Vinyl Sulfones in Solid-Phase Synthesis: Preparation of 4,5,6,7-Tetrahydroisoindole Derivatives

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The preparation of functionalized 4,5,6,7-tetrahydroisoindole via a traceless solid-phase sulfone linker strategy is described. Thermolytic extrusion of SO_2 from polymer-bound 3-(phenylsulfonyl)-3-sulfolene (**7**) generated polymer-bound 2-(phenylsulfonyl)-1,3-butadiene (**9**) in situ which underwent Diels−Alder cycloaddition with various dienophiles to furnish vinyl sulfone resins **10**−**14**. To complete a traceless linker cleavage strategy, (*p*-tolysulfonyl)methyl isocyanide or ethyl isocyanoacetate was employed to react with the vinyl sulfone moiety to liberate functionalized 4,5,6,7-tetrahydroisoindole products from the resin. Using this chemistry, nine tetrahydroisoindole derivatives (**6**, **15**−**22**) were prepared in 32−41% overall yields from polystyrene/divinylbenzene sulfinate **1**.

Introduction

Fueled by a rapidly growing interest in combinatorial chemistry, solid-phase organic synthesis (SPOS) is under intensive application and research.[1] SPOS enjoys several advantages over solution-phase synthesis: for example, reactions can be driven to completion by the use of excess reagent and product isolation by simple filtration is operationally simple and time efficient. In addition, solid-supported reactions are readily automated. These advantages offer the opportunity for rapid library synthesis of heterocyclic compounds for pharmaceutical and agrochemical discovery.[2] In previous studies from our laboratories, a sulfinate-functionalized resin (styrene/2% divinylbenzene copolymer beads; PS/DVB = ●) has been efficiently prepared and utilized in SPOS. The resulting sulfone linker was shown to be a robust and versatile traceless tether.[3] In extending this work, one of our research objectives was to explore the 2-(phenylsulfonyl)-1,3-butadiene moiety as a scaffold for C,C-bond and C,X-bond formations in the synthesis of heterocyclic compounds via SPOS. Because of the high reactivity of 2-(phenylsulfonyl)-1,3-dienes, chemical transformations employing it are potentially versatile and synthetically attractive. For example, 2-(phenylsulfonyl)-1,3-diene can participate in Diels−Alder cycloadditions,[4,5] Michael additions,[4] selective epoxidations,[6] and other chemical transformations.[7]

Here we report a solid-phase route where polymer-bound 3-(phenylsulfonyl)-3-sulfolene (**7**) is the precursor to polymer-bound 2-(phenylsulfonyl)-1,3-butadiene (**9**)—a transformation which proceeds via thermolytic sulfur dioxide extrusion. Subsequent Diels−Alder cycloaddition with various dienophiles delivers polymer-bound vinyl sulfones. A traceless linker cleavage strategy ensues upon treatment with (*p*-tolysulfonyl)methyl isocyanide (TosMIC) or ethyl isocyanoacetate to generate a pyrrole ring with simultaneous linker cleavage to liberate the desired 4,5,6,7-tetrahydroisoindole derivatives[8] from the resin.

This preparation of 4,5,6,7-tetrahydroisoindole derivatives (**2**) from sulfinate-functionalized resin (**1**; Scheme 1) proceeds via a three-step protocol consisting of (i) sulfinate *S*-alkylation (see Scheme 3), (ii) concomitant thermolytic sulfur dioxide extrusion and Diels−Alder cycloaddition (see Scheme 4), and (iii) pyrrole ring formation with release of the substrate from the solid support (see Scheme 5). The overall protocol appears suitable for library generation.

Results and Discussion

Solution-Phase Synthesis of 4,5,6,7-Tetrahydroisoindole 6. The preparation of 2-(phenylsulfonyl)-1,3-butadiene has been reported in solution phase.[9,10] Among various routes to 2-(phenylsulfonyl)-1,3-butadiene, employing 3-(phenylsulfonyl)-3-sulfolene[11] as the

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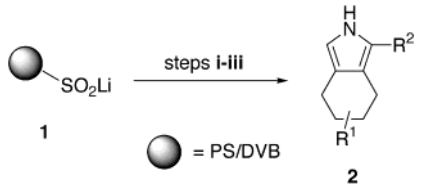
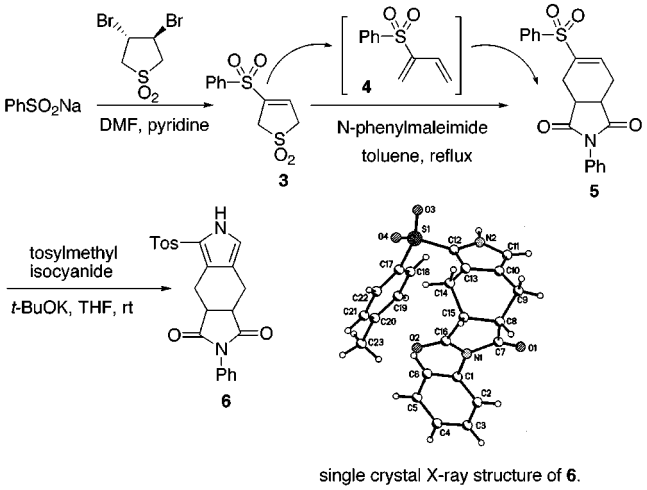
Scheme 1. Sulfone-Based SPOS Linker



