, 152.1, 145.1, 139.2, 139.0, 138.8, 135.4, 128.9, 128.4, 125.7, 123.5, 120.0, 118.0, 91.0, 81.2, 69.9, 57.6, 28.1. *m/z* (ESI, positive ion) 557 ([M + Na]$^+$, 100%). HRMS (ESI, positive ion) $C_{23}H_{23}IN_2O_5Na$ requires *m/z* 557.0549, found 557.0533.

*(*S*)-3-[3′-Amino-4′-iodo-(*E*)-cinnamoyl]-4-phenyloxazolidin-2-one **13***

N-Boc-protected aniline **39** (838 mg, 1.57 mmol) was dissolved in a solution of sulfuric acid in 1,4-dioxane (10 mL, 10% v/v) and stirred under ambient atmosphere at room temperature for 30 min. The reaction was quenched with saturated $NaHCO_3$(aq.) solution (30 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under vacuum to afford the crude product as a pale yellow solid. Purification by chromatography on silica afforded the title compound **13** as an off-white solid (608 mg, 89%), mp 185–187°C. Found C 49.9, H 3.5, N 6.4. $C_{18}H_{15}IN_2O_3$ requires C 49.8, H 3.5, N 6.5%. $[\alpha]_D^{[25]}$ −10.6° (*c* 1.0, $CHCl_3$). ν_{max}(NaCl)/cm^{-1} 3462, 3366, 3101, 3065, 3032, 2978, 2916, 2363, 1771, 1678, 1616, 1558. δ_H (300 MHz, $CDCl_3$) 7.88 (1H, d, *J* 15.7, ArC*H*CH), 7.63 (1H, d, *J* 8.1, 3′H), 7.61 (1H, d, *J* 15.7, ArCHC*H*), 7.42–7.31 (5H, m, Ph), 6.92 (1H, d, *J* 2.0, 6′H), 6.67 (1H, dd, *J* 2.0, 8.1, 4′H), 5.54 (1H, dd, *J* 3.9, 8.8, OC*H*H′), 4.73 (1H, t, *J* 8.8, OCH*H*′), 4.31 (1H, dd, *J* 3.9, 8.8, PhC*H*), 4.17 (2H, s, NH_2). δ_C (75 MHz, $CDCl_3$) 164.6, 147.2, 145.9, 139.4, 139.0, 135.6, 129.2, 128.7, 126.0, 120.0, 117.2, 113.6, 86.9, 70.0, 57.8. *m/z* 457 (ESI, positive ion) ([M + Na]$^+$, 71%). HRMS (ESI, positive ion) $C_{18}H_{15}IN_2O_3Na$ requires 457.0020, found 457.0036.

1-tert-*Butoxycarbonyl-3-[(2*S*,5*R*)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazin-2-ylmethyl]-6-(2-methoxycarbonylethenyl)-2-triethylsilanylindole **36***

Dry *N*,*N*-dimethylformamide (5 mL) was added to a flask containing lithium chloride (90 mg, 2.1 mmol), triphenylphosphine (105 mg, 0.4 mmol), Boc-protected aminoiodocinnamate **35** (403 mg, 1.0 mmol), palladium(II) acetate (44.0 mg, 0.2 mmol), sodium carbonate (318 mg, 3.00 mmol), and propargylglycine derivative **14** (484 mg, 1.3 mmol). The mixture was degassed (three freeze–thaw cycles) and then heated at 80°C under nitrogen for 48 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under a stream of nitrogen, and the residue was purified by chromatography on silica to afford the title compound **36** as a yellow oil (330 mg, 52%). δ_H (300 MHz, $CDCl_3$) 8.03 (1H, d, *J* 1.2, 7′H), 7.80 (1H, d, *J* 15.9, ArC*H*CH), 7.61 (1H, d, *J* 8.2, 4′H), 7.36 (1H, dd, *J* 1.2, 8.2, 5′H), 6.44 (1H, d, *J* 15.9, ArCHC*H*), 4.23–3.84 (6H, m, 2 × OCH_2CH_3 and 2 × α-H), 3.82 (3H, s, OCH_3), 3.54 (1H, dd, *J* 3.8, 14.1, C*H*CH′), 2.83 (1H, dd, *J* 10.0, 14.1, CHC*H*′), 2.26 (1H, m, C*H*CH_3), 1.73 (9H, s, $C(CH_3)_3$), 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.15 (3H, t, *J* 7.1, OCH_2CH_3), 1.03–0.94 (18H, m, $Si(CH_2CH_3)_3$ and $CHCH_3$), 0.67 (3H, d, *J* 6.8, $CHCH_3'$). δ_C (100 MHz, C_6D_6) 167.8, 163.4, 163.0, 151.2, 146.5, 137.7, 137.6, 134.7, 131.8, 130.4, 121.1, 120.8, 116.0, 115.5, 83.4, 60.8, 60.7, 60.5, 58.5, 51.6, 31.8, 30.9, 28.3, 19.1, 14.3, 14.2, 8.1, 5.6.

