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A Diels–Alder approach to biaryls (DAB): synthesis of the western portion of TMC-95

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Abstract

The rapid synthesis of the western biaryl portion of TMC-95 is disclosed via the use of a Diels–Alder reaction with *o*-nitrostyrene derivative and 1-silyloxy diene with excellent regiochemical control. Subsequent sequential substitutions of a *p*-iodo-phenol derivative followed by an *o*-bromo-nitrobenzene intermediate are employed to incorporate the western carbon framework of TMC-95.
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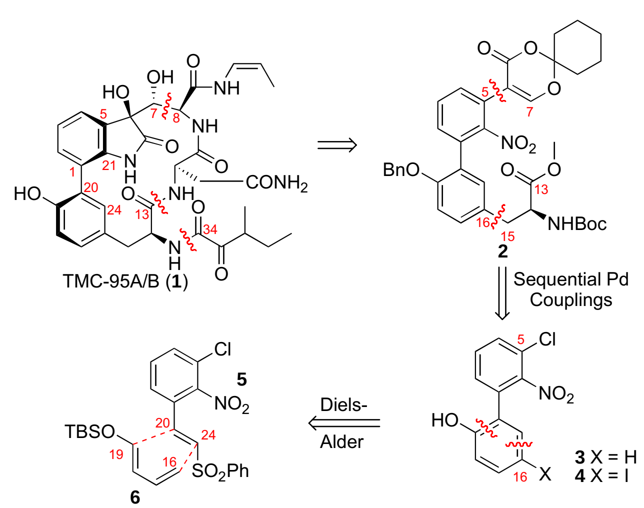
1. Introduction

Biaryl compounds have captured the attention of the synthetic community due to their presence in numerous pharmacologically active drugs[1] as well as their importance as ligands in metal-mediated transformations.[2] Recent attention in this area has been given to non-transition metal based methods for their construction.[3] One potential attractive method for biaryl synthesis is the use of a Diels–Alder cycloaddition. Our group[4] and others[5] have shown that a wide range of structurally complex biaryl compounds can be assembled via this approach. We have been particularly interested in systems which possess an *ortho*-nitrophenyl moiety on the dienophile for several reasons. The significant electron-withdrawing effect of the *ortho*-nitro moiety helps to not only activate the dienophile for the cycloaddition, but also control the regiochemical outcome of the resultant biaryl moiety. Additionally, the location of a nitro moiety in the *ortho* position relative to the σ biaryl linkage provides an excellent handle for subsequent functionalization to the *ortho*-amino moiety. In addition, the reaction of these dienophiles with oxygenated dienes inherently leads to placement of the remaining oxygen functionality in the *ortho* and/or *para* positions. This combination of an *ortho*-anilino and an *ortho*-phenolic substitution patterns is present in both ligands and natural products.

One such natural product possessing this *ortho*-substitution pattern is TMC-95 (**1**). Biaryl **1** was isolated from the fermentation broth of *Apiospora montagnei* Sacc TC 1093 and has displayed nanomolar (5.4 nM) chymotrypsin-like inhibitory activity of the 20S proteasome, which helps to regulate immune response, cell cycle, and cell differentiation (Scheme 1).[6] In addition, **1** has been shown to reduce trypsin-like and



Scheme 1. Retrosynthetic analysis for TMC-95A/B.

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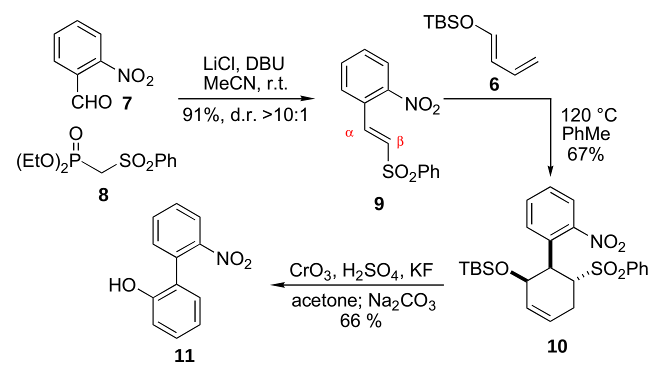
peptidylglutamyl-peptide hydrolyzing activity of the 20S proteasome (200 and 60 nM, respectively) while not inhibiting *m*-calpain, cathepsin L, and trypsin (up to 30 μM).[6a] This activity data indicate that TMC-95 may be a highly selective inhibitor for the 20S proteasome, thereby potentially leading to new anti-tumor and autoimmune treatments.[6b,7] The biological data, coupled with the unusual biaryl moiety embedded within a cyclic peptide backbone, have attracted considerable attention from the synthetic community.[8] To date, two total syntheses[9a,b] and one formal synthesis[9c] have been described toward the natural product. All of the reported approaches employ a metal-mediated strategy to construct the critical $C_{1,20}$ biaryl linkage.

An alternative method for the synthesis of the biaryl core of TMC-95 could involve the use of a Diels–Alder cycloaddition (Scheme 1). We recently reported the use of mono-substituted and di-substituted acetylenes for the synthesis of highly functionalized biaryls.[4] While these acetylenic dienophiles have proven useful in numerous systems, one current limitation is the inability to construct a 2-nitro-3-halo-2′-phenolic biaryl without additional oxygen substitution in the 4′ position.[4c] This substitution pattern is particularly germane with respect to TMC-95. Consequently, we were intrigued by the possibility of using *o*-nitrophenyl-styrene derivatives (e.g., **5**) in the key [4+2] reaction. To the best of our knowledge, no Diels–Alder cycloadditions have been reported on this class of dienophiles. Herein, we report the application of this Diels–Alder approach to the western portion of TMC-95.[10]

Our retrosynthetic strategy is outlined in Scheme 1. Disconnection at $C_{7,8}$ and the C_{13} and C_{34} peptide linkages leads back to the western subunit **2**. Compound **2** might be available by sequential metal-mediated couplings of the C_5 chloride and a C_{16} halide (via directed halogenation of the phenolic ring) from compound **4**. Finally, the chloride-containing biaryl moiety **3** would be accessible from a Diels–Alder reaction between the sulfone **5** and the known diene **6**.

2. Results and discussion

Prior to advancing on the chlorinated series **5**, we sought proof-of-concept for this Diels–Alder approach. Starting from the commercially available *o*-nitrobenzaldehyde (**7**), olefination using the Masamune–Roush modification[11] of the Wadsworth–Emmons olefination with phosphonate **8**[12] produced the required vinyl sulfone **9**[13] in high alkene selectivity (>10:1 *E*/*Z*) and yield (91%) (Scheme 2). Use of *n*-BuLi for the deprotonation of the sulfone **8** leads to inferior yields and low *E*/*Z* olefin selectivity. Heating of the sulfone **8** with 1-*tert*-butyldimethylsilyloxy-1,3-butadiene (**6**)[14] produced the Diels–Alder adduct **10** as a *single regio- and diastereomer* in 67% isolated yield. The stereochemical outcome of this transformation was established through X-ray crystal analysis (Fig. 1). The observed regiochemistry in the Diels–Alder cycloaddition can be explained by a larger orbital coefficient on the β carbon of the dienophile **9** due to the electron-withdrawing effect of the *o*-nitrotoluene function versus the sulfone moiety (e.g., pK_a of *o*-nitrotoluene=20 vs methyl phenyl sulfone=29).[15] Fluoride-containing Jones oxidation of the adduct **10** followed by a basic work-up (Na_2CO_3) induced silyl deprotection, oxidation, and aromatization to provide the biaryl species **11** in 66% yield.