Scheme 2. Solution-Phase Thermolytic SO_2 Extrusion, Diels–Alder Cycloaddition, and Pyrrole Ring Formation



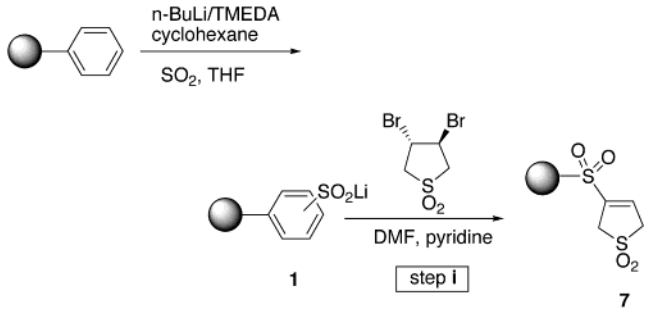
single crystal X-ray structure of **6**.

precursor appeared most suitable for our solid-phase requirements.[10,12] However, since no solid-phase route to sulfone-substituted dienes has been reported in the literature, preliminary solution-phase experiments were undertaken to survey reaction conditions and establish the modifications required for SPOS. For example, resin swelling properties led us to employ DMF as the solvent of choice (instead of MeOH)[12] for the *S*-alkylation of sodium phenylsulfinate with *trans*-3,4-dibromosulfolane. In the presence of pyridine, this solution-phase protocol furnishes 3-(phenylsulfonyl)-3-sulfolene (**3**) in 76% yield (see Scheme 2).

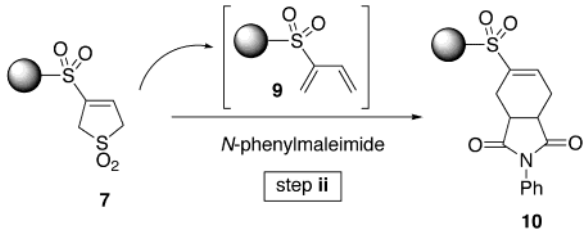
When 3-(phenylsulfonyl)-3-sulfolene is heated above 110 °C, SO_2 extrusion liberates 2-(phenylsulfonyl)-1,3-butadiene (**4**) which is susceptible to dimerization, even at room temperature, in the absence of trapping dienophiles.[4,13] To circumvent this dimerization problem, the SO_2 extrusion reaction was conducted in the presence of excess dienophile (e.g., *N*-phenylmaleimide) to generate cycloadduct **5**.[10,12] Subsequent treatment of **5** with TosMIC[14] and *t*-BuOK results in Michael addition followed by cyclization, elimination of the phenylsulfinate group, and tautomerization in one pot to deliver terahydroisoindole derivative **6** in 75% yield. The successful realization of these transformations in solution phase positioned us to explore the solid-phase variants.

Solid-Phase Synthesis of 4,5,6,7-Tetrahydroisoindole Derivatives. Following our published protocol[3] and

Scheme 3. Preparation of Solid-Phase Sulfolene Phenyl Sulfone



Scheme 4. Solid-Phase Thermolytic SO_2 Extrusion and Diels–Alder Cycloaddition



others,[15] polymer-bound lithiophenylsulfinate (**1**) was prepared with a loading of 0.8 mmol/g as determined by titration.[3] Sulfinate *S*-alkylation of this functionalized resin was accomplished by treating a DMF-swollen suspension of resin **1** with *trans*-3,4-dibromosulfolane in the presence of pyridine (80 °C, 48 h) which delivered resin-bound 3-(phenylsulfonyl)-3-sulfolene (**7**; Scheme 3). This transformation could be monitored by FTIR [polymer-bound lithiophenylsulfinate **1** (1200, 1028, 980 cm^{-1}) → polymer-bound 3-(phenylsulfonyl)-3-sulfolene **7** (1322 (s), 1133 (s), 1029, 757 cm^{-1})].

Heating polymer-bound 3-(phenysulfonyl)-3-sulfolene (**7**) in toluene (reflux, 16 h) containing excess *N*-phenylmaleimide effected SO_2 extrusion with in situ generation of polymer-bound 2-(phenylsulfonyl)-1,3-butadiene (**9**). Concomitant cycloaddition with *N*-phenylmaleimide (20 equiv) furnished polymer-bound cycloadduct (**10**; see Scheme 4). Formation of **10** from **7** could be monitored by FTIR on the basis of the appearance of an amide absorption peak at 1710 cm^{-1}.[16,17] Subsequent treatment of resin **10** with TosMIC in the presence of *t*-BuOK successfully cleaved the desired 4,5,6,7-tetrahydroisoindole **6** from the resin (Scheme 5; 28% overall yield of **6** for the three steps from starting resin **1**). Unfortunately, similar conditions employing dienophiles such as diethyl fumarate or diisopropyl fumarate resulted in the generation of only medium carbonyl absorption peaks in the 1730 cm^{-1} region. Cleavage with TosMIC delivered **16** and **18** but with overall yields from starting resin **1** in the 12–15% range. These unsatisfactory results led us

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(16) The IR absorption peak intensity at 1710 cm^{-1} (C=O in product **10**) is weaker when a two-step procedure (i.e., **7** → **9** and **9** → **10**) is employed instead of a one-step procedure (i.e., **7** → [**9**] → **10**). This is presumably due to significant dimerization of **9** (i.e., site–site interaction at this high temperature and loading) when formed in the absence of a dienophile (see ref 17).

