Synthesis of New Dehydro 2-Azatryptophans and Derivatives via Heck Cross-Coupling Reactions of 3-Iodoindazoles with Methyl 2-(Acetylamino)acrylate

François Crestey, Valérie Collot,* Silvia Stiebing, Sylvain Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), UPRES EA-3915, U.F.R. des Sciences Pharmaceutiques, Université de Caen Basse-Normandie, 5 rue Vaubénard, 14032 Caen Cedex, France
Fax +33(2)31931188; E-mail: valerie.collot@unicaen.fr

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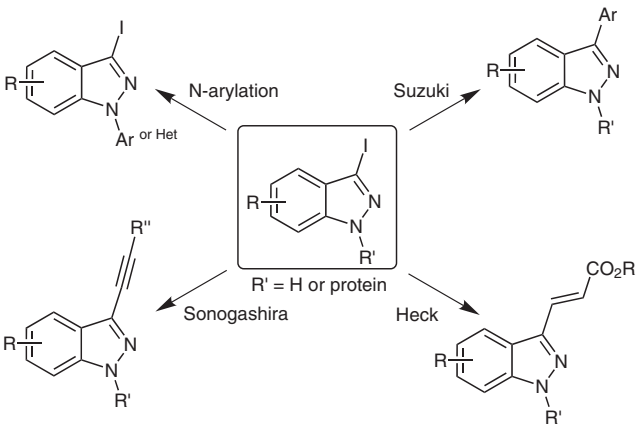
Abstract: This paper describes the Heck cross-coupling reaction of 3-iodoindazoles with methyl 2-(acetylamino)acrylate as a general route to new dehydro 2-azatryptophans and protected amino acid derivatives after catalytic hydrogenation.

Key words: dehydro 2-azatryptophans, protective amino acid derivatives, catalytic hydrogenation, Heck cross-coupling reaction, 3-iodoindazoles, 2-(acetylamino)acrylate

Amongst the heterocyclic scaffolds available for the preparation of valuable new building-blocks in medicinal chemistry, the indazole nucleus[1] is probably the least studied. In contrast to the plentiful literature on its bioisosteres (indole, quinoline or benzimidazole), there is a derth of indazole chemistry literature, presumably a result of the fact that this moiety is rather scarce in natural products. Moreover, its utility as a starting point for the synthesis of simple functionalized compounds is sometimes limited. Despite these drawbacks, however, some indazole-derivative lead compounds have been developed such as lonidamine (cytotoxic modulator),[2] benzydamine (nonsteroidal anti-inflammatory drug),[3] granisetron (5HT-3 receptor antagonist),[4] YC-1 (guanylyl cyclase activator),[5] 7-NI (nitric oxide synthase inhibitor),[6] and recently, new kinase Chk1 inhibitors[7] and inhibitors of the receptor tyrosine kinases.[8]

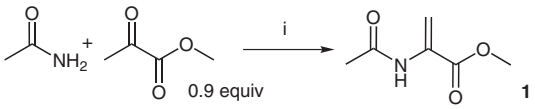
We have long been interested in the design and synthesis of new polyfunctionalized indazole libraries, particularly those derived from the 2-aza bioisosteres of tryptamine, serotonin or melatonin.[9]

To this end we have previously studied a number of metal-catalyzed reactions of 3-iodoindazoles (Scheme 1) and have reported a mild and flexible Sonogashira reaction that allows access to new aza analogues of tryptamine derivatives,[9a] a very efficient Suzuki cross-coupling reaction leading to 3-arylindazoles,[10a] combined, selective C- and N-arylations[10b] and a range of sequential cross-coupling reactions of dihalogenated indazoles.[10c] We also developed a general and versatile pathway leading to 3-indazolylpropionic acid and derivatives via a straightforward palladium-catalyzed Heck cross-coupling reaction of 3-iodoindazoles with methyl acrylate.[9b] As part of our ongoing program on the synthesis of functionalized indazoles, we became interested in developing strategies for the synthesis of 2-azatryptophans.[11] With the aim of improving molecular diversity, we decided to examine the Heck reaction with methyl 2-(acetylamino)acrylate **1**. Herein, we report a methodology for the synthesis of new dehydro 2-azatryptophans that allow access to a number of protected amino acid derivatives.



Scheme 1

Initially, we attempted to prepare acrylate **1** by the reaction of acetamide with methyl pyruvate in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) under reflux conditions in toluene (Dean–Stark). The yields were consistently lower than 50%, presumably due to acrylate polymerization; however, addition of 4-methoxyphenol (0.1%) significantly improved the yield and acrylate **1** was then obtained with 61% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) PTSA (cat.), 4-methoxyphenol (0.001 equiv), toluene, reflux, Dean–Stark, 61%.

In our previous work we reported that a protecting group in the N-1 position was necessary to avoid the formation of Michael adducts.[9b] Indazole **6a** was therefore synthesised, in very good yields, by direct iodination of indazole **4a**,[10a] followed by protection with 2-(trimethylsilanyl)ethoxymethyl chloride (SEM-Cl)[14] in a biphasic

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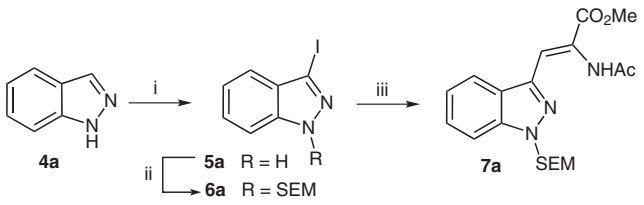
CH_2Cl_2/KOH mixture in the presence of a catalytic amount of tetrabutylammonium bromide. Preliminary coupling reactions were then performed by combining protected 3-iodoindazole **6a** with a slight excess of acrylate **1**, a slight excess of an amine base, 1 mol% of palladium acetate and 2 mol% of triphenyl or tri(*o*-tolyl)phosphine. Surprisingly, the reaction of *N*-SEM-3-iodoindazole **6a** with acrylate **1** using triarylphosphine under the standard Heck conditions[12] yielded none of the desired product. Alternative conditions,[9b] using $PdCl_2$(dppf) catalyst in a mixture of DMF–H_2O containing triethylamine and tetrabutylammonium iodide (TBAI), gave either unprotected 3-iodoindazole (when R = Boc) or the deiodinated indazole along with unreacted starting material (when R = SEM).

Previously reported Heck-coupling reactions of acrylate **1** have often been conducted in sealed tubes[13a–h] in the presence of $NaHCO_3$ or K_2CO_3 as base, and a phase-transfer agent such as a quaternary ammonium salt,[13c–i] in DMF, acetonitrile or under solvent-free conditions. With this in mind, we applied this Heck-coupling reaction to *N*-SEM-3-iodoindazole **6a** under the conditions described by RajanBabu[13c] (1.2 equiv of acrylate **1** and TBACl, 2.7 equiv of $NaHCO_3$ and 0.11 equiv of $Pd(OAc)_2$ in a sealed tube at 80 °C without solvent) and found that the reaction gave, after 24 hours, the desired product **7a** in 27% yield (Scheme 3).

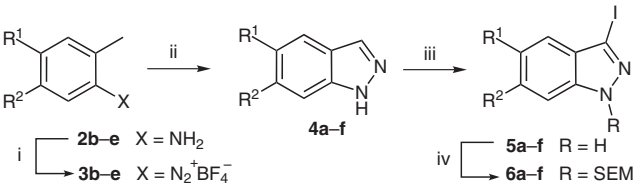


Scheme 3 *Reagents and conditions*: (i) I_2 (2 equiv), KOH (3.75 equiv), DMF, r.t., 92% (ii) SEM-Cl (1.1 equiv), CH_2Cl_2/KOH aq 50%, TBAB (0.01 equiv), r.t., 99% (iii) acrylate **1** (1.2 equiv), $Pd(OAc)_2$ (0.11 equiv), TBAB (1.2 equiv), $NaHCO_3$ (2.7 equiv), sealed tube, 90 °C.