Scheme 2. Proof-of-concept study in Diels–Alder reaction.

With a good appreciation for the selectivity in the Diels–Alder reaction, we sought to apply this strategy to TMC-95 (Scheme 3). The necessary dienophile **5** was synthesized from the commercially available acid **12** in three steps. Aldehyde **13** had been reported previously;[16] however, we have developed a more direct and higher yielding two-step

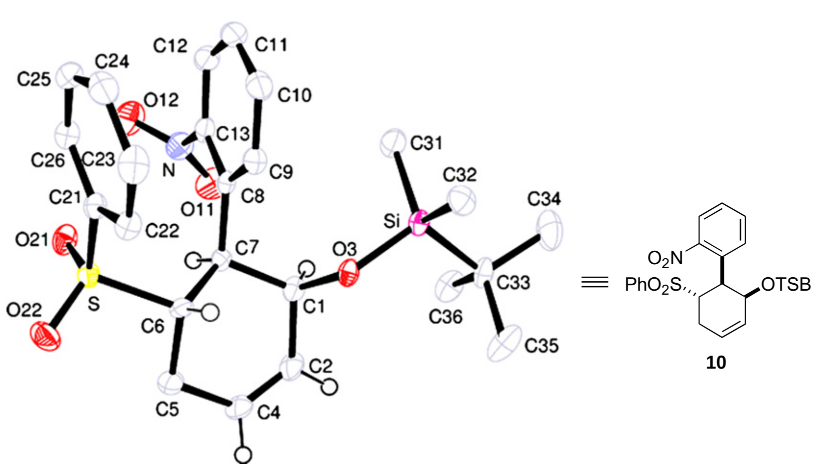
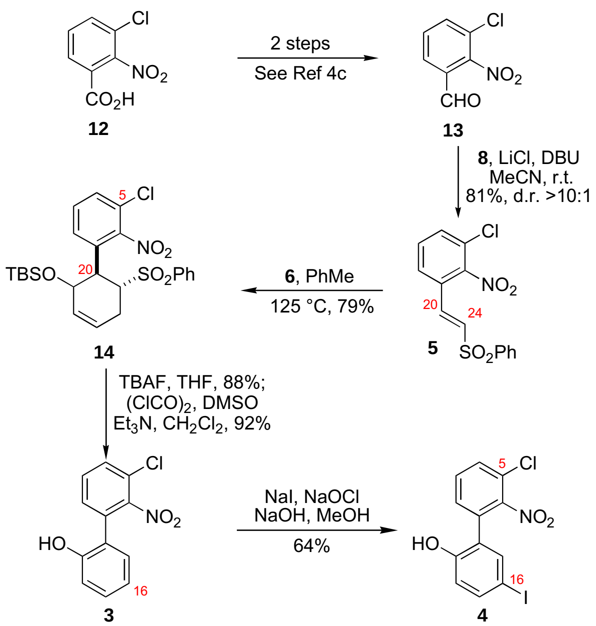


Figure 1. ORTEP representation of compound **10**.

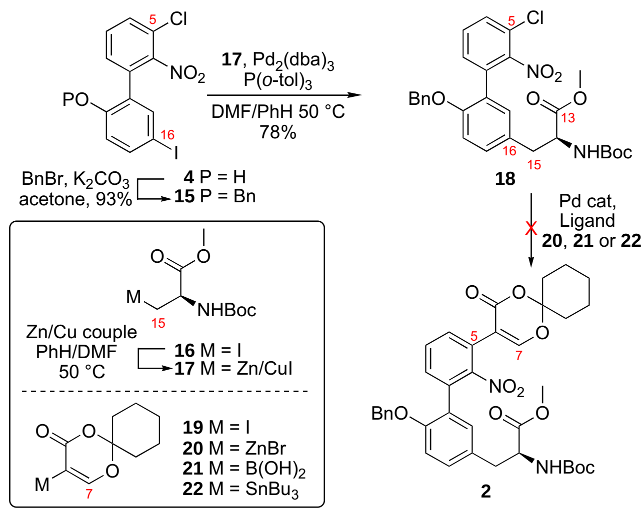
approach.[4c] Diels–Alder reaction of dienophile **5** with the diene **6** provided the adduct **14**, again as approximately a 3.5:1 mixture (*endo*/*exo* isomers). The stereochemistry of **14** was confirmed by X-ray crystal analysis of both diastereomers derived from **14**.[17] Use of our previous fluoride-containing Jones oxidation proved ineffective on adduct **10**. Fortunately, TBAF deprotection and Swern oxidation induced in situ elimination and aromatization to produce the $C_{1,20}$ linked biaryl **3**. Mono-iodination[18] provided the poly-functionalized biaryl **4**.



Scheme 3. Diels–Alder approach to halogenated biaryls.

At this point, it is worth noting that each of the two palladium-couplings required on a substrate such as **4** or **15** possesses inherent challenges (Scheme 4). The synthesis of aryl amino acid derivatives via a palladium-mediated approach (including the pioneering efforts of Jackson and co-workers[19]) has met with reasonable success to date.[20] Jackson has published two nice recent reviews on the subject.[21] These impressive accomplishments aside, it should be noted that the yields for these transformations are often modest unless a large excess of the organozinc species is used. For example, Jackson's *Organic Synthesis* preparation of (*N*-*tert*-butoxycarbonyl)-β-[4-(methoxycarbonyl)phenyl]alanine methyl ester provides only a 35–39% yield of the product.[22] For the required functionalization at C_5 of the *o*-chloro-nitrobenzene derivative (e.g., **18**), successful metal-mediated couplings have been reported only on relatively unfunctionalized systems, primarily through Suzuki–Miyaura couplings.[23] No examples of palladium-mediated couplings of 3-substituted, 2-nitrochlorobenzene derivatives have been reported. In contrast, the required palladium coupling for the TMC-95 synthesis necessitates the reaction on the poly-functionalized biaryl-containing aryl chloride with a coupling partner that would generate a reactive Michael acceptor in **2**.