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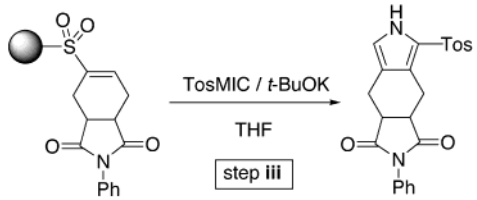
Scheme 5. Solid-Phase 4,5,6,7-Tetrahydroisoindole Formation



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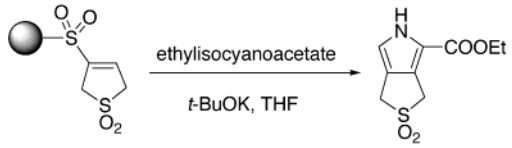
Scheme 6. Solid-Phase Pyrrole-Fused 3-Sulfolene Formation



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to further scrutinize the reaction conditions of each solid-phase transformation.

We first set out to validate the *S*-alkylation of resin **1** to **7**. Our strategy was to liberate pyrrole-fused 3-sulfolene **8** by treating resin **7** with ethyl isocyanoacetate in the presence of *t*-BuOK (Scheme 6). The solid-phase yield of 35% overall for **1** → **8** compared well with the solution-phase yield (38% overall from sodium pheylsulfinate to **8**) and indirectly indicated that solid-phase sulfinate *S*-alkylation (**1** → **7**) is not problematic.[18]

To investigate the concomitant SO_2 extrusion and Diels−Alder cycloaddition on solid phase, diethyl fumarate was selected as the dienophile in reactions employing two different slovents (toluene and xylene). The progress of each reaction was monitored by comparing the relative intensities of IR absorption peaks at 1733 cm^{-1} (C═O) against a polystyrene absorption peak at 1600 cm^{-1} (Figure 1).[19] Whereas the transformation was sluggish in toluene, the reaction was judged as complete (constant C═O intensity) in xylene at 145 °C after 36 h. This information led us to select xylene/145 °C as the conditions of choice for the solid-phase SO_2 extrusion/Diels−Alder cycloaddition step.

We next employed various dienophiles in the reaction with polymer-bound 3-(phenysulfonyl)-3-sulfolene **7** (see Scheme 7). With *N*-phenylmaleimide, diethyl fumarate, and diisopropyl fumarate, cycloadduct carbonyl absorption peaks for the amide or ester functional groups [**10** (1710 cm^{-1}), **11** (1733 cm^{-1}), and **12** (1734 cm^{-1})] were observed by FTIR. In contrast, cycloadducts **13** and **14**, derived by reaction of resin **7** with cyclopentadiene and cyclohexandiene, respectively,[20] exhibited no reliably diagnostic absorption peaks in the IR spectra.

Treating resin **13** with ethyl isocyanoacetate/*t*-BuOk liberated target molecule **21** (Figure 2) in 40% overall yield. Substrate **21** incorporates a C5,C6-double bond which, because of regioselectivity in the Diels−Alder reaction and subsequent pyrrole-forming process, is situated as depicted relative to the carboalkoxy group at

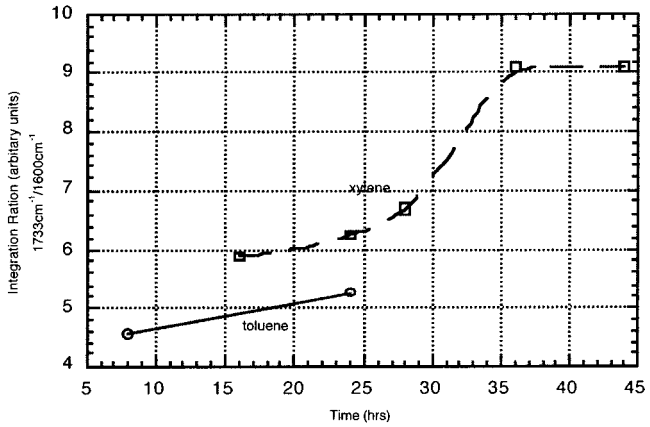

Figure 1. Progress of transformation (**7** to **11**) by FTIR analysis. The developing absorbance at 1733 cm^{-1} (C═O) was compared against a static peak at 1600 cm^{-1}.

C2 of the pyrrole. Formation of this one regioisomer of **21** demonstrates indirectly that **7** → **13** proceeds with excellent regioselectivity. Finally, as can be seen in Scheme 7, tetrahydroisoindoles **6** and **15**−**22** were obtained from resins **10**−**14** and the overall yields from starting resin **1** were in the 32−41% range.