This encouraging result prompted us to study this reaction with a range of other *N*-SEM-3-iodoindazoles **6** (Scheme 4 and Table 1). Except for indazole **4a** and 5-nitroindazole **4f**, which were both commercially available, indazoles **4** were obtained by diazotization of 2-methylanilines **2** with aqueous sodium nitrite in fluoroboric acid (50% solution in water)[15] to give the corresponding diazonium tetrafluoroborate salts **3b–e** in excellent yields (84–99%).

Cyclization of these salts, promoted by potassium acetate and 18-crown-6 in dry chloroform, gave indazoles **4b–e** in good yields (44–80%). Iodination in DMF or 1,4-dioxane,[11] at room temperature or at 65 °C, followed by protection with the SEM group, gave indazoles **6a–f** in excellent yields (Scheme 4 and Table 1).

In order to find more efficient Heck coupling conditions, we focused on *N*-SEM-3-iodo-5-methoxyindazole **6b**, as



Scheme 4 *Reagents and conditions*: (i) aq 50% HBF_4, $NaNO_2$ aq (1 equiv), 0 °C, 84–99% (ii) KOAc (2 equiv), 18-crown-6 (0.05 equiv), $CHCl_3$, r.t., 44–80% (iii) I_2 (2 equiv), KOH (3.75 equiv), DMF or 1,4-dioxane, r.t. or 65 °C, 84–100% (iv) SEM-Cl (1.1 equiv), CH_2Cl_2/KOH aq 50%, TBAB (0.01 equiv), r.t., 79–99%.

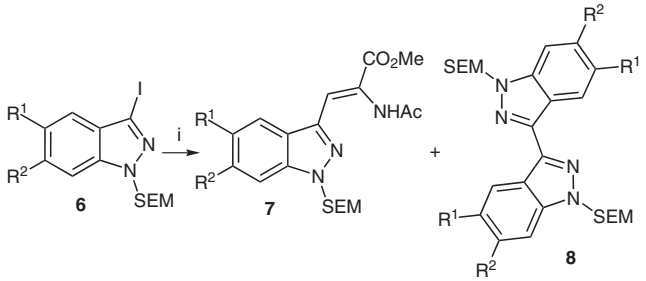
Table 1 Synthesis of *N*-SEM-3-Iodoindazoles **(6a–f)**

	a	**b**	**c**	**d**	**e**	**f**
R^1	H	OMe	OBn	Br	I	NO_2
R^2	H	H	Me	H	H	H
Yield of **3** (%)	–	98	99	98	84	–
Yield of **4** (%)	–[a]	79	44	80	74	–[a]
Yield of **5** (%)	92	100	100	94	84	100
Yield of **6** (%)	99	98	79	99	79	98

[a] Commercially available.

a reference reaction. To this end, we modified the solvent (DMF, toluene), the amount of acrylate **1** (1.2 to 1.7 equiv), the phase-transfer agent (TBABr or TBACl), and the reaction temperature (110 to 135 °C). The optimum conditions were found to be a **6b/1**/TBAB/$NaHCO_3$/$Pd(OAc)_2$ ratio of 1:1.6:1.9:3:0.12 in DMF at 125 °C for two hours. Under these conditions, dehydro 2-azatryptophan **7b** was obtained in 54% yield. It should be noted that the homocoupled product **8b** was also isolated in 10% yield, the structure of which was confirmed by 2D NOESY NMR experiments.[16] This minor product could be easily separated from indazole **7b** by column chromatography. In order to decrease this process of homocoupling, the iodine atom in position 3 was replaced by bromine, since the order of reactivity is usually I > Br >> Cl in palladium-assisted coupling of aryl halides. However, no reaction occurred and only starting material was recovered. Use of a larger excess of olefin **1** also had no effect on either the extent of homocoupling or on the yield of **7b**. Moreover, when the reaction was conducted in the absence of olefin **1**, compound **8b** was formed as the sole product in 73% yield. It would appear that the competitive formation of this interesting by-product seems to be faster than that of the desired dehydro compound.

When the optimized reaction conditions were applied to other substituted indazoles **6** (Scheme 5 and Table 2), dehydro 2-azatryptophans **7** were obtained in 23–54% yields. The nature of the substituent on the benzene moiety of the indazole did not appear to influence the course of the coupling reaction. As noted previously,[13e,17] we obtained dehydro compounds **7** predominantly in the *Z* con-



Scheme 5 *Reagents and conditions*: (i) **1** (1.6 equiv), $Pd(OAc)_2$ (0.12 equiv), TBAB (1.9 equiv), $NaHCO_3$ (3 equiv), DMF, sealed tube, 125 °C.

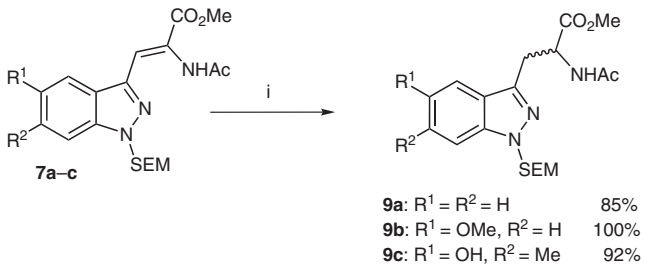
Table 2 Synthesis of Protected Dehydro Indazoles (**7a–f**) and Homocoupled Products (**8**)

	a	b	c	d	e	f
R^1	H	OMe	OBn	Br	I	NO_2
R^2	H	H	Me	H	H	H
7 (%)	30	54	45	39	–[a]	23
8 (%)	20	10	10	–	–	8

[a] Product **7e** was detected with LCMS but not isolated.

figuration, except for compound **7a** ($R^1 = R^2 = H$) which proved to be an isomeric mixture in a 2:1, *Z*/*E* ratio. Importantly, substrates bearing either a bromine or an iodine atom at position 5 were exclusively functionalized at position 3. Moreover some new, potentially valuable, products **8** were isolated with 8–20% yields. When the substituent at position 5 of indazole was bromine or iodine, however, only a small amount of de-iodinated product was observed.

Efforts were then focused on the reduction of the double bond of the dehydro compounds **7**. Preliminary attempts with sodium borohydride in the presence of Ni(II) chloride hexahydrate in methanol[9b,18] gave the desired products albeit in low yields (<50%). However, catalytic hydrogenation with palladium on activated carbon in methanol[13e] gave amino acid derivatives **9** with very good yields (Scheme 6). In the case of compound **7c**, both the double bond and the benzyloxy group on the aromatic nucleus were reduced, leading to compound **9c**.



Scheme 6 *Reagents and conditions*: (i) H_2, Pd/C (15 mol%), 1 atm, MeOH, r.t.

In conclusion, we have described a method for the synthesis of new dehydro 2-azatryptophans, obtained from a Heck-coupling reaction between methyl 2-(acetylamino)acrylate and a range of *N*-SEM-3-iodoindazoles. Some of these compounds have been hydrogenated to give the corresponding protected amino acids derivatives. Since orthogonal protecting groups are present, these dehydro 2-azatryptophans and unnatural amino acid derivatives could provide valuable building blocks for a wide range of applications, in particular in the development of new peptidomimetics with specific structural features and for the synthesis of serotonin receptors ligands (5HT).

All commercial reagents were used as received without further purification. Reaction mixtures were stirred magnetically and monitored by TLC using 0.2 mm Macherey-Nagel Polygram SIL G/UV_{254} coated plates. Column chromatography was performed using CarloErba-SDS 60A 70–200 μm silica gel. Melting points (uncorrected) were determined on a Kofler melting point apparatus. IR spectra were taken with a Perkin-Elmer spectrum X FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 Spectrometer instrument. 2D NOESY NMR spectra (mixing time: 500 ms) were recorded on a Brucker Avance DRX 400 instrument. Chemical shifts (δ) are expressed in parts per million downfield from TMS as an internal standard, and the coupling constants are in Hertz. Mass spectra were recorded on a JEOL JMS GCMate with ionising potential of 70 eV and with perfluorokerosene as internal standard for high-resolution measurements. Elemental analyses were performed at the Institut de Recherche en Chimie Organique Fine (Rouen, France).