With these important considerations in mind, attachment of the remaining two side arms was explored (Scheme 4). After

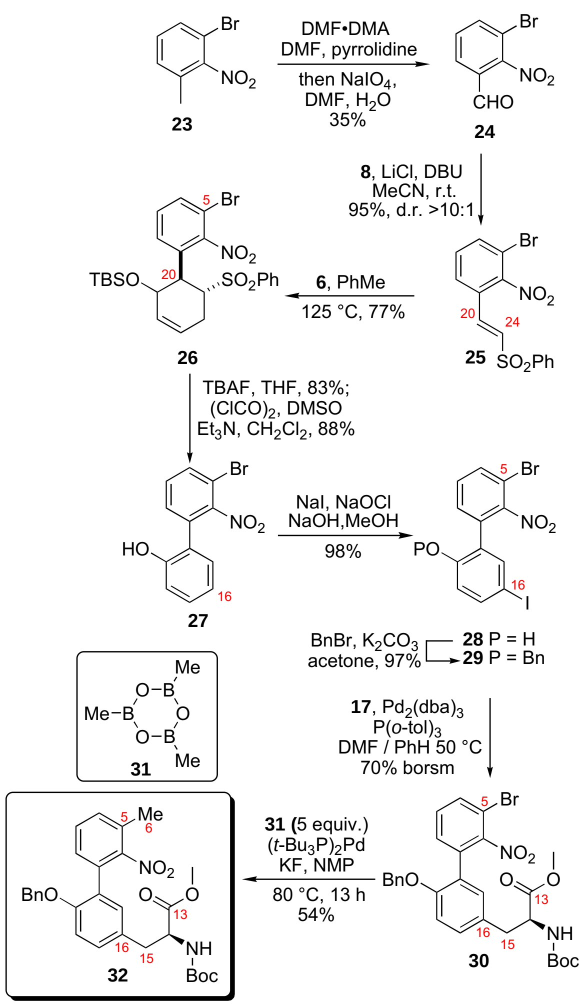


Scheme 4. Attempted synthesis of western portion of TMC-95.

some experimentation, we found that selective palladium coupling [$Pd_2(dba)_3$/P(*o*-tol)$_3$] of iodide **15** with the organometallic species **17** gave the amino acid derivative **18** in a good yield (78%). Interestingly, use of the analogous catalyst derived from a Pd(II) source, Pd(P(*o*-tol)$_3$)$_2$Cl$_2$, gave an inferior yield (50%). Also, the use of the organometallic species **17** derived from zinc/copper couple was critical to the success of this reaction. Next, our initial efforts focused on a Suzuki-based strategy for the incorporation of the final side arm. To this end, boronic acid was constructed from the known iodide **19**[24] [*i*-PrMgCl, THF;[25] B(OMe)$_3$]; however, the boronic acid rapidly fragmented upon reaction under a series of Suzuki coupling conditions.[26] The analogous organozinc species was constructed [*i*-PrMgCl, THF; $ZnBr_2$];[27] however, the Negishi-style coupling did not provide any of the desired adduct **2** under a range of conditions. A similar outcome was observed under a range of Stille conditions. We attribute the lack of success under the palladium-mediated conditions to the 3-substituent, which forces the nitro moiety out of the plane of the aromatic ring, thereby making oxidative addition difficult. In fact, treatment of **18** with 1 equiv of (*t*-Bu$_3$P)$_2$Pd at 120 °C (THF, dioxane, 16 h) did *not* consume the aryl chloride.

Based on this knowledge, we decided to synthesize the analogous 3-bromo-2-nitro-1-substituted biaryl **30** (Scheme 5). 3-Bromo-2-nitrobenzaldehyde (**24**) is readily available from 3-bromo-2-nitrotoluene (**23**) via a modified version[4] of a Pfizer protocol.[28] Initial formation of the enamine via treatment with DMF·DMA followed by cleavage with $NaIO_4$ gave the aldehyde **24** in modest yield. We reason that the orthogonality of the nitro group due to the adjacent bromine atom is the major factor for the lower yield. Conversion to the α,β-unsaturated sulfone **25** and Diels–Alder cycloaddition with diene **5** followed by deprotection and oxidation gave the biaryl **27**. Iodination using the NaI and NaOCl procedure followed by benzylation gave the required coupling precursor **29**. Use of our previously optimized conditions for the Negishi-style coupling gave the desired amino acid **30** in good yield.

Fortunately, our initial attempts at coupling the aryl bromide have been met with greater success. While appending the remaining side arm continued to prove challenging, we were grateful to find that coupling of the bromide **30** with methyl boroxine (**31**) using Fu's catalyst gave the desired coupling product **32**. Use of more elaborate metallo species derived from iodide **19** in place of boroxine **31** led to sole dehalogenation of the *ortho*-bromide moiety present in **30**.



Scheme 5. Revised approach to western portion of TMC-95.

In conclusion, the utility of a Diels–Alder approach to the synthesis of the biaryl core **32** of TMC-95 has been demonstrated (11 steps from the commercially available toluene **23**). The future application of this *D*iels–Alder *a*pproach to *b*iaryl compounds (DAB) will be reported in due course.

3. Experimental section

3.1. General

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer, neat unless otherwise indicated. ^{1}H NMR spectra were recorded on a Brüker 300 spectrometer at 300 MHz or a Brüker 400 spectrometer at 400 MHz in the indicated solvent and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded on Brüker 300 spectrometer at 75 MHz or a Brüker 400 spectrometer at 100 MHz in the solvent indicated and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. Optical rotations were recorded on a Perkin Elmer 243 polarimeter using a sodium lamp at 589 nm in $CHCl_3$.

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum back TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gelurian silica gel.

Air and/or moisture sensitive reactions were performed under usual inert atmospheric conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120 °C or by a Bunsen flame, and then cooled under argon. Solvents and commercial reagents were purified in accord with Perrin and Armarego[29] or used without further purification.

3.2. Diene *6*

To a stirring solution of freshly distilled 2-butenal (3.15 g, 44.9 mmol, 3.72 mL) in pentane (108 mL) were added sequentially TBSCl (8.50 g, 56.4 mmol), triethylamine (7.81 mL, 5.67 g, 55.9 mmol), CH_3CN (55.8 mL), and NaI (8.39 g, 55.9 mmol) at rt. After 18 h, the solution was warmed to 40 °C. After 6 h, the reaction was quenched with ice (110 g) and extracted with pentane (3×150 mL). The dried extract ($MgSO_4$) was purified by vacuum distillation (41–43 °C, 1 mm Hg) to give the known **6**[30] (5.20 g, 28.2 mmol, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, J=10.5 Hz, 1H), 6.24 (dt, J=10.8, 16.8 Hz, 1H), 5.75 (t, J=10.9 Hz, 1H), 5.00 (dd, J=1.9, 16.8 Hz, 1H), 4.83 (dd, J=1.8, 10.5 Hz, 1H), 0.93 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 133.7, 114.5, 112.2, 26.0, 18.7, −4.85.