Summary

This work demonstrates that the sulfone moiety is a durable and robust linker which, via a vinyl sulfone intermediate, engages a specific cleavage protocol that generates a heterocyclic pyrrole ring with simultaneous cleavage of the sulfone linker. Thus, the sulfone moiety provides a versatile and useful traceless linker. In addition, we have also developed a solid-phase synthetic route to functionalized 4,5,6,7-tetrahydroisoindole derivatives where the key solid-phase chemical transformation incorporates concomitant thermolytic SO2 extrusion and in situ Diels−Alder cycloaddition. The solid-phase preparation of nine functionalized 4,5,6,7-tetrahydroisoindole derivatives has been accomplished.

Experimental Section

General Procedures. All chemicals were obtained from commercial suppliers and used without purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70−230 mesh). NMR spectra (^1H at 300 MHz, ^{13}C at 75 MHz) were recorded in $CDCl_3$ as solvent, and chemical shifts are expressed in parts per million related to internal TMS. CC refers to column chromatography. Concentration refers rotoevaporation.

3-(Phenylsulfonyl)-3-sulfolene (3). A solution of sodium phenylsulfinate (2.3 g, 14 mmol), pyridine (1.2 mL, 14 mmol), and *trans*-3,4-dibromosulfonlane (2 g, 7.2 mmol) in DMF (20 mL) was stirred at 80 °C for 36 h at which time the reaction was cooled to room temperature and quenched with water. The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were washed again with water. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by CC (33% EtOAc in hexanes) to give **3** (1.4 g, 76%) as a white solid. The spectral data are identical with those reported in the literature.[11]

5-Benzenesulfonyl-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (5). 3-(Phenylsulfony)-3-sulfolene (**3**; 0.5 g, 1.93 mmol) was refluxed in toluene (10 mL) containing pyridine (1.2 equiv, 2.32 mmol, 0.18 mg), hydroquinone (ca. 8 mg), and *N*-phenylmaleimide (10 equiv, 3.3 g, 19.3 mmol). The reaction

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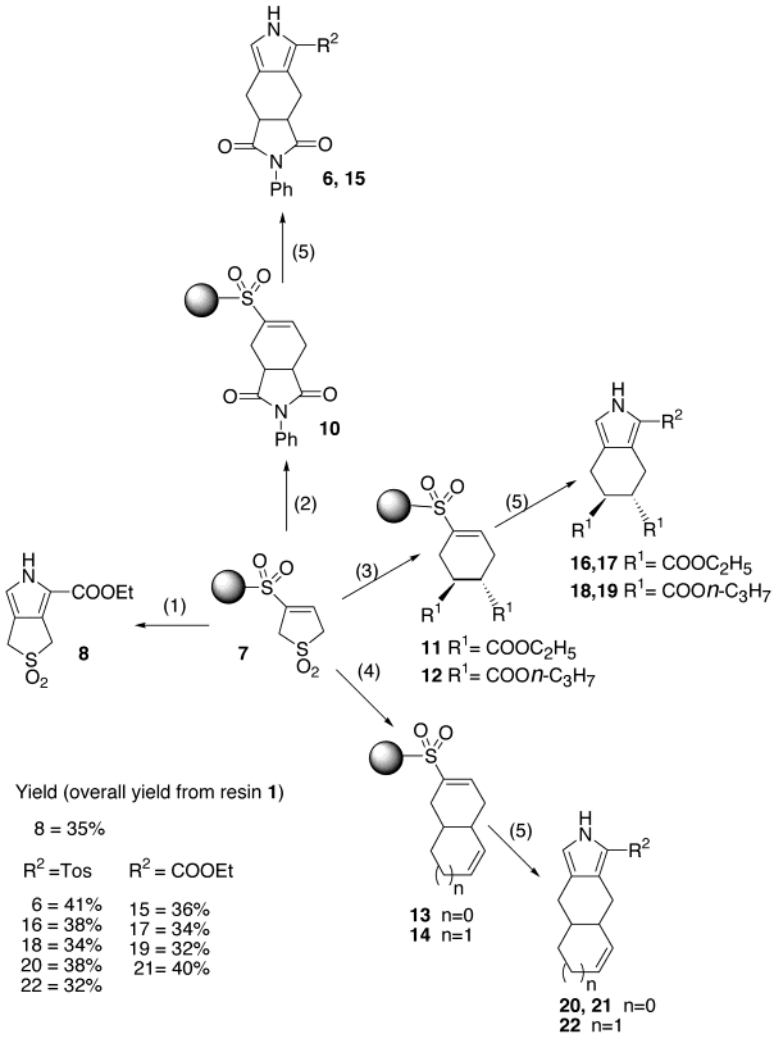
Scheme 7. Solid-Phase Synthesis of Functionalized 4,5,6,7-Tetrahydroisoindoles[a]



[a] Reagents and conditions: (1) ethylisocyanoacetate, *t*-BuOK, THF, rt, 24 h; (2) *N*-phenylmaleimide, xylene, 145 °C, 36 h; (3) ethyl fumarate or *n*-propyl fumarate, xylene, 145 °C, 36 h; (4) cyclopentadiene or cyclohexadiene, xylene, 145 °C, 36 h; (5) TosMIC or ethyl isocyanoacetate, *t*-BuOK, THF, rt, 24 h.