Methyl 2-(Acetylamino)acrylate (1)[19]

A round-bottom flask equipped with a Dean–Stark trap was charged successively with acetamide (1.5 g, 25.4 mmol), methyl pyruvate (2.1 mL, 22.9 mmol, 0.9 equiv), a catalytic amount of *p*-TsOH, 4-methoxyphenol (4 mg, 25,4 μmol, 0.001 equiv) and toluene (50 mL). The stirred mixture was heated under reflux for 26 h then concentrated in vacuo. The resulting yellow oil was taken up in CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (100 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give methyl 2-(acetylamino)acrylate (**1**).

Yield: 2.0 g (61%); light-yellow solid; mp 48 °C.

IR (KBr): 3364, 2957, 1728, 1678, 1636, 1520, 1441, 1372, 1204, 1172, 995, 904, 806 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.14 (s, 3 H), 3.85 (s, 3 H), 5.88 (s, 1 H), 6.60 (s, 1 H), 7.75 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 24.7, 53.0, 108.7, 130.9, 164.6, 168.9.

MS (EI): *m*/*z* (%) = 143 (60) [M^+], 113 (28), 112 (14), 102 (30), 101 (100).

Synthesis of 2-Methylbenzenediazonium Tetrafluoroborate Salts (3b–e); General Procedure (GP 1)

To a cooled solution of the 2-methylaniline **2b–e** dissolved in fluoroboric acid (50% soln in H_2O) was added at 0 °C, dropwise, a cooled solution of $NaNO_2$ (1 equiv in the minimum of H_2O). After the end of the addition, the mixture was stirred for 1 h at 0 °C then for 2 h at r.t.. The resulting precipitate was filtered and washed with Et_2O (3 × 100 mL) to obtain the desired 2-methylphenyldiazonium tetrafluoroborate salts **3b–e**.

4-Methoxy-2-methylbenzenediazonium Tetrafluoroborate Salt (3b)
Obtained by GP 1, starting from 4-methoxy-2-methylaniline (**2b**; 12.8 g, 93.6 mmol), and fluoroboric acid (25 mL).

Yield: 21.7 g (98%); pink solid; mp 144 °C.

IR (KBr): 3400, 2231, 1591, 1264, 1063 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.67 (s, 3 H), 4.02 (s, 3 H), 7.32 (dd, *J* = 9.3 Hz, *J* = 1.9 Hz, 1 H), 7.39 (d, *J* = 1.9 Hz, 1 H), 8.57 (d, *J* = 9.2 Hz, 1 H).

4-Benzyloxy-2,5-dimethylphenyldiazonium Tetrafluoroborate Salt (3c)
Obtained by GP 1, starting from 4-benzyloxy-2,5-dimethylaniline (**2c**; 5 g, 22.0 mmol) and fluoroboric acid (6 mL).

Yield: 7.1 g (99%); beige solid; mp 131 °C.

IR (KBr): 3420, 2236, 1230, 1057 cm^{-1}.

4-Bromo-2-methylbenzenediazonium Tetrafluoroborate Salt (3d)
Obtained by GP 1, starting from 4-bromo-2-methylaniline (**2d**; 10 g, 53.8 mmol) and fluoroboric acid (28 mL).

Yield: 15 g (98%); beige solid; mp 176 °C.

IR (KBr): 3416, 2279, 2260, 1587, 1548, 1207, 1033 cm^{-1}.

4-Iodo-2-methylbenzenediazonium Tetrafluoroborate Salt (3e)
Obtained by GP 1, starting from 4-iodo-2-methylaniline (**2e**; 5 g, 21.5 mmol) and fluoroboric acid (7 mL).

Yield: 6 g (84%); mauve solid; mp 175 °C.

IR (KBr): 3416, 2274, 2253, 1579, 1542, 1203, 1060, 1033 cm^{-1}.

Synthesis of Indazoles (4b–e); General Procedure (GP 2)
The diazonium tetrafluoroborate salt **3b–e** was added in one portion, under nitrogen, to a stirred mixture of KOAc (2 equiv) and 18-crown-6 (0.05 equiv) in dry $CHCl_3$ (500 mL). After 2 h at r.t., the resulting precipitate was filtered, washed with $CHCl_3$ (2 × 100 mL) and the organic layer was concentrated in vacuo. The residual gum was purified by column chromatography on silica gel (EtOAc–cyclohexane, 1:6 to 2:3) to give the desired indazoles **4b–e**.

5-Methoxy-1*H*-indazole (4b)[15b]
Obtained by GP 2, starting from 4-methoxy-2-methylphenyldiazonium tetrafluoroborate salt (**3b**; 14 g, 59.3 mmol).

Yield: 7 g (79%); beige solid; mp 170–171 °C; R_f = 0.2 (EtOAc–cyclohexane, 1:2).

IR (KBr): 3152, 2940, 1508, 1229, 1157, 957, 810 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.87 (s, 3 H), 7.07–7.11 (m, 2 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 8.00 (s, 1 H), 10.18 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 55.7, 100.0, 110.6, 119.2, 123.6, 134.4, 135.9, 154.8.

MS (EI): *m*/*z* (%) = 148 (100) [M^+], 133 (95), 105 (54), 78 (21).

Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.17; H, 5.23; N, 18.33.

5-Benzyloxy-6-methyl-1*H*-indazole (4c)
Obtained by GP 2, starting from 4-benzyloxy-2,5-dimethylphenyldiazonium tetrafluoroborate salt (**3c**; 28.9 g, 88.6 mmol).

Yield: 9.3 g (44%); brown solid; mp 141 °C; R_f = 0.1 (EtOAc–cyclohexane, 1:4).

IR (KBr): 3179, 2924, 1454, 1304, 1223, 1164, 1128, 954 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 5.12 (s, 2 H), 7.10 (s, 1 H), 7.28 (s, 1 H), 7.34 (d, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.48 (d, *J* = 7.3 Hz, 2 H), 7.94 (s, 1 H), 10.04 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 17.8, 70.2, 100.1, 110.7, 121.8, 127.1, 127.8, 128.5, 129.8, 134.3, 135.9, 137.4, 152.8.

MS (EI): *m*/*z* (%) = 238 (50) [M^+], 147 (40), 126 (16), 91 (100).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.32; H, 5.44; N, 11.25.

5-Bromo-1*H*-indazole (4d)
Obtained by GP 2, starting from 4-bromo-2-methylphenyldiazonium tetrafluoroborate salt (**3d**; 12.1 g, 42.3 mmol).

Yield: 6.7 g (80%); orange solid; mp 122 °C; R_f = 0.45 (EtOAc–cyclohexane, 2:3).

IR (KBr): 3177, 2933, 1490, 1190, 1069, 952, 878, 782 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.41 (d, *J* = 8.8 Hz, 1 H), 7.48 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 1 H), 7.92 (d, *J* = 1.7 Hz, 1 H), 8.02 (s, 1 H), 10.18 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 111.2, 114.2, 123.4, 124.8, 130.1, 134.3, 138.7.

MS (EI): *m*/*z* (%) = 198 (97) [M + H^+], 196 (100) [M – 1], 117 (51), 90 (50).

Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.39; H, 2.35; N, 14.13.

5-Iodo-1*H*-indazole (4e)[14b]
Obtained by GP 2, starting from 4-iodo-2-methylphenyldiazonium tetrafluoroborate salt (**3e**; 5.7 g, 17.2 mmol).

Yield: 3.1 g (74%); yellow solid; mp 156 °C; R_f = 0.5 (EtOAc–cyclohexane, 2:3).

IR (KBr): 3131, 2923, 1471, 1283, 1082, 959, 892, 808 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.40 (d, *J* = 8.7 Hz, 1 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 8.01 (s, 1 H), 8.17 (s, 1 H), 13.23 (br s, 1 H).