3.3. Phosphonate *8*

To a stirring solution of methyl phenyl sulfone (8.48 g, 54.2 mmol) and THF (54.2 mmol) was added n-BuLi (47.7 mL, 119 mmol, 2.5 M in hexanes) at 0 °C. After 30 min, freshly distilled diethyl chlorophosphate (9.41 mL, 11.2 g, 65.1 mmol) was added dropwise. After 1 h, the reaction was quenched with satd aq NH_4Cl (10 mL). The organic volatiles were removed in vacuo and the residue was extracted with CH_2Cl_2 (2×100 mL). The dried extract (Na_2SO_4) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 60–100% EtOAc/hexanes, to give the known **8**[31] (13.5 g, 46.2 mmol, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–8.03 (m, 2H), 7.68–7.72 (m, 1H), 7.57–7.62 (m, 2H), 4.14–4.19 (m, 4H), 4.14 (d, J=16.9 Hz, 2H), 1.31 (td, J=7.0, 0.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (d, J_{C-P}<10 Hz, 1C), 134.5, 129.5, 128.8, 63.8 (d, J_{C-P}<10 Hz, 1C), 54.25 (d, J_{C-P}= 140 Hz, 1C), 16.6 (d, J_{C-P}<10 Hz, 1C).

3.4. *E-2-(2-Nitro-phenyl)-1-phenylsulfonyl-ethene (**9**)*

To a suspension of LiCl (0.600 g, 14.2 mmol) in anhydrous CH_3CN (75 mL) was added a solution of **8** (2.73 g, 9.33 mmol) in CH_3CN (3 mL). An additional portion of CH_3CN was used to wash the phosphonate flask (3×2 mL). Promptly, DBU (1.16 mL, 1.16 mL) was added to form a yellow mixture. A solution of 2-nitrobenzaldehyde (1.17 g, 7.75 mmol) in CH_3CN (5 mL) was then added dropwise and an additional portion of CH_3CN was then added to wash the aldehyde flask (3×1.3 mL). The resulting light brown mixture was stirred for 110 min, quenched with satd aq NH_4Cl (20 mL), and the volatiles were removed in vacuo. The organics were then extracted with CH_2Cl_2 (4×60 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–28% EtOAc/hexanes, to yield **9** as a pale yellow solid (2.02 g, 7.00 mmol, 90%). Mp=145–46 °C; IR (neat) 3033, 2854, 1522, 1446, 1351, 1140, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J=8.1, 1.4 Hz, 1H), 7.52–7.58 (m, 4H), 7.40–7.45 (m, 2H), 7.30–7.35 (m, 1H), 7.23 (td, J=7.6, 1.3 Hz, 1H), 5.91–5.96 (m, 2H), 5.84–5.88 (m, 1H), 4.47 (t, J=3.9 Hz, 1H), 4.14 (td, J=10.0, 3.8 Hz, 1H), 2.50–2.69 (m, 2H), 0.80 (s, 9H), −0.14 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.3, 140.2, 139.5, 134.5, 134.2, 132.6, 131.6, 130.0, 129.9, 129.4, 128.4, 125.6; HRMS (CI^+) calcd for $C_{14}H_{12}NO_4S$ (M+H) 290.04870, found 290.04806.

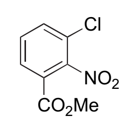
3.5. *TBS Diels–Alder adduct **10***

To a suspension of **9** (543 mg, 1.88 mmol) in PhMe (2.13 mL) was added diene **6** (1.63 mL, 7.51 mmol). The reaction tube was then sealed and heated to 120 °C. After 3.5 days, the rust orange solution was allowed to cool, and volatiles were then removed in vacuo and purified by chromatography over silica gel, eluting with 8–35% EtOAc/hexanes (with 1% Et_3N), to give **10** as a white solid in 67% yield (615 mg, 1.30 mmol). Mp=115–17 °C; IR (neat) 3033, 2854, 1522, 1446, 1351, 1140, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J=8.1, 1.4 Hz, 1H), 7.52–7.58 (m, 4H), 7.40–7.45 (m, 2H), 7.30–7.35 (m, 1H), 7.23 (td, J=7.6, 1.3 Hz, 1H), 5.91–5.96 (m, 2H), 5.84–5.88 (m, 1H), 4.47 (t, J=3.9 Hz, 1H), 4.14 (td, J=10.0, 3.9 Hz, 1H), 2.50–2.69 (m, 2H), 0.80 (s, 9H), −0.14 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.1, 138.9, 134.8, 133.8, 131.4, 130.6, 129.7, 129.5, 128.7, 128.2, 125.9, 123.9, 67.3, 59.7, 41.6, 26.6, 26.2, −18.4, −4.58, −5.06; HRMS (CI^+) calcd for $C_{24}H_{32}NO_5SSi$ (M+H) 474.17839, found 474.17844.

3.6. *2′-Nitro-biphenyl-2-ol (**11**)*

To a stirred solution of Diels–Alder adduct **10** (155 mg, 0.328 mmol) in acetone (1.64 mL) at 0 °C were added KF (44 mg, 0.754 mmol) and Jones reagent[32] (0.187 mL, 0.22 mmol) in a sequential fashion. The orange solution was then allowed to warm to rt and stirred for 26 h. An additional portion of Jones reagent (90 μL, 0.0026 mmol) was added over during this period. Isopropanol (1.0 mL), H_2O (0.7 mL), and Na_2CO_3 (0.634 g, 5.98 mmol) were then added sequentially. After 8 h, the reaction mixture was filtered through Celite, concentrated in vacuo, and purified by chromatography over silica gel, eluting with 8–18% EtOAc/hexanes, to give the known **11**[33] as a yellow oil in 49% yield (34.8 mg, 0.162 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J=8.1, 1.3 Hz, 1H), 7.70 (td, J=7.6, 1.3 Hz, 1H), 7.53–7.57 (m, 1H), 7.48 (dd, J=7.6, 1.2 Hz, 1H), 7.29–7.34 (m, 1H), 7.28 (dd, J=7.6, 1.7 Hz, 1H), 7.08 (td, J=7.5, 1.1 Hz, 1H), 6.87 (dd, J=8.1, 1.1 Hz, 1H), 5.10 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.7, 150.1, 133.3, 133.1, 132.9, 130.3, 128.9, 125.5, 124.6, 121.8, 116.1, 30.1.

3.7. *3-Chloro-2-nitro-benzoic acid methyl ester (**33**)*



33

To a stirred solution of **12** (0.740 g, 3.67 mmol) in DMF (3.67 mL) were added K_2CO_3 (1.52 g, 11.0 mmol) and MeI (1.04 g, 0.457 mL, 7.34 mmol) sequentially at rt. The solution was warmed to 40 °C for 1 h, and then diluted with EtOAc (50 mL), washed with H_2O (2×25 mL), and satd aq NaCl (25 mL). The dried extract (Na_2SO_4) was concentrated in vacuo to give the known **33**[4c] (0.745 g, 3.46 mmol, 94%) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–8.03 (dd, J=1.3, 7.9 Hz, 1H), 7.74–7.76 (dd, J=1.3, 7.9 Hz, 1H), 7.54–7.57 (t, J=7.9 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 149.8, 135.2, 131.1, 130.1, 126.7, 124.8, 53.8.