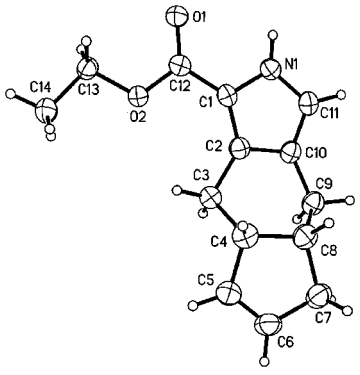


Figure 2. Single-crystal X-ray structure of **21**.

was refluxed for 16 h and monitored by TLC. After removing the solvent, the mixture residue was purified by CC (50% EtOAc in hexanes) to give **5** (0.45 g, 65%) as white solid. The spectral data are identical with those reported in the literature.[10]

7,7-Dioxo-6-phenyl-2,4,4a,5,6,7,7a,8-octahydropyrrolo-[3,4-*f*]isoindole-1-sulfinic Acid *p*-Tolyl Ester (6). In solution phase, cycloaddition product **5** (0.2 g, 0.54 mmol) was reacted with TosMIC (3 equiv, 0.32 g, 1.6 mmol) and *t*-BuOK (3.5 equiv, 0.2 g, 1.8 mmol) in THF (5 mL) at room temperature. The reaction was stirred for 16 h, monitored by TLC, quenched by water, extracted with EtOAc, dried ($MgSO_4$), and concentrated. The residue was purified by CC (33% EtOAc in hexanes) to give **6** (0.17 g 75%) as pale yellow solid: IR (neat) 1704 (s), 1596, 1498, 1386, 1317, 1214, 1139 cm^{-1}; ^1H NMR δ 2.31 (s, 3H), 2.72 (dd, 1H, J = 15, 5.7 Hz), 2.93 (dd, 1H, J = 15.6, 6.6 Hz), 3.23 (d, 1H, J = 15 Hz), 3.41 (m, 2H), 3.74 (d, 1H, J = 15.6 Hz), 6.63 (d, 1H, J = 6.3 Hz), 6.74 (s, 1H), 7.15 (d, 2H, J = 8.1 Hz), 7.21−7.31 (m, 3H), 7.76 (d, 2H, J = 8.1 Hz), 9.02 (s, 1H); ^{13}C NMR δ 178.2, 177.8, 143.6, 139.2, 131.5, 129.7, 128.6, 128.2, 126.6, 126.0, 123.8, 123.0, 120.1, 118.6, 40.2, 39.6, 21.9, 21.8, 21.6. Anal. Calcd for $C_{23}H_{20}N_2O_4S\cdot 0.3H_2O$: C, 64.86; H, 4.87; N, 6.57. Found: C, 65.08; H, 5.09; N, 6.41.

In solid phase, a THF (15 mL) suspension of resin **10** (1 g, 0.68 mmol) containing TosMIC (3 equiv, 0.40 g, 2.0 mmol) and *t*-BuOK (3.5 equiv, 0.27 g, 2.4 mmol) was stirred at room temperature for 24 h and quenched with water. The resin was removed by filtration and washed with THF (2 × 20 mL), THF/H_2O (1:1, 20 mL), THF (20 mL), and ether (30 mL). The combined filtrate and washings were concentrated to remove organic solvent, and the residue was extracted with EtOAc, dried (MgSO4), and concentrated. The mixture was purified by CC (33% EtOAc in hexanes) to give target molecule **6** (120 mg, 41% overall yield from starting resin) as a pale yellow solid.

3-(PS/DVBsulfonyl)-3-sulfonene (7). A suspension of resin **1** (10 g, 8 mmol), *trans*-3, 4-dibromosulfonlane (11 g, 40 mmol), and pyridine (3.2 mL, 40 mmol) was stirred at 80 °C for 48 h at which time the reaction was cooled to room temperature, quenched with water, and filtered. The resin was washed with THF (2 × 50 mL), MeOH (40 mL), CH_2Cl_2 (2 × 50 mL), and ether (40 mL) to give the pale yellow resin **7**: IR (single bead reflectance) 1598 1492, 1450, 1322 (s), 1133 (s), 1029, 757 cm^{-1}.

Pyrrole-Fused 3-Sulfolene (8).[18] In solution phase, a THF (8 mL) solution of 3-(phenylsulfonyl)-3-sulfolene (0.2 g, 0.77 mmol), ethyl isocyanoacetate (3 equiv, 2.3 mmol, 0.26 g), and *t*-BuOK (3 equiv, 0.3 g) was stirred at room temperature for 16 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by CC (33% EtOAc in hexances) to give **8** (88 mg, 50%) as a white solid: ^{1}H NMR δ 1.35 (t, 3H, J = 6.9 Hz), 4.19 (s, 2H), 4.29−4.35 (m, 4H), 6.90 (s, 1H), 9.47 (br s, 1H); ^{13}C NMR δ 159.9, 120.6, 118.1, 117.6, 115.7, 60.9, 54.1, 53.1, 14.5.

On solid phase, a THF (8 mL) suspension of 3-(PS/DVBsulfonyl)-3-sulfonene (**7**; 0.4 g, 0.30 mmol) containing ethyl isocyanoacetate (3 equiv, 0.9 mmol, 0.10 g) and *t*-BuOK (3 equiv, 0.11 g) was stirred at room temperature for 24 h, at which time the resin was removed by filtration and washed with THF (2 × 15 mL), THF/H_2O (10 mL) 1:1, THF (10 mL), and ether (20 mL). The combined filtrate and washings were concentrated to remove organic solvent, and the residue was extracted with EtOAc, dried ($MgSO_4$), and concentrated. The mixture was purified by CC (33% EtOAc in hexanes) to give target molecule **8** (24 mg, 35% overall yield from starting resin **1**) as a white solid.