MS (EI): *m*/*z* (%) = 244 (100) [M^+], 135 (27), 117 (34), 91 (39).

Anal. Calcd for $C_7H_5IN_2$: C, 34.45; H, 2.07; N, 11.48. Found: C, 33.91; H, 2.19; N, 10.75.

Synthesis of 3-Iodoindazoles (5); General Precedure
Method A

Iodine (2 equiv) and KOH pellets (3.75 equiv) were successively added to a solution of the indazole **4** in DMF (60 mL) at r.t. under stirring. After 1 h, the reaction mixture was poured into aq $NaHSO_3$ (10%, 200 mL) and extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with H_2O (3 × 150 mL) and brine (3 × 150 mL), dried over $MgSO_4$, and the solvent evaporated in vacuo. The solid residue was washed with petroleum ether to give desired 3-iodoindazoles **5**.

Method B

KOH pellets (5.8 equiv) and iodine (2 equiv) were successively added to a cooled 1,4-dioxane solution (60 mL) of indazole **4** under stirring. The reaction mixture was stirred for 1 h at 0 °C then 2 h at r.t.. The pH value was adjusted to pH 5 through the addition of 20% aqueous citric acid then sat. $Na_2S_2O_3$ (200 mL) was added and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with H_2O (3 × 150 mL) and brine (3 × 150 mL), dried over $MgSO_4$, and the solvent evaporated in vacuo. The solid residue was washed with petroleum ether to give desired 3-iodoindazoles **5**.

Method C

The reaction was carried out as described in method B but the stirred mixture was heated at 65 °C.

Method D

The reaction was carried out as described in method A but the stirred mixture was heated at 65 °C.

3-Iodo-1*H*-indazole (5a)[10a]
Obtained by method A, starting from 1*H*-indazole (**4a**; 3.8 g, 31.9 mmol).

Yield: 6.9 g (92%); white solid; mp 141 °C; R_f = 0.5 (EtOAc–cyclohexane, 1:2).

IR (KBr): 3154, 2904, 1239, 1014, 739 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.20 (t, *J* = 7.3 Hz, 1 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 10.72 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 93.0, 110.4, 120.3, 121.5, 127.2, 127.6, 140.6.

MS (EI): *m*/*z* (%) = 244 (100) [M^+], 117 (80), 90 (43).

Anal. Calcd for $C_7H_5IN_2$: C, 34.45; H, 2.07; N, 11.48. Found: C, 34.33; H, 2.22; N, 11.27.

3-Iodo-5-methoxy-1*H*-indazole (5b)[15a]
Obtained by method B, starting from 5-methoxy-1*H*-indazole (**4b**; 3 g, 20.4 mmol).

Yield: 5.6 g (100%); yellow solid; mp 178–179 °C; R_f = 0.4 (EtOAc–cyclohexane, 1:2).

IR (KBr): 3184, 2902, 1506, 1483, 1288, 1172, 1028, 1004, 944, 822 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.80 (s, 3 H), 6.75 (s, 1 H), 7.06 (d, *J* = 8.8 Hz, 1 H), 7.45 (d, *J* = 9.0 Hz, 1 H), 13.37 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 55.4, 92.2, 99.2, 111.7, 119.5, 127.1, 136.1, 154.6.

MS (EI): *m*/*z* (%) = 274 (100) [M^+], 259 (13), 147 (97), 132 (10), 128 (20), 120 (25), 104 (20), 78 (20).

Anal. Calcd for $C_8H_7IN_2O$: C, 35.06; H, 2.57; N, 10.22. Found: C, 35.27; H, 2.54; N, 10.17.

5-Benzyloxy-3-iodo-6-methyl-1*H*-indazole (5c)
Obtained by method C, starting from 5-benzyloxy-6-methyl-1*H*-indazole (**4c**; 1.1 g, 4.6 mmol).

Yield: 1.7 g (100%); beige solid; mp 152 °C; R_f = 0.25 (EtOAc–cyclohexane, 1:4).

IR (KBr): 3256, 1728, 1474, 1446, 1281, 1192, 1137, 991, 870 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.32 (s, 3 H), 5.17 (s, 2 H), 6.82 (s, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.36 (s, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 13.24 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 17.3, 69.4, 92.1, 99.5, 111.3, 125.5, 127.3, 127.7, 128.4, 129.4, 135.9, 137.4, 152.4.

MS (EI): *m*/*z* (%) = 364 (26) [M^+], 273 (11), 91 (100).

Anal. Calcd for $C_{15}H_{13}IN_2O$: C, 49.47; H, 3.60; N, 7.69. Found: C, 49.47; H, 2.91; N, 7.02.

5-Bromo-3-iodo-1*H*-indazole (5d)
Obtained by method A, starting from 5-bromo-1*H*-indazole (**4d**; 1.1 g, 5.5 mmol).

Yield: 1.7 g (94%); yellow solid; mp 196 °C; R_f = 0.3 (EtOAc–cyclohexane, 1:3).

IR (KBr): 3436, 3122, 2893, 1464, 1255, 1234, 912, 783 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38 (d, *J* = 8.8 Hz, 1 H), 7.53 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 1 H), 7.68 (d, *J* = 1.7 Hz, 1 H), 10.62 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 93.0, 111.7, 115.2, 124.2, 129.4, 131.5, 139.4.

MS (EI): *m*/*z* (%) = 324 (97) [M + H^+], 322 (100) [M – 1], 197 (57), 195 (58), 116 (46).

Anal. Calcd for $C_7H_4BrIN_2$: C, 26.04; H, 1.25; N, 8.67. Found: C, 26.08; H, 1.39; N, 8.63.

3,5-Diiodo-1*H*-indazole (5e)[14b]
Obtained by method A, starting from 5-iodo-1*H*-indazole (**4e**; 1 g, 4.1 mmol).

Yield: 1.3 g (84%); yellow solid; 198–200 °C (dec); R_f = 0.65 (EtOAc–cyclohexane, 2:3).

IR (KBr): 3426, 3150, 2928, 1460, 1257, 1236, 900, 778 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.28 (d, *J* = 8.7 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.90 (s, 1 H), 10.55 (br s, 1 H).

MS (EI): *m*/*z* (%) = 370 (100) [M^+], 243 (50), 116 (45).

Anal. Calcd for $C_7H_4I_2N_2$: C, 22.73; H, 1.07; N, 7.57. Found: C, 23.75; H, 0.84; N, 7.41.

3-Iodo-5-nitro-1*H*-indazole (5f)
Obtained by method D, starting from 5-nitro-1*H*-indazole (**4f**; 5 g, 30.7 mmol).

Yield: 6.4 g (100%); yellow solid; mp 214 °C; R_f = 0.4 (EtOAc–cyclohexane, 1:2).

IR (KBr): 3097, 1340, 1084, 1004 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.75 (d, *J* = 9.3 Hz, 1 H), 8.22 (dd, *J* = 9.3 Hz, *J* = 2.0 Hz, 1 H), 8.30 (d, *J* = 2.0 Hz, 1 H), 14.12 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 97.2, 111.8, 118.1, 122.0, 126.3, 142.1, 142.5.

MS (EI): *m*/*z* (%) = 289 (100) [M^+], 259 (16), 116 (30).

Anal. Calcd for $C_7H_4IN_3O_2$: C, 29.09; H, 1.39; N, 14.54. Found: C, 28.79; H, 1.76; N, 14.06.

Synthesis of *N*-SEM-3-iodoindazoles (6); General Procedure (GP 3)
To a cooled solution of the 3-iodoindazole **5**, TBAB (0.01 equiv) and KOH (50% solution in H_2O, 7–15 mL) in CH_2Cl_2 (15–20 mL) was added at 0 °C, dropwise, SEM-Cl (1.1 equiv). After the end of the addition, the mixture was stirred rapidly at 0 °C for 1 h then 2 h at r.t. CH_2Cl_2 (50 mL) and H_2O (70 mL) were added, and the organic layer was washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc–cyclohexane, 1:6) to give a mixture of (N-1 and N-2)-SEM-3-iodoindazoles **6**.