*3-[(2*S*,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-ylmethyl]-6-(2-methoxycarbonylethenyl)-2-triethylsilylindole **33***

Dry *N*,*N*-dimethylformamide (5 mL) was added to a flask that contained lithium chloride (85 mg, 2.0 mmol), aminoiodocinnamate methyl ester **32** (303 mg, 1.0 mmol), 1,1′-bis(diphenylphosphino)-ferrocenylpalladium chloride dichloromethane complex (41.0 mg, 50 μmol), sodium carbonate (318 mg, 3.0 mmol), and propargylglycine derivative **14** (484 mg, 1.3 mmol). The mixture was degassed (three freeze–thaw cycles) and heated at 100°C under nitrogen for 36 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under a stream of nitrogen, and the residue purified by chromatography on silica to afford the title compound **33** as a yellow oil (284 mg, 53%), $[\alpha]_D^{[25]}$ +5.6° (*c* 0.97, $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3385, 2955, 2935, 2908, 2873, 2251, 1701, 1628, 1605, 1558. δ_H (400 MHz, $CDCl_3$) 8.16 (1H, s, NH), 7.82 (1H, d, *J* 15.9, ArC*H*CH), 7.74 (1H, d, *J* 8.4, 4′H), 7.48 (1H, d, *J* 1.1, 7′H), 7.27 (1H, dd, *J* 1.4, 8.4, 5′H), 6.45 (1H, d, *J* 15.9, ArCHC*H*), 4.25–3.96 (5H, m), 3.91 (1H, t, *J* 3.4), 3.73 (3H, s, OCH_3), 3.50 (1H, dd, *J* 3.5, 14.2, C*H*CH′), 2.84 (1H, dd, *J* 9.7, 14.2, CHC*H*′), 2.27 (1H, m, C*H*CH_3), 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.04–0.96 (18H, m, $Si(CH_2CH_3)_3$ and $CHCH_3$), 0.68 (3H, d, *J* 6.8, $CHCH_3'$). δ_C (100 MHz, $CDCl_3$) 168.1, 163.5, 162.9, 146.8, 138.4, 135.1, 131.6, 128.3, 124.2, 121.0, 118.0, 114.9, 111.7, 60.7, 60.6, 60.5, 58.6, 51.5, 31.9, 31.6, 19.1, 16.6, 14.4, 14.2, 7.4, 3.5. *m/z* (EI) 539 ($M^{+\bullet}$, 86%), 510 (69), 508 (100); HRMS (ESI, positive ion) $C_{30}H_{46}N_3O_4Si$ requires *m/z* 540.3254, found 540.3243.

*3-[(2*S*,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-ylmethyl]-6-(2-carboxyethenyl)-2-triethylsilylindole **34***