5-(PS/DVBsulfonyl)-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (10). A xylene (12 mL) suspension of resin **7** (1.0 g, 0.74 mmol) containing *N*-phenylmaleimide (20 equiv, 2.56 g, 14.8 mmol), pyridine (5 equiv, 3.7 mmol, 0.3 mL), and hydroquinone (ca. 16 mg, 20% mol) was heated to reflux for 36 h. After the reaction was cooled to room temperature, resin **10** was isolated by filtration and washed with THF/H_2O (1:1, 30 mL), THF (30 mL), MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and ether (20 mL each): IR (single bead reflectance) 1710, 1596, 1492, 1452, 1378, 1305, 1178, 1143, 1027 cm^{-1}.

4-(PS/DVBsulfonyl)cyclohex-4-ene-1,2-dicarboxylic Acid, Diethyl Ester (11). The preparation of polymer **10** was modified as follows to give polymer **11**. Polymer **7** (1.0 g, 0.74 mmol), dipropyl fumarate (20 equiv, 2.96 g 14.8 mmol), pyridine (5 equiv, 3.7 mmol, 0.3 mL), hydroquinone (ca. 16 mg, 20% mol), and xylene (10 mL) were refluxed for 36 h to give polymer **11** which was washed with THF/H_2O (1:1, 30 mL), THF (30 mL), MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and ether (20 mL each): IR (single bead reflectance) 1731, 1596, 1492, 1450, 1299, 1180, 1145, 1029 cm^{-1}.

4-(PS/DVBsulfonyl)cyclohex-4-ene-1,2-dicarboxylic Acid, Dipropyl Ester (12). The preparation of polymer **10** was modified as follows to give polymer **12**. Polymer **7** (1.0 g, 0.74 mmol), diethyl fumarate (20 equiv, 2.54 g 14.8 mmol), pyridine (5 equiv, 3.7 mmol, 0.3 mL), hydroquinone (ca. 16 mg, 20% mol), and xylene (10 mL) were refluxed for 36 h to give polymer **12** which was washed with THF/H_2O (1:1, 30 mL), THF (30 mL), MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and ether (20 mL each): IR (KBr) 1734(s), 1599, 1492, 1459,1303, 1148, 1144(s) cm^{-1}.

6-(PS/DVBsulfonyl)-3a,4,7,7a-tetrahydro-1*H*-indene (13). The preparation of polymer **10** was modified as follows to give polymer **13**. Polymer **7** (1.0 g, 0.74 mmol), fresh cyclopentadiene (20 equiv, 2.54 g 14.8 mmol), xylene (10 mL), pyridine (5 equiv, 3.7 mmol, 0.3 mL), hydroquinone (ca. 16 mg, 20% mol), and xylene (10 mL) were refluxed for 36 h to give polymer **13** which was washed with THF/H_2O (1:1, 30 mL), MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and ether (20 mL each): IR (single bead reflectance) 1596, 1492, 1450, 1300, 1145, 1029 cm^{-1}.

7-(PS/DVBsulfonyl)-1,2,4a,5,8,8a-hexahydronaphthalene (14). The preparation of polymer **10** was modified as follows to give polymer **14**. Polymer **7** (1.0 g, 0.74 mmol), 1,3-cyclohexadiene (20 equiv, 1.18 g, 14.8 mmol), pyridine (5 equiv, 3.7 mmol, 0.3 mL), hydroquinone (ca. 16 mg, 20% mol), and xylene (12 mL) were refluxed for 36 h to give polymer **14** which was washed with THF/H_2O (1:1, 30 mL), MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and ether (20 mL each): IR (single bead reflectance) 1600, 1492, 1450, 1301, 1144, 1027 cm^{-1}.

5,7-Dioxo-6-phenyl-2,4,4a,5,6,7,7a,8-octahydropyrrolo-[3,4-*f*]isoindole-1-carboxylic Acid, Ethyl Ester (15).[18] A suspension of resin **10** (1.0 g, 0.68 mmol) in THF (15 mL) containing ethyl isocyanoacetate (3 equiv, 0.23 g, 2.0 mmol) and *t*-BuOK (3.5 equiv, 0.27 g, 2.4 mmol) was stirred at room temperature for 24 h and quenched with water. The resin was removed by filtration and washed with THF (2 × 30 mL), THF/H_2O (1:1, 20 mL), THF (30 mL), and ether (30 mL). The combined filtrate and washings were concentrated to remove organic solvent, and the residue was extracted with EtOAc, dried (MgSO4), and concentrated. The mixture was purified by CC (25% EtOAc in hexanes) to give target molecule **15** (83 mg, 36% overall yield from starting resin **1**) as a pale yellow solid: IR ($CDCl_3$) 3324, 1702, 1384, 1321, 1276, 1189, 1141, 1097, 1025 cm^{-1}; ^{1}H NMR δ 1.38 (t, 3H, J = 7 Hz), 2.81 (dd, 1H, J = 14.7, 6 Hz), 2.94 (dd, 1H, J = 15.3, 6.6 Hz), 3.32 (dd, 1H, J = 14.7, 2.1 Hz), 3.44 (m, 2H), 3.81 (dd, 1H, J = 15.3, 2.1 Hz), 4.31 (q, 2H, J = 7 Hz), 6.74 (s, 1H), 7.02 (d, 2H, J = 6.9 Hz), 7.37 (m, 3H), 8.87 (s, 1H); ^{13}C NMR δ 178.8, 178.5, 161.2, 131.7, 128.9, 128.4, 126.2, 124.2, 119.3, 118.3, 118.0, 60.3, 40.5, 40.1, 22.3, 22.1, 14.5.