3-Iodo-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (6a)
Obtained by GP 3, starting from 3-iodo-1*H*-indazole (**5a**; 1.5 g, 6.2 mmol).

Yield: 2.3 g (99%); light-yellow oil; R_f = 0.8 (EtOAc–cyclohexane, 1:3).

IR (KBr): 3060, 2952, 1615, 1490, 1460, 1317, 1249, 1194, 1174, 1081, 860, 836, 745 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.11 (s, 9 H), 0.83 (t, *J* = 8.3 Hz, 2 H), 3.53 (t, *J* = 8.3 Hz, 2 H), 5.65 (s, 2 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 7.34–7.41 (m, 2 H), 7.46 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.6, 66.5, 77.8, 93.2, 109.7, 121.5, 121.9, 127.8, 128.9, 140.1.

MS (EI): *m/z* (%) = 374 (23) [M$^+$], 331 (10), 329 (20), 316 (26), 258 (55), 257 (36), 243 (43), 175 (35), 174 (86), 131 (52), 130 (30), 103 (30), 73 (100).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}IN_2OSi$: 375.0390; found: 375.0375.

3-Iodo-5-methoxy-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (6b)

Obtained by GP 3, starting from 3-iodo-5-methoxy-1*H*-indazole (**5b**; 3.5 g, 12.8 mmol).

Yield: 5.1 g (98%); orange solid; mp <46 °C; R_f = 0.7 (EtOAc–cyclohexane, 1:6).

IR (KBr): 2953, 1500, 1285, 1249, 1062, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.05 (s, 9 H), 0.87 (t, *J* = 8.7 Hz, 2 H), 3.56 (t, *J* = 8.7 Hz, 2 H), 3.99 (s, 3 H), 5.64 (s, 2 H), 6.72 (d, *J* = 1.7 Hz, 1 H), 7.06 (dd, *J* = 9.0 Hz, *J* = 1.7 Hz, 1 H), 7.36 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –0.9, 18.5, 56.1, 66.3, 78.6, 92.6, 100.8, 111.5, 120.7, 130.0, 136.4, 156.3.

MS (EI): *m/z* (%) = 404 (58) [M$^+$], 359 (25), 346 (42), 288 (23), 287 (37), 205 (31), 204 (50), 189 (17), 161 (33), 160 (27), 145 (15), 102 (18), 73 (100).

Anal. Calcd for $C_{14}H_{21}IN_2O_2Si$: C, 41.59; H, 5.24; N, 6.93. Found: C, 41.36; H, 4.87; N, 6.49.

5-Benzyloxy-3-Iodo-6-methyl-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (6c)

Obtained by GP 3, starting from 5-benzyloxy-3-iodo-6-methyl-1*H*-indazole (**5c**; 1.7 g, 4.6 mmol).

Yield: 1.8 g (79%); light-brown solid; 74–76 °C (dec); R_f = 0.6 (EtOAc–cyclohexane, 1:4).

IR (KBr): 2952, 2920, 1475, 1277, 1204, 1160, 1077, 830 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.08 (s, 9 H), 0.85 (t, *J* = 8.6 Hz, 2 H), 2.40 (s, 3 H), 3.52 (t, *J* = 8.7 Hz, 2 H), 5.22 (s, 2 H), 5.63 (s, 2 H), 6.79 (s, 1 H), 7.32 (s, 1 H), 7.33 (d, *J* = 7.3 Hz, 1 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.48 (d, *J* = 7.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.8, 17.9, 66.5, 70.3, 78.0, 91.2, 100.4, 110.9, 127.1, 127.8, 127.8, 128.5, 131.1, 135.7, 137.0, 153.7.

MS (EI): *m/z* (%) = 494 (45) [M$^+$], 436 (14), 377 (23), 345 (84), 287 (17), 251 (17), 203 (22), 91 (100), 73 (67).

Anal. Calcd for $C_{21}H_{27}IN_2O_2Si$: C, 51.01; H, 5.50; N, 5.67. Found: C, 51.46; H, 5.44; N, 5.43.

5-Bromo-3-iodo-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (6d)

Obtained by GP 3, starting from 5-bromo-3-iodo-1*H*-indazole (**5d**; 6 g, 18.6 mmol).

Yield: 8.3 g (99%); orange oil; R_f = 0.7 (EtOAc–cyclohexane, 1:3).

IR (KBr): 2952, 2895, 1473, 1251, 1192, 1083, 859, 796 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.06 (s, 9 H), 0.87 (t, *J* = 8.3 Hz, 2 H), 3.55 (t, *J* = 8.3 Hz, 2 H), 5.70 (s, 2 H), 7.44 (d, *J* = 8.8 Hz, 1 H), 7.54 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 1 H), 7.66 (d, *J* = 1.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.3, 17.9, 67.0, 78.4, 91.8, 111.6, 115.5, 124.4, 130.8, 131.3, 139.2.

MS (EI): *m/z* (%) = 454 (13) [M + H]$^+$, 452 (12) [M – 1], 396 (21), 394 (21), 338 (28), 337 (19), 336 (28), 335 (18), 255 (16), 254 (39), 253 (16), 252 (37), 211 (20), 210 (17), 209 (23), 208 (15), 74 (100).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{13}H_{18}BrIN_2OSi$: 451.9416; found: 451.9426.

3,5-Diiodo-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (6e)[14b]

Obtained by GP 3, starting from 3,5-diiodo-1*H*-indazole (**5e**; 0.8 g, 2 mmol).

Yield: 0.8 g (79%); orange oil; R_f = 0.7 (EtOAc–cyclohexane, 1:4).

IR (KBr): 2952, 2895, 1470, 1256, 1190, 1080, 858, 835 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.06 (s, 9 H), 0.86 (t, *J* = 8.3 Hz, 2 H), 3.54 (t, *J* = 8.3 Hz, 2 H), 5.68 (s, 2 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 7.71 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 1 H), 7.87 (d, *J* = 1.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.7, 66.8, 78.2, 85.3, 91.4, 111.7, 130.6, 131.4, 136.3, 139.4.

MS (EI): *m/z* (%) = 500 (23) [M$^+$], 442 (24), 384 (37), 300 (40), 257 (33), 256 (16), 150 (16), 103 (30), 101 (25), 74 (100).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{13}H_{18}I_2N_2OSi$: 499.9278; found: 499.9272.

3-Iodo-5-nitro-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (6f)

Obtained by GP 3, starting from 3-iodo-5-nitro-1*H*-indazole (**5f**; 1.8 g, 6.1 mmol).

Yield: 2.5 g (98%); yellow solid; 88–90 °C (dec); R_f = 0.7 (EtOAc–cyclohexane, 1:4).

IR (KBr): 2953, 1500, 1285, 1249, 1062, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.08 (s, 9 H), 0.87 (t, *J* = 8.6 Hz, 2 H), 3.58 (t, *J* = 8.6 Hz, 2 H), 5.75 (s, 2 H), 7.65 (d, *J* = 9.3 Hz, 1 H), 8.30 (dd, *J* = 9.3 Hz, *J* = 1.9 Hz, 1 H), 8.40 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.6, 67.1, 78.4, 95.4, 110.6, 119.2, 122.7, 128.6, 143.2, 143.8.

MS (EI): *m/z* (%) = 419 (12) [M$^+$], 376 (34), 374 (19), 361 (51), 303 (87), 302 (23), 219 (51), 176 (25), 175 (18), 103 (14), 74 (100).

Anal. Calcd for $C_{13}H_{12}IN_3O_3Si$: C, 37.24; H, 4.33; N, 10.02. Found: C, 37.42; H, 4.18; N, 10.04.