3.8. *3-Chloro-2-nitro-benzaldehyde (**13**)*

To a stirred solution of **33** (723 mg, 3.35 mmol) in CH_2Cl_2 (16.8 mL) at −78 °C was slowly added DIBAL-H (5.03 mL, 5.03 mmol, 1.0 M in CH_2Cl_2) over 10 min. After 1 h, the reaction was quenched with MeOH (0.55 mL) and warmed to rt. Following dilution with CH_2Cl_2 (5 mL), satd aq sodium tartrate (10 mL) was added and the solution was stirred vigorously for 15 min. The product was extracted with CH_2Cl_2 (2×8 mL), and washed with H_2O (30 mL) and satd aq NaCl (30 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and recrystallized with EtOAc/hexanes to give the known **13**[4c,16] (0.575 g, 3.10 mmol, 92%) as a white crystalline solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.88–7.90 (dd, J=1.4, 7.7 Hz, 1H), 7.78–7.80 (dd, J=1.4, 8.1 Hz, 1H), 7.64–7.68 (dd, 7.8. 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 152.5, 136.4, 131.9, 129.8, 129.0, 127.1.

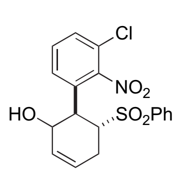
3.9. *E-2-(3-Chloro-2-nitro-phenyl)-1-phenylsulfonyl-ethene (**5**)*

To a stirred solution of LiCl (0.311 g, 7.34 mmol) and CH_3CN (36 mL) were added sequentially **8** (1.71 g, 8.86 mmol) in CH_3CN (6 mL), DBU (0.892 g, 0.876 mL, 5.86 mmol), and **13** (0.892 g, 4.89 mmol) in CH_3CN (6 mL) at rt. After 1.5 h, the reaction was quenched with satd aq NH_4Cl (20 mL) and volatiles were removed in vacuo. The residue was extracted with CH_2Cl_2 (60 mL) and washed with satd aq NH_4Cl (60 mL). The aqueous phase was extracted once with CH_2Cl_2 (20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by recrystallization from EtOAc to yield **5** as a white solid. The mother liquor was purified by chromatography over silica gel, eluting with 20–50% EtOAc/hexanes, to yield **5** (total of 1.27 g, 3.92 mmol, 80%) as a white solid. Mp=166–167 °C; IR (neat) 3067, 1528, 1363, 1303, 1149, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.98 (m, 2H), 7.62 (d, J=16.3 Hz, 1H), 7.29–7.72 (m, 6H), 6.96 (d, J=16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 134.5, 134.4, 134.3, 133.0, 131.8, 130.0, 128.4, 127.4, 126.8, 126.7; HRMS (CI^+) calcd for $C_{14}H_{10}NO_4SCl$ (M^+) 324.00973, found 324.00849.

3.10. *TBS Diels–Alder adduct **14***

To a stirred solution of **5** (576 mg, 1.78 mmol) in PhMe (3.6 mL) in a sealed tube was added **6** (1.31 g, 1.53 mL, 7.11 mmol). After 72 h, the volatiles were removed in vacuo. The crude material was purified by chromatography over silica gel, eluting with 50% CH_2Cl_2/hexanes/1% Et_3N, to give **14** as two *exo*/*endo* adducts (714 mg, 1.41 mmol, 79%) in a 3.5:1 ratio. *endo* Isomer: Mp=174–175 °C; IR (neat) 2929, 1537, 1307, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, J=1.1, 6.3 Hz, 2H), 7.58 (dd, J=1.2, 8.0 Hz, 1H), 7.49 (t, J=6.5 Hz, 2H), 7.42 (dd, J=1.1, 8.1 Hz, 1H), 7.36 (dd, J=1.1, 8.1 Hz, 1H), 7.11 (t, J=11.2 Hz, 1H), 5.81–5.90 (m, 2H), 4.34 (t, J=4.2 Hz, 1H), 4.03 (dt, J=8.2, 10.0 Hz, 1H), 3.20 (dd, J=4.0, 10.0 Hz, 1H), 2.53–2.55 (m, 2H), 0.79 (s, 9H), −0.09 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 134.1, 132.1, 131.1, 129.6, 129.5, 129.3, 129.0, 128.9, 126.0, 124.5, 66.98, 59.43, 42.07, 26.19, 25.79, 18.33, −4.50, −5.08; HRMS (EI^+) calcd for $C_{24}H_{31}NO_5SiSCl$ (M^+) 508.1365, found 508.1381.

3.11. *5-Benzenesulfonyl-6-(3-chloro-2-nitro-phenyl)-cyclohex-2-enol (**34**)*



34

To a stirred solution of **14** (334 mg, 0.657 mmol) in THF (1 mL) was added a solution of TBAF in AcOH [100 μL AcOH in 900 μL of 10% TBAF (1.0 M in THF)] at rt. After stirring for 1 h was added TBAF (1 mL) followed by two additional 1 mL portions of TBAF at 30 min. intervals. After a total of 2.5 h, the solution was quenched with H_2O (10 mL), diluted with Et_2O (10 mL), and washed with brine (10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 60% EtOAc/hexanes, to give **34** (229 mg, 0.583 mmol, 88%) as a white solid. Mp=155–157 °C; IR (neat) 3484, 1535, 1305, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.65 (m, 2H), 7.54–7.59 (m, 1H), 7.43 (t, J=7.4 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.08 (t, J=8.0 Hz, 1H), 3.87–3.98 (m, 2H), 4.27–4.35 (m, 1H), 3.95–4.08 (m, 1H), 3.20 (dd, J=3.6, 9.8 Hz, 1H), 2.54–2.59 (m, 2H), 1.63 (d, J=5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 138.8, 134.1, 130.9, 130.7, 129.7, 129.6, 129.4, 128.9, 128.0, 127.7, 125.2, 66.4, 58.7, 41.9, 26.1; HRMS (CI^+) calcd for $C_{18}H_{17}NO_5SCl$ (M+H) 394.0579, found 394.05159.

3.12. *3′-Chloro-2′-nitro-biphenyl-2-ol (**3**)*

To a stirred solution of oxalyl chloride (130 μL, 202 mg, 1.59 mmol) in CH_2Cl_2 (2.5 mL) was added DMSO (230 μL, 249 mg, 3.18 mmol) at −78 °C. After 15 min, **34** (209 mg, 0.531 mmol) in CH_2Cl_2 (2.0 mL) and DMSO (0.2 mL) was added. After stirring for an additional 15 min, Et_3N (1.08 g, 10.6 mmol, 1.49 mL) was added. The solution was allowed to warm to rt over 1 h. Next, the solution was quenched with satd aq NH_4Cl (10 mL), diluted with CH_2Cl_2 (10 mL), and washed with H_2O (10 mL) and satd aq NaCl (10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/hexanes, to give **3** (122 mg, 0.489 mmol, 92%) as a white solid. Mp=94–96 °C; IR (neat) 3484, 1536, 1450, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J=1.6, 8.1 Hz, 1H), 7.49 (t, J=8.1 Hz, 1H), 7.34 (dd, J=1.6, 9.9 Hz, 1H), 7.29 (ddd, J=1.7, 7.7 Hz, 1H), 7.15 (dd, J=1.2, 7.6 Hz, 1H), 6.98 (td, J=1.0, 7.6 Hz, 1H), 6.91 (dd, J=0.8, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 150.1, 132.7, 131.32, 131.3, 130.9, 130.7, 130.5, 126.1, 122.6, 121.6, 116.8; HRMS (CI^+) calcd for $C_{12}H_9NO_3Cl$ (M+H) 250.0273, found 250.0271.