1-(Toluene-4-sulfonyl)-4,5,6,7-tetrahydro-2*H*-isoindole-5,6-dicarboxylic Acid, Diethyl Ester (16). The preparation of **15** was modified as follows to give **16**. Polymer **11** (0.7 g, 0.46 mmol), TosMIC (3 equiv, 0.27 g, 1.4 mmol), *t*-BuOK (3.5 equiv, 0.18 g, 1.6 mmol), THF (12 mL), and CC (20% EtOAc in hexanes) gave **16** (78 mg, 38% overall yield from starting resin 1) as a pale yellow oil: IR ($CDCl_3$) 1727, 1301, 1182 cm^{-1}; ^{1}H NMR δ 1.24 (m, 6H, J = 7 Hz), 1.39 (s, 3H), 2.59−2.72 (m, 2H), 2.88−2.96 (m, 3H), 3.29 (dd, 1H, J = 4, 16 Hz), 3.15 (m, 4H, J = 7 Hz), 6.69 (s, 1H), 7.27 (d, 2H, J = 8 Hz), 7.74 (d, 2H, J = 8 Hz), 9.39(s, 1H); ^{13}C NMR δ 174.2, 174.1, 143.7, 139.2, 128.7, 126.3, 123.1, 121.8, 119.6, 119.0, 60.8, 60.7, 42.4, 42.2, 24.6, 24.5, 21.6, 14.2. Anal. Calcd for $C_{21}H_{25}NO_6S\cdot 0.8H_2O$: C, 58.13; H, 6.18; N, 3.22. Found: C, 58.11; H, 6.43; N, 3.05.

4,5,6,7-Tetrahydro-2*H*-isoindole-1,5,6-tricarboxylic Acid, Triethyl Ester (17).[21] The preparation of **15** was modified as follows to give **17**. Polymer **11** (0.8 g, 0.53 mmol), ethyl isocyanoacetate (3 equiv, 0.18 g, 1.6 mmol), *t*-BuOK (3.5 equiv, 0.21 g, 1.8 mmol), THF (15 mL), and CC (20% EtOAc in hexanes) gave **17** (65 mg, 34% overall yield from starting resin **1**) as a pale yellow oil: ^{1}H NMR δ 1.23−1.35 (m, 9H), 2.63−2.84 (m, 2H), 2.94−3.03 (m, 3H), 3.38 (dd, 1H, J = 4, 16 Hz), 4.10−4.30 (m, 6H), 6.65 (d, 1H, J = 3 Hz), 9.06 (s, 1H); ^{13}C NMR δ 174.6, 174.5, 161.0, 124.5, 118.9, 118.2, 117.5, 60.4, 59.9, 59.8, 42.5, 25.8, 24.6, 14.3, 13.9.

1-(Toluene-4-sulfonyl)-4,5,6,7-tetrahydro-2*H*-isoindole-5,6-dicarboxylic Acid, Dipropyl Ester (18). The preparation of **15** was modified as follows to give **18**. Polymer **12** (0.8 g, 0.54 mmol), TosMIC (3 equiv, 0.31 g, 1.6 mmol), *t*-BuOK (3.5 equiv, 0.21 g, 1.9 mmol), THF (12 mL), and CC (20% EtOAc in hexanes) gave **18** (77 mg, 34% overall yield from starting resin **1**) as a pale yellow oil: IR ($CDCl_3$) 1727, 1299, 1180, 1137 cm^{-1}; ^{1}H NMR δ 0.92 (m, 6H), 1.58 (m, 4H), 2.32 (s, 3H), 2.61 (m, 2H), 2.90 (m, 3H), 3.22 (m, 1H), 4.02 (m, 4H), 6.68 (d, 1H, J = 3 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz), 9.46 (s, 1H); ^{13}C NMR δ 174.2, 174.1, 143.6, 139.2, 129.7, 126.3, 123.1, 121.8, 119.6, 119.0, 66.4, 66.3, 42.4, 42.2, 24.7, 24.5, 21.9, 21.6, 10.4.