To a solution of methyl ester **33** (284 mg, 0.53 mmol) in methanol (12 mL) and tetrahydrofuran (6 mL) was added lithium hydroxide (38.0 mg, 1.58 mmol) in distilled water (6 mL). The resulting solution was stirred under nitrogen for 5 days at room temperature. The reaction mixture was concentrated under vacuum, partitioned between ethyl acetate (30 mL) and hydrochloric acid (1 M, 30 mL), and the aqueous layer extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum to afford the title compound **34** (276 mg, 100%) as a yellow oil, $[\alpha]_D^{[25]}$ +4.8° (*c* 1.0, $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3358, 2957, 2934, 2909, 2874, 1689, 1628, 1605, 1562. δ_H (400 MHz, $CDCl_3$) 8.10 (1H, s, NH), 7.85 (1H, d, *J* 15.8, ArC*H*CH), 7.77 (1H, d, *J* 8.8, 4′H), 7.50 (1H, d, *J* 1.0, 7′H), 7.29 (1H, dd, *J* 1.0, 8.8, 5′H), 6.40 (1H, d, *J* 15.8, ArCHC*H*), 4.23–3.95 (5H, m), 3.93 (1H, t, *J* 3.4), 3.52 (1H, dd, *J* 3.6, 14.2, C*H*H′), 2.85 (1H, dd, *J* 9.8, 14.2, CH*H*′), 2.29 (1H, m, C*H*CH_3), 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.22 (3H, t, *J* 7.1, OCH_2CH_3), 1.05–0.95 (18H, m, $Si(CH_2CH_3)_3$ and $CHCH_3$), 0.70 (3H, d, *J* 6.8, $CHCH_3'$). δ_C (100 MHz, $CDCl_3$) 172.2, 163.7, 163.2, 148.4, 138.42, 135.5, 131.8, 128.1, 124.0, 121.0, 118.4, 114.6, 111.9, 60.9, 60.7, 60.6, 58.4, 31.9, 31.7, 19.1, 16.7, 14.4, 14.3, 7.4, 3.6. *m/z* (ESI, positive ion) 526 ([M + H]$^+$, 100%). HRMS (ESI, positive ion) $C_{29}H_{43}N_3O_4Si$ requires *m/z* 526.3096, found 526.3090.

*3-[(2*S*,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-ylmethyl]-6-{3-oxo-3-[2-oxo-(4*S*)-phenyloxazolidin-1-yl]prop-1-enyl}-2-triethylsilylindole **40***

Dry *N*,*N*-dimethylformamide (4 mL) was added to a flask that contained lithium chloride (50 mg, 1.18 mmol), palladium(II) acetate (13 mg, 59 μmol), sodium carbonate (375 mg, 3.54 mmol), and propargylglycine derivative **14** (559 mg, 1.53 mmol). A solution of the iodoaniline derivative **13** (630 mg, 1.18 mmol) in *N*,*N*-dimethylformamide (2 mL) was added and the mixture was degassed (three freeze–thaw cycles) and then heated at 100°C under nitrogen for 48 h. The reaction was allowed to cool to room temperature, the solvent was removed under vacuum, and the residue was purified by chromatography on silica to afford the title compound **40** (318 mg, 40%) as a yellow oil, $[\alpha]_D^{[25]}$ −33.8° (*c* 1.2, $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3392, 2957, 2872, 1784, 1772, 1734, 1684, 1628, 1648, 1595, 1558. δ_H (400 MHz, $CDCl_3$) 8.10 (1H, br s, NH), 7.93 (2H, s, ArH), 7.73 (1H, d, *J* 8.4, 4′H), 7.56 (1H, d, *J* 1.0, 2′H),

7.41–7.33 (6H, m), 5.58 (1H, d, *J* 3.8, 8.7, OC*H*H′), 4.74 (1H, t, *J* 8.7, OCH*H*′), 4.32 (1H, dd, *J* 3.8, 8.7, PhC*H*), 4.22–4.06 (5H, m), 3.90 (1H, t, *J* 3.4), 3.49 (1H, dd, *J* 3.5, 14.2, C*H*H′), 2.83 (1H, dd, *J* 9.7, 14.2, CH*H*′), 2.26 (1H, m, ^{i}Pr*H*), 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.03–0.93 (18H, m, $Si(CH_2CH_3)_3$ and $CHCH_3$), 0.67 (3H, d, *J* 6.8, $CHCH_3'$). δ_C (100 MHz, $CDCl_3$) 165.1, 163.5, 162.9, 153.9, 148.9, 139.3, 138.4, 135.7, 132.0, 129.1, 128.5, 128.4, 125.9, 124.2, 120.9, 118.9, 113.7, 112.2, 69.9, 60.7, 60.6, 60.5, 58.6, 57.9, 31.8, 31.6, 19.1, 16.6, 14.4, 14.3, 7.4, 3.5. *m/z* (ESI, positive ion) 693 ($[M + Na]^+$, 59%), 671 ($[M + H]^+$, 100%). HRMS (ESI, positive ion) $C_{38}H_{50}N_4O_5SiNa$ requires *m/z* 693.3445, found 693.3435.

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