3.13. *3′-Chloro-5-iodo-2′-nitro-biphenyl-2-ol (**4**)*

To a stirred solution of **3** (81.0 mg, 0.324 mmol) in MeOH (2.2 mL) were added NaI (48.6 mg, 0.324 mmol) and NaOH (13.0 mg, 0.324 mmol) at rt. Solution was cooled to 0 °C before the slow addition of NaOCl (392 mg, 0.324 mmol, w/v in H_2O) over 45 min. After 1 h, the reaction was quenched with 10% aq sodium thiosulfate (10 mL) and satd aq NH_4Cl (10 mL), diluted with Et_2O (10 mL), and washed with H_2O (10 mL) and satd aq NaCl (10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% CH_2Cl_2/hexanes, to give **4** (93.0 mg, 0.248 mmol, 76%) as a white solid. Mp=154–155 °C; IR (neat) 3456, 1534, 1364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J=1.4, 8.1 Hz, 1H), 7.56 (d, J=2.2 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.48 (d, J=2.2 Hz, 1H), 7.35 (dd, J=1.4, 7.6 Hz, 1H), 6.68 (d, J=8.6 Hz, 1H), 5.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 149.9, 139.9, 139.0, 131.6, 131.5, 131.0, 130.8, 126.3, 125.2, 118.9, 83.1; HRMS (FAB^+) calcd for $C_{12}H_7NO_3ClI$ (M^+) 374.9169, found 374.9159.

3.14. 2′-Benzyloxy-3-chloro-5′-iodo-2-nitro-biphenyl (15)

To a stirred solution of **4** (108 mg, 0.288 mmol) in acetone (2.88 mL) were added K_2CO_3 (47.7 mg, 0.0345 mmol) and BnBr (37 μL, 54.2 mg, 0.317 mmol). After heating at 70 °C for 1 h, the clear solution was diluted with Et_2O (10 mL), and washed with H_2O (10 mL) and satd aq NaCl (10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% CH_2Cl_2/hexanes, to give **15** (124 mg, 0.266 mmol, 93%) as a white solid. Mp=127–128 °C; IR (neat) 1536 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J=2.3, 8.7 Hz, 1H), 7.54 (d, J=1.5 Hz, 1H), 7.50 (dd, J=1.5, 4.7 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.21–7.34 (m, 6H), 6.69 (d, J=8.7 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 149.4, 139.6, 139.1, 136.6, 132.6, 131.1, 130.8, 130.5, 129.0, 128.4, 127.3, 127.2, 125.9, 115.6, 63.4, 71.0; HRMS (CI^+) calcd for $C_{19}H_{13}NO_3ClI$ (M^+) 464.9632, found 464.9629.

3.15. Chloro amino acid derivative 18

To a stirred solution of Zn/Cu couple[34] (330 mg, 2.56 mmol) in PhH (8.4 mL) and DMF (9.3 mL) was added **16** (611 mg, 1.86 mmol). After heating at 50 °C for 30 min, Pd_2dba_3 (17.0 mg, 0.0188 mmol), P(o-tol)$_3$ (22.6 mg, 0.0742 mmol), and **15** (173 mg, 0.371 mmol) in PhH (4 mL) were added. After 2 h at 50 °C, the solution was quenched with 10% aq citric acid (15 mL), diluted with Et_2O (20 mL), and washed with H_2O (15 mL) and satd aq NaCl (15 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–50% EtOAc/hexanes, to give **18** (156 mg, 0.288 mmol, 78%) as an off-white solid. Mp=62–64 °C; $[\alpha]_D$ +37.2 (c 1.52, $CHCl_3$); IR (neat) 3364, 2977, 1744, 1712, 1538, 1501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J=1.1, 7.8 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 7.27–7.36 (m, 6H), 7.12 (dd, J=2.2, 8.5 Hz, 1H), 7.00 (d, J=2.1 Hz, 1H), 6.90 (d, J=8.5 Hz, 1H), 5.06 (s, 2H), 4.52–4.62 (m, 1H), 3.73 (s, 3H), 3.05–3.08 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 155.5, 155.1, 149.6, 137.1, 133.9, 131.8, 131.7, 131.0, 130.6, 130.0, 129.1, 128.9, 128.2, 172.2, 125.7, 125.3, 113.5, 80.4, 70.9, 54.82, 52.75, 37.83, 28.70; HRMS (CI^+) calcd for $C_{28}H_{30}N_2O_7Cl$ (M+H) 541.1723, found 541.1742.

3.16. Organozinc 20

To a stirred solution of **19** (41.9 mg, 0.142 mmol) in THF (0.7 mL) at −40 °C was added a solution of i-PrMgCl (0.100 mL, 0.156 mmol, 1.57 M in THF). After 10 min, $ZnBr_2$ (48.1 mg, 0.214 mmol) was added. The mixture was stirred at −40 °C for 10 min and then let warm to rt and the organozinc species **20** was used in situ.

3.17. Boronic acid 21

To a stirred solution of **19** (164 mg, 0.558 mmol) in THF (1.6 mL) at −40 °C was added i-PrMgCl (0.39 mL, 0.614 mmol, 1.57 M in THF). After 10 min, freshly distilled $B(OMe)_3$ (86.9 mg, 0.0932 mL, 0.836 mmol) was added. The solution was stirred for an additional 30 min before warming to rt. The mixture was quenched with satd aq NH_4Cl (10 mL), diluted with EtOAc (15 mL), and washed with H_2O (10 mL) and satd aq NaCl. The dried extract ($MgSO_4$) was purified by chromatography over silica gel, eluting with 3–6% MeOH/CH_2Cl_2, to give **21** (88.3 mg, 0.368 mmol, 80%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 5.82 (br s, 2H), 1.93–2.07 (m, 4H), 1.51–1.77 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 166.1, 109.1, 53.9, 34.2, 24.8, 22.4.

3.18. Stannane 22

To a stirred solution of **19** (57.7 mg, 0.232 mmol) in THF (0.66 mL) at −40 °C was added i-PrMgCl (0.162 mL, 0.225 mmol, 1.57 M in THF). After 10 min, Bu_3SnCl (113 mg, 0.0940 mL, 0.348 mmol) was added. The yellow solution was stirred for an additional 30 min before warming to rt. The mixture was quenched with satd aq NH_4Cl (10 mL), diluted with EtOAc (15 mL), and washed with H_2O (10 mL) and satd aq NaCl. The dried extract ($MgSO_4$) was used crude.