4,5,6,7-Tetrahydro-2*H*-isoindole-1,5,6-tricarboxylic Acid, 1-Ethyl Ester, 5,6-Dipropyl Ester (19). The preparation of **15** was modified as follows to give **19**. Polymer **12** (0.8 g, 0.54 mmol), ethyl isocyanoacetate (3 equiv, 0.18 g, 1.6 mmol), *t*-BuOK (3.5 equiv, 0.21 g, 1.9 mmol), THF (15 mL), and CC (20% EtOAc in hexanes) gave **19** (58 mg, 32% overall yield from starting resin **1**) as a pale yellow oil: IR ($CDCl_3$) 1731-(s), 1600, 1452, 1022; ^{1}H NMR δ 0.90−0.96 (m, 6H), 1.32 (t, 3H, J = 7.2 Hz), 1.58−69 (m, 4H), 2.63−2.83 (m, 2H), 2.93−3.03 (m, 3H), 3.38 (dd, 1H, J = 16.5, 4.2 Hz), 3.99−4.12 (m, 4H), 4.28 (q, 2H, J = 7.2 Hz), 6.66 (d, 1H, J = 2.7 Hz), 9.08 (s,

1H); ^{13}C NMR δ 174.6, 174.5, 161.1, 124.5, 118.9, 118.4, 117.5, 66.283, 66.282, 60.0, 42.7, 26.1, 24.9, 21.9, 14.5, 10.4. Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.16; H, 7.57; N, 3.88.

1-(Toluene-4-sulfonyl)-2,4,4a,5,7a,8-hexahydro-2-aza-*s*-indacene (20). The preparation of **15** was modified as follows to give **20**. Polymer **13** (1.5 g, 1.1 mmol), TosMIC (3 equiv, 0.64 g, 3.3 mmol), *t*-BuOK (3.5 equiv, 0.43 g, 3.8 mmol), THF (20 mL), and CC (20% EtOAc in hexanes) gave **20** (130 mg, 38% overall yield from starting resin) as a pale yellow oil: IR ($CDCl_3$) 1607, 1302, 1137, 1090; ^{1}H NMR δ 1.88−1.96 (d, 1H, J = 15 Hz), 2.23−2.30 (m, 1H), 1.38 (s, 3 H), 2.52−2.66 (m, 4H), 2.90−2.98 (dd, 1H, J = 7.5, 15 Hz), 3.04 (s, 1H), 5.41−5.54 (m, 2H), 6.65 (d, 1H, J = 3 Hz), 7.23−7.77(m, 4H), 8.82 (s, 1H); ^{13}C NMR δ 143.2, 140.1, 134.2, 129.7, 129.5, 128.1, 126.3, 123.9, 121.9, 118.1, 44.4, 39.9, 35.4, 26.4, 24.4, 21.6

2,4,4a,5,7a,8-Hexahydro-2-aza-*s*-indacene-1-carboxylic Acid, Ethyl Ester (21). The preparation of **15** was modified as follows to give **21**. Polymer **13** (1.0 g, 0.73 mmol), ethyl isocyanoacetate (3 equiv, 0.24 g, 2.2 mmol), *t*-BuOK (3.5 equiv, 0.28 g, 2.5 mmol), THF (15 mL), and CC (20% EtOAc in hexanes) gave **21** (70 mg, 40% overall yield from statring resin **1**) as a pale yellow solid: IR ($CDCl_3$) 3320, 2923, 1675(s), 1452, 1417, 1299, 1143, 908; ^{1}H NMR (300 MHz) δ 1.41 (t, 3H, J = 6.9 Hz), 2.01 (d, 1H, J = 14.1 Hz), 2.31 (q, 1H, J = 8.5 Hz), 2.71−2.53 (m, 4H), 3.08 (d, 1H, J = 10.5 Hz), 4.35 (q, 2H, J = 6.9 Hz), 5.59−5.61 (m, 2H), 6.69 (s, 1H), 8.52 (s, 1H); ^{13}C NMR δ 161.8, 135.1, 129.8, 129.5, 123.6, 117.8, 60.0, 44.9, 40.2, 36.2, 26.7, 25.7, 14.9. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.56; N, 5.91.

1-(Toluene-4-sulfonyl)-4,4a,5,6,8a,9-hexahydro-2*H*-benzo[*f*]isoindole (22). The preparation of **15** was modified as follows to give **22**. Polymer **14** (1.0 g, 0.72 mmol), TosMIC (3 equiv, 0.42 g, 2.2 mmol), *t*-BuOK (3.5 equiv, 0.28 g, 2.5 mmol), THF (15 mL), and CC (20% EtOAc in hexanes) gave **22** (74 mg, 32% overall yield from starting resin **1**) as a pale yellow oil: IR ($CDCl_3$) 1301, 1138, 911; ^{1}H NMR δ 1.54−1.60 (m, 2H), 2.09 (m, 3H), 2.38 (s, 3H), 2.40−2.66 (m, 4H), 2.94 (dd, 1H, J = 16.8, 6.0 Hz), 5.61−5.66 (m, 2H), 6.65 (s, 1H), 7.26 (d, 2H, J = 9 Hz), 7.77 (d, 2H, J = 9 Hz), 9.36 (9s, 1H); ^{13}C NMR δ 143.2, 139.7, 131.6, 129.6, 129.5, 126.0, 126.3, 124.7, 121.1, 119.3, 32.7, 31.0, 26.0, 25.1, 24.8, 24.4, 21.5. Anal. Calcd for $C_{19}H_{21}NO_2S\cdot0.4H_2O$: C, 68.19; H, 6.74; N, 4.18. Found: C, 68.34; H, 6.91; N, 3.90.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **18** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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