Heck Cross-Coupling of Protected Dehydro 2-Azatryptophans (7); General Procedure (GP 4)

A mixture of $NaHCO_3$ (3 equiv), methyl 2-(acetylamino)acrylate (**1**; 1.6 equiv), TBAB (1.9 equiv), *N*-SEM-3-iodoindazoles **6**, and DMF (3–4 mL) was flushed with argon in a sealed tube. After 10 min, palladium acetate (0.12 equiv) was added and the mixture was heated at 130 °C in an oil bath for 2 h. After cooling to r.t., the resulting mixture was taken up in EtOAc (80 mL) and washed with H_2O (3 × 150 mL). The aqueous layer was extracted with EtOAc (2 × 80 mL), and the combined organic layers were filtered through Celite then concentrated in vacuo. The residual brown oil was purified by column chromatography on silica gel (EtOAc–cyclohexane, 1:6 to 1:1) to afford desired protected dehydro 2-azatryptophans **7** and homocoupling products **8**.

(*Z*)-2-Acetylamino-3-{1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic Acid Methyl Ester (7a) and 1,1′-Bis[2-(trimethylsilanyl)ethoxymethyl]-[3,3′]biindazolyl (8a)

Obtained by GP 4, starting from 3-iodo-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (**6a**; 2.5 g, 6.7 mmol).

7a

Yield: 0.8 g (30%); yellow oil; R_f = 0.6 (EtOAc–cyclohexane, 1:1).

IR (KBr): 3310, 2953, 1732, 1694, 1644, 1506, 1347, 1248, 1080, 837, 749 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.07 (s, 9 H), 0.90 (t, *J* = 8.3 Hz, 2 H), 2.22 (s, 3 H), 3.57 (t, *J* = 8.3 Hz, 2 H), 3.90 (s, 3 H), 5.76 (s, 2 H), 6.85 (s, 1 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 9.87 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.7, 23.6, 52.6, 66.9, 78.1, 108.7, 109.8, 119.9, 122.3, 124.2, 127.8, 130.1, 139.9, 141.0, 165.5, 168.6.

MS (EI): *m*/*z* (%) = 389 (9) [M$^+$], 289 (13), 167 (14), 149 (35), 73 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{19}H_{27}N_3O_4Si$: 389.1771; found: 389.1753.

8a

Yield: 0.6 g (20%); light-orange solid; 82–84 °C (dec).

IR (KBr): 2955, 1464, 1379, 1303, 1249, 1079, 836, 744 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.09 (s, 18 H), 0.93 (t, *J* = 8.3 Hz, 4 H), 3.67 (t, *J* = 8.3 Hz, 4 H), 5.84 (s, 4 H), 7.28 (t, *J* = 8.3 Hz, 2 H), 7.46 (t, *J* = 8.3 Hz, 2 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 8.53 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.7, 66.5, 77.7, 109.4, 121.8, 123.1 127.6, 134.0, 139.7, 140.6.

MS (EI): *m*/*z* (%) = 494 (8) [M$^+$], 377 (10), 203 (26), 177 (20), 175 (73), 148 (40), 132 (73), 131 (100), 103 (16), 84 (25), 74 (89).

Anal. Calcd for $C_{26}H_{38}N_4O_2Si_2$: C, 63.12; H, 7.74; N, 11.32. Found: C, 63.03; H, 7.71; N, 10.87.

(*Z*)-2-Acetylamino-3-{5-methoxy-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic Acid Methyl Ester (7b) and 5,5′-Dimethoxy-1,1′-bis[2-(trimethylsilanyl)ethoxymethyl]-[3,3′]biindazolyl (8b)

Obtained by GP 4, starting from 3-iodo-5-methoxy-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (**6b**; 2.2 g, 5.4 mmol).

7b

Yield: 1.2 g (54%); pale-yellow solid; 68–70 °C (dec); R_f = 0.1 (EtOAc–cyclohexane, 1:3).

IR (KBr): 3342, 2953, 2923, 2902, 1732, 1699, 1496, 1328, 1306, 1277, 1086, 1044, 839 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.07 (s, 9 H), 0.88 (t, *J* = 8.0 Hz, 2 H), 2.21 (s, 3 H), 3.55 (t, *J* = 8.0 Hz, 2 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 5.69 (s, 2 H), 6.80 (s, 1 H), 7.07 (d, *J* = 2.2 Hz, 1 H), 7.11 (dd, *J* = 9.0 Hz, *J* = 2.2 Hz, 1 H), 7.45 (d, *J* = 9.0 Hz, 1 H), 9.79 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.5, 17.6, 23.5, 52.4, 55.6, 66.7, 78.2, 98.8, 108.4, 110.8, 119.9, 124.7, 129.3, 135.6, 140.0, 155.8, 165.5, 168.5.

MS (EI): *m*/*z* (%) = 419 (54) [M$^+$], 361 (15), 319 (37), 302 (44), 260 (22), 85 (55), 73 (100).

Anal. Calcd for $C_{20}H_{29}N_3O_5Si$: C, 57.26; H, 6.97; N, 10.02. Found: C, 57.32; H, 6.87; N, 9.94.

8b

Yield: 0.3 g (10%); light-orange solid; mp 110–112 °C; R_f = 0.6 (EtOAc–cyclohexane, 2:3).

IR (KBr): 3430, 2952, 2927, 1625, 1490, 1449, 1305, 1247, 1206, 1167, 1071, 1053, 1033, 834, 801 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.07 (s, 18 H), 0.92 (t, *J* = 8.0 Hz, 4 H), 3.66 (t, *J* = 8.0 Hz, 4 H), 3.95 (s, 6 H), 5.83 (s, 4 H), 7.15 (dd, *J* = 8.8 Hz, *J* = 2.2 Hz, 2 H), 7.51 (d, *J* = 9.0 Hz, 2 H), 7.94 (d, *J* = 2.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.8, 55.8, 66.5, 78.1, 102.7, 110.5, 119.1, 123.5, 136.5, 139.0, 155.6.

MS (EI): *m*/*z* (%) = 554 (22) [M$^+$], 438 (19), 278 (39), 233 (19), 220 (33), 178 (28), 162 (61), 161 (92), 148 (16), 118 (17), 84 (38), 74 (100).

Anal. Calcd for $C_{28}H_{42}N_4O_4Si_2$: C, 60.61; H, 7.63; N, 10.10. Found: C, 59.44; H, 7.92; N, 9.98.

(*Z*)-2-Acetylamino-3-{5-benzyloxy-6-methyl-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic Acid Methyl Ester (7c) and 5,5′-Dibenzyloxy-6,6′-dimethyl-1,1′-bis[2-(trimethylsilanyl)ethoxymethyl]-[3,3′]biindazolyl (8c)

Obtained by GP 4, starting from 5-benzyloxy-3-iodo-6-methyl-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (**6c**; 3.1 g, 6.2 mmol).

7c

Yield: 1.4 g (45%); pale-yellow solid; 102–104 °C (dec).

IR (KBr): 3273, 2950, 2917, 1735, 1665, 1525, 1489, 1434, 1305, 1256, 1223, 1082, 858, 835 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.06 (s, 9 H), 0.90 (t, *J* = 8.3 Hz, 2 H), 2.21 (s, 3 H), 2.43 (s, 3 H), 3.55 (t, *J* = 8.3 Hz, 2 H), 3.90 (s, 3 H), 5.13 (s, 2 H), 5.69 (s, 2 H), 6.81 (s, 1 H), 7.12 (s, 1 H), 7.37 (s, 1 H), 7.34 (d, *J* = 6.8 Hz, 1 H), 7.41 (t, *J* = 7.1 Hz, 2 H), 7.49 (d, *J* = 7.3 Hz, 2 H), 9.87 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.5, 17.6, 17.8, 23.5, 52.5, 66.7, 70.1, 78.1, 98.8, 108.6, 110.8, 123.0, 127.0, 127.9, 128.5, 129.3, 130.8, 135.4, 136.9, 140.0, 153.8, 165.6, 168.5.

MS (EI): *m*/*z* (%) = 510 (16) [M$^+$], 328 (19), 300 (17), 270 (16), 258 (30), 91 (55), 84 (19), 76 (43), 74 (100).