3.19. 3-Bromo-2-nitro-benzaldehyde (24)

To a stirred solution of **23** (10.02 g, 46.38 mmol) in DMF (37 mL) were added DMF·DMA (19.0 mL, 16.91 g, 141.91 mmol) and pyrrolidine (3.80 mL, 3.29 g, 46.29 mmol) at rt. The solution was then heated to 115 °C. After 22 h, the solution was cooled to rt and added dropwise to a stirring solution of $NaIO_4$ (29.80 g, 139.2 mmol), DMF (75 mL), and H_2O (100 mL) at 0 °C. The reaction mixture was then allowed to warm to rt. After 3 h at rt, the reaction mixture was filtered through sand, eluting with EtOAc (400 mL). The organic layer was then washed with H_2O (3×200 mL). The dried extract ($MgSO_4$) was purified by chromatography over silica gel, eluting with 5–40% EtOAc/hexanes, to give **24** (3.70 g, 16.09 mmol, 35%) as a dark red solid. Mp=75–77 °C; IR (neat) 1702, 1539, 1368, 1191, 1118, 912, 847, 785, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.96–7.99 (m, 2H), 7.62 (t, J=8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 185.7, 150.5, 139.1, 131.7, 130.2, 128.7, 114.7; HRMS (CI^+) calcd for $C_7H_4BrNO_3$ (M^+) 228.9377, found 228.9375.

3.20. E-2-(3-Bromo-2-nitro-phenyl)-1-phenylsulfonyl-ethene (25)

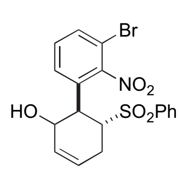
To a stirring solution of LiCl (0.481 g, 11.35 mmol) and CH_3CN (55 mL) at rt was added sequentially a solution of **8**

(3.99 g, 13.68 mmol) in CH_3CN (9.8 mL), DBU (1.36 g, 8.97 mmol), and a solution of **24** (1.72 g, 7.48 mmol) in CH_3CN (12.5 mL). After 12 h, the reaction was quenched with sat. aq. NH_4Cl (75 mL) and the organic solvents were removed in vacuo. The residue was then extracted with CH_2Cl_2 (50 mL), washed with satd aq. NH_4Cl (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by recrystallization from EtOAc to yield **25** (2.62 g, 7.12 mmol, 95%) as an orange solid. Mp=175–78 °C; IR (neat) 1534, 1445, 1364, 1308, 1149, 1085, 963, 830, 728, 748, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J=8.0 Hz, 2H), 7.76 (d, J=8.0 Hz, 1H), 7.642–7.725 (m, 1H), 7.561–7.642 (m, 4H), 7.43 (t, J=8.0 Hz, 1H), 6.94 (d, J=15.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.3, 135.7, 13.0, 134.0, 131.5, 129.6, 128.1, 127.1, 127.0, 114.2; HRMS (CI^+) calcd for $C_{14}H_{11}NO_4SBr$ (M+H) 367.9592, found 367.9610.

3.21. Bromo Diels–Alder adduct 26

To diene **6** (4.38 g, 23.8 mmol) in a sealed tube were added **25** (2.18 g, 5.93 mmol) and PhMe (12.1 mL). The neat solution was then heated to 135 °C. After 5 days, the volatiles were removed in vacuo and were purified by chromatography over silica gel, eluting with 5–40% EtOAc/hexanes, to give **26** (2.53 g, 4.57 mmol, 77%) as a yellow solid. IR (neat) 2954, 2929, 2890, 2856, 1538, 1363, 1307, 1256, 1145, 1082, 1062, 837, 777, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J=7.6 Hz, 2H), 7.60–7.64 (m, 1H), 7.44–7.52 (m, 4H), 7.04 (t, J=8.0 Hz, 1H), 5.82–5.87 (m, 2H), 4.02 (dd, J=8.0, 17.6 Hz, 1H), 3.20 (dd, J=4.0, 10.0 Hz, 1H), 2.55 (d, J=7.6 Hz, 2H), 0.79 (s, 9H), −0.09 (s, 3H), −0.37 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.5, 138.3, 133.7, 132.3, 132.1, 130.8, 129.2, 129.1, 128.8, 128.7, 125.6, 111.9, 66.6, 59.1, 41.8, 25.3, 25.2, 17.9, −4.9, −5.5; HRMS (CI^+) calcd for $C_{24}H_{31}NO_5SBr$ (M+H) 552.08755, found 552.08841.

3.22. Bromo alcohol 35



35

To biaryl **26** (1.23 g, 2.23 mmol) was added a premixed solution of AcOH (0.5 mL) and TBAF (9.5 mL, 9.5 mmol, 1.0 M in THF) at rt. The solution was stirred for 45 min and additional TBAF (15 mL, 15 mmol, 1 M in THF) was added portionwise over a period of 2 h. After an additional 1 h, the solution was quenched with H_2O (50 mL), diluted with Et_2O (50 mL), and washed with satd aq NaCl (50 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica, eluting with 60% EtOAc/hexanes, to give **35** (814 mg, 1.86 mmol, 83%) as a white solid. Mp=168–9 °C; IR (neat) 3484, 1656, 1534, 1449, 1360, 1303, 1143, 1080, 1027, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.5 Hz, 2H), 7.33–7.52 (m, 2H), 7.43 (t, J=7.5 Hz, 2H), 7.02 (t, J=8.1 Hz, 1H), 5.84–6.00 (m, 2H), 4.32 (s, 1H), 4.03 (dd, J=8.7, 17.8 Hz, 1H), 3.22 (dd, J=3.5, 10.8 Hz, 1H), 2.58 (d, J=7.5 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 151.5, 138.5, 133.7, 132.5, 131.0, 130.5, 129.2, 129.1, 128.1, 127.7, 127.6, 127.3, 112.6, 66.0, 58.3, 41.6, 25.7; HRMS (CI^+) calcd for $C_{18}H_{17}NO_5SBr$ (M+H) 438.00107, found 437.99984.

3.23. 3′-Bromo-2′-nitro-biphenyl-2-ol (27)

To a solution of DMSO (69.8 mg, 0.894 mmol, 63.4 μL) in CH_2Cl_2 (750 μL) at −78 °C was added oxalyl chloride (56.7 mg, 0.447 mmol, 39.0 μL). After 15 min, a solution of **35** (65.3 mg, 0.149 mmol) in CH_2Cl_2 (550 μL) and DMSO (100 μL) was added. After 15 min, Et_3N (304 mg, 2.98 mmol, 418 μL) was added. The solution was allowed to warm to rt over 1 h. After an additional 1 h, the solution was quenched with satd aq NH_4Cl (5 mL), diluted with CH_2Cl_2 (5 mL), and washed sequentially with H_2O (5 mL) and satd aq NaCl (2 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 60% EtOAc/hexanes, to give **27** (38.5 mg, 0.131 mmol, 88%) as a white solid. Mp=111–114 °C; IR (neat) 3442, 2090, 1646, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J=4.0, 5.2 Hz, 1H), 7.45–7.44 (m, 2H), 7.04 (ddd, J=1.6, 8.0, 15.2 Hz, 1H), 7.17 (dd, J=1.6, 7.6 Hz, 1H), 6.99 (t, J=7.2 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 5.51 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.8, 133.2, 132.6, 131.2, 131.1, 130.8, 130.2, 122.3, 121.0, 116.4, 113.4, 29.7; HRMS (CI^+) calcd for $C_{12}H_8NO_3IBr$ (M^+) 292.9688, found 294.9667.