Anal. Calcd for $C_{27}H_{35}N_3O_5Si$: C, 63.63; H, 6.92; N, 8.24. Found: C, 63.26; H, 6.22; N, 7.94.

8c

Yield: 0.7 g (10%); light-brown solid; mp 139 °C; R_f = 0.7 (EtOAc–cyclohexane, 2:3).

IR (KBr): 3430, 2948, 2914, 1479, 1462, 1249, 1157, 1083, 864, 834 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.09 (s, 18 H), 0.92 (t, *J* = 8.3 Hz, 4 H), 2.44 (s, 6 H), 3.63 (t, *J* = 8.3 Hz, 4 H), 5.19 (s, 4 H), 5.79 (s, 4 H), 7.33 (d, *J* = 7.1 Hz, 2 H), 7.39 (s, 2 H), 7.40 (t, *J* = 7.7 Hz, 4 H), 7.52 (d, *J* = 7.6 Hz, 4 H), 7.93 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = –1.4, 17.8, 17.9, 66.3, 70.3, 78.0, 102.6, 110.5, 121.8, 127.4, 127.8, 128,5, 129.7, 136.2, 137.6, 139,2, 153.5.

MS (EI): *m*/*z* (%) = 735 (1) [M$^+$], 469 (70), 467 (66), 427 (33), 425 (33), 411 (20), 409 (19), 369 (63), 367 (61), 353 (36), 352 (69), 350 (59), 310 (25), 308 (27), 304 (27), 294 (26), 292 (23), 256 (31), 245 (17), 142 (8), 74 (100).

Anal. Calcd for $C_{42}H_{54}N_4O_4Si_2$: C, 68.63; H, 7.40; N, 7.62. Found: C, 68.67; H, 7.01; N, 7.23.

(*Z*)-2-Acetylamino-3-{5-bromo-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic Acid Methyl Ester (7d)

Obtained by GP 4, starting from 5-bromo-3-iodo-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (**6d**; 2.7 g, 6 mmol).

Yield: 1.1 g (39%); yellow oil.

^{1}H NMR ($CDCl_3$): δ = –0.07 (s, 9 H), 0.88 (t, *J* = 8.3 Hz, 2 H), 2.21 (s, 3 H), 3.54 (t, *J* = 8.3 Hz, 2 H), 3.89 (s, 3 H), 5.72 (s, 2 H), 6.76 (s, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.55 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 1 H), 7.94 (d, *J* = 1.7 Hz, 1 H), 9.69 (br s, 1 H).

MS (EI): *m*/*z* (%) = 469 ([M + 1], 7), 467 ([M – 1], 7), 389 (14), 352 (5), 350 (5), 142 (15), 85 (67), 83 (100), 74 (32).

HRMS (EI): *m*/*z* [M$^+$] Calcd for $C_{19}H_{26}BrN_3O_4Si$: 467.0876; found 467.0871.

(*Z*)-2-Acetylamino-3-{5-nitro-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic Acid Methyl Ester (7f) and 5,5′-Dinitro-1,1′-bis[2-(trimethylsilanyl)ethoxymethyl]-[3,3′]biindazolyl (8f)

Obtained by GP 4, starting from 3-iodo-5-nitro-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazole (**6f**; 2.5 g, 6.1 mmol).

7f

Yield: 0.6 g (23%); light-brown oil; R_f = 0.4 (EtOAc–cyclohexane, 2:3).

IR (KBr): 3331, 2951, 1738, 1700, 1520, 1330, 1250, 1082, 837 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.13 (s, 9 H), 0.82 (t, *J* = 8.0 Hz, 2 H), 2.15 (s, 3 H), 3.50 (t, *J* = 8.0 Hz, 2 H), 3.83 (s, 3 H), 5.73 (s, 2 H), 6.70 (s, 1 H), 7.60 (d, *J* = 9.3 Hz, 1 H), 8.25 (dd, *J* = 9.8 Hz, *J* = 2.1 Hz, 1 H), 8.65 (d, *J* = 2.1 Hz, 1 H), 9.51 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.6, 17.6, 23.4, 52.7, 67.3, 78.6, 105.8, 110.4, 117.5, 122.6, 123.2, 131.6, 141.6, 143.1, 143.3, 164.9, 168.3.

MS (EI): *m*/*z* (%) = 434 (25) [M^+], 392 (21), 376 (14), 334 (22), 317 (21), 259 (12), 215 (18), 103 (12), 74 (100).

HRMS (EI): *m*/*z* [$M]^+$ Calcd for $C_{19}H_{26}N_4O_6Si$: 434.1621; found 434.1601.

8f

Yield: 0.3 g (8%); yellow solid; mp 170 °C; R_f = 0.6 (EtOAc–cyclohexane, 1:3).

IR (KBr): 3435, 3097, 2953, 1612, 1520, 1343, 1251, 1105, 1076, 859, 836 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.08 (s, 18 H), 0.91 (t, *J* = 8.3 Hz, 4 H), 3.70 (t, *J* = 8.3 Hz, 4 H), 5.88 (s, 4 H), 7.70 (d, *J* = 9.0 Hz, 2 H), 8.37 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 2 H), 9.46 (d, *J* = 2.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = –1.5, 17.8, 67.3, 78.6, 110.4, 120.9, 122.2, 122.6, 140.8, 142.4, 143.7.

MS (EI): *m*/*z* (%) = 584 (10) [M^+], 468 (37), 409 (11), 350 (23), 74 (100).

Anal. Calcd for $C_{26}H_{36}N_6O_6Si_2$: C, 53.40; H, 6.21; N, 14.37. Found: C, 53.32; H, 6.49; N, 14.09.

Hydrogenation of Protected 2-Azatryptophans (9); General Procedure (GP 5)

A mixture of protected dehydro 2-azatryptophan **7** and palladium on activated carbon (15–20 mol%) in MeOH (80–100 mL) was hydrogenated in a Parr apparatus at 1 atm at r.t. for 24 h. The solution was filtered through Celite then concentrated in vacuo to give desired protected amino acids **9**.

2-Acetylamino-3-{1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}propanoic Acid Methyl Ester (9a)

Obtained by GP 5, starting from 2-acetylamino-3-{1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic acid methyl ester (**7a**; 0.5 g, 1.2 mmol).

Yield: 0.4 g (85%); yellow oil.

^1H NMR ($CDCl_3$): δ = –0.05 (s, 9 H), 0.90 (t, *J* = 8.0 Hz, 2 H), 2.01 (s, 3 H), 3.44–3.60 (m, 4 H), 3.67 (s, 3 H), 5.03–5.07 (m, 1 H), 5.69 (s, 2 H), 6.54 (d, *J* = 7.6 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 1 H), 7.54 (d, *J* = 8.1 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.5, 17.8, 23.2, 28.6, 51.5, 52.4, 66.4, 77.5, 110.7, 120.0, 121.2, 124.1, 127.1, 140.5, 141.4, 169.7, 171.7.

MS (EI): *m*/*z* (%) = 391 (42) [M^+], 319 (21), 287 (20), 278 (32), 277 (51), 274 (95), 273 (94), 272 (42), 216 (86), 215 (100), 203 (56), 202 (18), 132 (17), 74 (98).

HRMS (EI): *m*/*z* [$M]^+$ calcd for $C_{19}H_{29}N_3O_4Si$: 391.1928; found 391.1930.

2-Acetylamino-3-{5-methoxy-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}propanoic Acid Methyl Ester (9b)

Obtained by GP 5, starting from 2-acetylamino-3-{5-methoxy-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic acid methyl ester (**7b**; 1.2 g, 2.7 mmol).

Yield: 1.2 g (100%); white solid; mp 92–94 °C.

IR (KBr): 3284, 3076, 2953, 1757, 1652, 1548, 1506, 1315, 1239, 1075, 1035, 859, 833 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.04 (s, 9 H), 0.90 (t, *J* = 8.0 Hz, 2 H), 2.01 (s, 3 H), 3.45–3.59 (m, 4 H), 3.67 (s, 3 H), 3.86 (s, 3 H), 5.01–5.05 (m, 1 H), 5.64 (s, 2 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 7.01 (s, 1 H), 7.09 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.5, 17.7, 23.1, 28.6, 51.5, 52.3, 55.6, 66.2, 77.6, 99.1, 110.7, 119.2, 124.3, 136.3, 140.5, 155.0, 169.7, 171.7.

MS (EI): *m*/*z* (%) = 421 (51) [M^+], 362 (65), 317 (24), 305 (23), 304 (100), 303 (63), 302 (26), 246 (45), 245 (83), 233 (82), 232 (26), 187 (18), 161 (20), 73 (90).

Anal. Calcd for $C_{20}H_{31}N_3O_5Si$: C, 56.98; H, 7.41; N, 9.97. Found: C, 56.65; H, 7.47; N, 9.84.

2-Acetylamino-3-{5-hydroxy-6-methyl-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}propanoic Acid Methyl Ester (9c)

Obtained by GP 5, starting from 2-acetylamino-3-{5-benzyloxy-6-methyl-1-[2-(trimethylsilanyl)ethoxymethyl]-1*H*-indazol-3-yl}acrylic acid methyl ester (**7c**; 1.4 g, 2.7 mmol).

Yield: 1.1 g (92%); brown oil; R_f = 0.5 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3372, 2953, 1743, 1652, 1536, 1435, 1373, 1250, 1080, 838 cm^{-1}.

^1H NMR ($CDCl_3$): δ = –0.07 (s, 9 H), 0.88 (t, *J* = 8.0 Hz, 2 H), 2.00 (s, 3 H), 2.37 (s, 3 H), 3.41–3.52 (m, 4 H), 3.65 (s, 3 H), 4.94–5.01 (m, 1 H), 5.60 (s, 2 H), 6.29 (br s, 1 H), 6.63–6.72 (m, 1 H), 6.99 (s, 1 H), 7.24 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = –1.6, 17.6, 17.9, 22.8, 30.7, 51.8, 52.2, 66.0, 76.8, 101.5, 110.4, 122.8, 127.6, 136.0, 139.7, 150.9, 170.5, 171.6.

MS (EI): *m*/*z* (%) = 421 (10) [M^+], 304 (35), 245 (27), 233 (27), 208 (28), 165 (37), 163 (29), 123 (26), 86 (33), 84 (42), 74 (100).

HRMS (EI): *m*/*z* [$M]^+$ calcd for $C_{20}H_{31}N_3O_5Si$: 421.2033; found 421.2041.

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References

(1) (a) Elderfield, R. C. In *Heterocyclic Compounds*, Vol. 5; Elderfield, R. C., Ed.; John Wiley and Sons, Inc.: New York, **1957**, 162. (b) Behr, L. C.; Fusco, R.; Jacobe, C. H. In *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Wiley, R. H., Ed.; International Wiley Science: New York, **1969**, 289. (c) Elguero, J. In *Comprehensive Heterocyclic Chemistry*, Vol 5; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, **1984**, 167.

(2) Villa, R.; Orlandi, L.; Berruti, A.; Dogliotti, L.; Zaffaroni, N. *Int. J. Oncol.* **1999**, *14*, 133.

(3) Palazzo, G.; Corsi, G.; Baiocchi, L.; Silvestrini, B. *J. Med. Chem.* **1966**, *9*, 38.
(4) Sanger, G. J.; Nelson, D. R. *Eur. J. Pharmacol.* **1989**, *159*, 113.
(5) Wu, C. C.; Ko, F. N.; Kuo, S. C.; Lee, F. Y.; Teng, C. M. *Br. J. Pharmacol.* **1995**, *116*, 1973.
(6) Moore, P. K.; Wallace, P.; Gaffen, Z.; Hart, S. L.; Babbedge, R. C. *Br. J. Pharmacol.* **1993**, *110*, 219.
(7) Foloppe, N.; Fisher, L. M.; Francis, G.; Howes, R.; Kierstan, P.; Potter, A. *Bioorg. Med. Chem.* **2006**, *14*, 1792.
(8) McBride, C. M.; Renhowe, P. A.; Heise, C.; Jansen, J. M.; Lapointe, G.; Ma, S.; Piñeda, R.; Vora, J.; Wiesmann, M.; Shafer, C. M. *Bioorg. Med. Chem Lett.* **2006**, *16*, 3595.
(9) (a) Arnautu, A.; Collot, V.; Calvo Ros, J.; Alayrac, C.; Witulski, B.; Rault, S. *Tetrahedron Lett.* **2002**, *43*, 2695. (b) Collot, V.; Varlet, D.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 4363.
(10) (a) Collot, V.; Dallemagne, P.; Bovy, P. R.; Rault, S. *Tetrahedron* **1999**, *55*, 6917. (b) Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 9053. (c) Witulski, B.; Azcon, J. R.; Alayrac, C.; Arnautu, A.; Collot, V.; Rault, S. *Synthesis* **2005**, 771.
(11) Crestey, F.; Collot, V.; Stiebing, S.; Rault, S. *Tetrahedron* **2006**, *62*, 7772.
(12) (a) Heck, R. F. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M., Ed.; Pergamon: New York, **1991**, Chap. 4.3. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (c) Cutolo, M.; Fiandanese, V.; Naso, F.; Sciacovelli, O. *Tetrahedron. Lett.* **1983**, *24*, 4603. (d) Fournier Dit Chabert, J.; Gozzi, C.; Lemaire, M. *Tetrahedron. Lett.* **2002**, *43*, 1829. (e) Xin, Z.; Oost, T. K.; Abad-Zapatero, C.; Hajduk, P. J.; Pei, Z.; Szczepankiewicz, B. G.; Hutchins, C. W.; Ballaron, S. J.; Stashko, M. A.; Lubben, T.; Trevillyan, J. M.; Jirousek, M. R.; Liu, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1887. (f) Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 1374.
(13) (a) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (b) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335. (c) Gallou-Dagommer, I.; Gastaud, P.; RajanBabu, T. V. *Org. Lett.* **2001**, *3*, 2053. (d) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584. (e) Carlström, A.-S.; Frejd, T. *Synthesis* **1989**, 414. (f) Basu, B.; Chattopadhyay, S. K.; Ritzen, A.; Frejd, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1841. (g) Ritzen, A.; Basu, B.; Chattopadhyay, S. K.; Dossa, F.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 503. (h) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (i) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(14) (a) Kania, R. S.; Bender, S. L.; Borchardt, A. J.; Braganza, J. F.; Cripps, S. J.; Hua, Y.; Johnson, M. D.; Johnson, T. O. Jr.; Luu, H. T.; Palmer, C. L.; Reich, S. H.; Tempczyk-Russell, A. M.; Teng, M.; Thomas, C.; Varney, M. D.; Wallace, M. B. WO 0102369 A2, **2001**; *Chem. Abstr.* **2001**, *134*, 100864. (b) Reich, S. H.; Bleckman, T. M.; Kephart, S. E.; Romines, W. H. III; Wallace, M. B. WO 0153268 A2, **2001**; *Chem. Abstr.* **2001**, *135*, 137505.
(15) (a) Schumann, P.; Collot, V.; Hommet, Y.; Gsell, W.; Dauphin, F.; Sopkova, J.; McKenzie, E. T.; Duval, D.; Boulouard, M.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1153. (b) Bartsch, R. A.; Yang, I.-W. *J. Heterocycl. Chem.* **1984**, *21*, 1063.
(16) Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392.
(17) (a) Shimohigashi, Y.; Nitz, T. J.; Stammer, C. H.; Unubushi, T. *Tetrahedron Lett.* **1982**, *23*, 3235. (b) Crombie, A. L.; Kane, J. L. Jr.; Shea, K. M.; Danheiser, R. L. *J. Org. Chem.* **2004**, *69*, 8652.
(18) (a) Rousseau, J.-F.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 2731. (b) Beecher, J. E.; Tirrell, D. A. *Tetrahedron Lett.* **1998**, *39*, 3927.
(19) Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433.