3.24. 3′-Bromo-5-iodo-2′-nitro-biphenyl-2-ol (28)

To a solution of **27** (331 mg, 1.13 mmol) in MeOH (7.5 mL) were added NaOH (45.0 mg, 1.13) and NaI (169 mg, 1.13 mmol) at rt. The solution was then cooled to 0 °C. Next, NaOCl (1.36 mL, 83.8 mg, 1.13 mmol, 6.15% w/v in H_2O) was added to the reaction over a period of 45 min. After an additional 1 h, the reaction was quenched with aq sodium thiosulfate (30 mL, 10%), diluted with EtOAc (30 mL), and washed sequentially with satd aq NH_4Cl (30 mL), H_2O (30 mL), and satd aq NaCl (30 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified via chromatography over silica gel, eluting with 75% CH_2Cl_2/hexanes, to give **28** (474 mg, 1.13 mmol, 98%) as a white solid. Mp=164–167 °C; IR (neat) 3441, 2090, 1646, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J=1.2, 8 Hz, 1H), 7.62 (dd, J=2.2, 8.6 Hz, 1H), 7.78 (dd, J=1.8, 8.0 Hz, 2H), 7.40 (dd, J=1.2, 7.9 Hz, 1H), 6.73 (d, J=8.6 Hz, 1H), 4.90 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.7, 139.6, 138.6, 133.9, 131.3, 131.0, 130.8, 124.9, 118.7, 113.7, 82.8; HRMS

(CI^+) calcd for $C_{12}H_7NO_3IBr$ (M^+) 418.8654, found 418.8654.

3.25. 2′-Benzyloxy-3-bromo-5′-iodo-2-nitrobiphenyl (*29*)

To a solution of **28** (474 mg, 1.13 mmol) in acetone (11 mL) were added K_2CO_3 (469 mg, 3.39 mmol) and BnBr (0.389 mL, 0.580 mg, 3.39 mmol) at rt. The solution was heated to 70 °C. After 1 h, the solution was cooled to rt, diluted with EtOAc (30 mL), and washed sequentially with satd aq NH_4Cl (30 mL), H_2O (30 mL), and satd aq NaCl (30 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified via chromatography over silica gel, eluting with 10–33% CH_2Cl_2/hexanes, to give **29** (538 mg, 1.05 mmol, 97%) as a white solid. Mp=126–127 °C; IR (neat) 1536, 1489, 1453, 1366, 1276, 1227, 1028, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J=0.8, 7.7 Hz, 1H), 7.62 (dd J=2.2, 7.7 Hz, 1H), 7.53 (d, J=2.2 Hz, 1H), 7.30–7.42 (m, 6H), 7.26 (d, J=7.0 Hz, 2H), 6.73 (d, J=8.7 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.6, 139.2, 138.7, 136.2, 133.2, 131.0, 130.8, 128.6, 127.9, 127.4, 126.8, 115.2, 113.3, 82.9, 70.6, 29.7; HRMS (CI^+) calcd for $C_{19}H_{13}NO_3IBr$ (M^+) 508.9124, found 508.9124.

3.26. Bromo amino acid derivative *30*

To a stirred solution of Zn/Cu couple[34] (182 mg, 2.79 mmol) in PhH (5.5 mL) and DMA (0.4 mL) was added **16** (517 mg, 1.57 mmol). After heating at 50 °C for 30 min, Pd_2dba_3 (3.6 mg, 0.00390 mmol), P(*o*-tol)$_3$ (5.80 mg, 0.0191 mmol), and **29** (40.5 mg, 0.0794 mmol) were added. After 8 h at 50 °C, the solution was quenched with 10% aq citric acid (10 mL), diluted with Et_2O (10 mL), and washed with H_2O (10 mL) and satd aq NaCl (10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5–10% EtOAc/hexanes, to give **30** (21.0 mg, 0.0359 mmol, 46%, 70% borsm) as an off-white solid. Mp=45–48 °C; $[\alpha]_D$ +39.2 (*c* 1.03, $CHCl_3$); IR (neat) 3318, 2978, 1717, 1540, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, J=5.1 Hz, 1H), 7.31–7.42 (m, 5H), 7.28 (d, J=7.2 Hz, 2H), 7.12 (d, J=8.4 Hz, 1H), 6.99 (s, 1H), 6.90 (d, J=8.4 Hz, 1H), 5.06 (s, 3H), 4.59 (d, J=6.9 Hz, 1H), 3.72 (s, 3H), 3.01–3.11 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.2, 155.1, 154.7, 151.0, 136.7, 133.5, 132.8, 131.4, 131.3, 130.6, 128.7, 128.5, 127.8, 126.8, 125.0, 124.9, 113.1, 80.0, 70.5, 54.4, 52.4, 37.43, 28.3; HRMS (CI^+) calcd for $C_{28}H_{29}N_2O_7Br$ (M^+) 584.1158, found 585.1236.

3.27. Western fragment *32*

To a pressure vessel were added bromide **30** (41.0 mg, 0.0700 mmol), KF (36.6 mg, 0.630 mmol), (t-$Bu_3P)_2Pd$ (3.6 mg, 0.00700 mmol), NMP (0.35 mL), and methyl boroxine **31** (43.4 mg, 48.7 μL, 0.350 mmol) at rt. After heating at 80 °C for 13 h, the dark brown solution was quenched with satd aq NH_4Cl (15 mL), diluted with EtOAc (20 mL), and washed with H_2O (15 mL) and satd aq NaCl (15 mL). The dried extract ($MgSO_4$) was purified via chromatography over silica gel, eluting with 10–30% EtOAc/hexanes, to give **32** (19.9 mg, 0.0384 mmol, 54%) as a clear oil. $[\alpha]_D$ +34.9 (*c* 1.05, $CHCl_3$); IR (neat) 2980, 1745, 1715, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, J=7.6 Hz, 1H), 7.24–7.34 (m, 7H), 7.07 (dd, J=8.5, 2.2 Hz, 1H), 6.99 (d, J=2.2 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 5.03 (s, 2H), 5.02–5.05 (br s, 1H), 4.55–4.61 (m, 1H), 3.72 (s, 3H), 3.05 (d, J=5.0 Hz, 2H), 2.43 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.3, 155.1, 154.7, 151.0, 136.9, 131.8, 131.5, 130.6, 130.5, 130.1, 130.0, 129.7, 128.6, 128.4, 127.6, 126.7, 126.6, 113.0, 70.5, 54.5, 52.3, 37.5, 28.3, 18.3; HRMS (CI^+) calcd for $C_{29}H_{33}N_2O_7$ (M+H) 521.22878, found 521.22638.

4. Supplementary material

Supplementary material (experimental procedure for the preparation of compound **19**, copies of ^1H and ^{13}C NMR spectra, and crystallographic data for compounds **10**, **14**, and **34**) is available via the internet at www.sciencedirect.com.

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