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CYCLOADDITION REACTIONS OF AZIDE, FURAN, AND PYRROLE UNITS WITH BENZYNES GENERATED BY THE HEXADEHYDRO-DIELS–ALDER (HDDA) REACTION

Junhua Chen, Beeraiah Baire, and Thomas R. Hoye*

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA
hoye@umn.edu

This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday. May all be so fortunate as to share even a portion of Victor's vim for science, for discovery, for history, and for life.

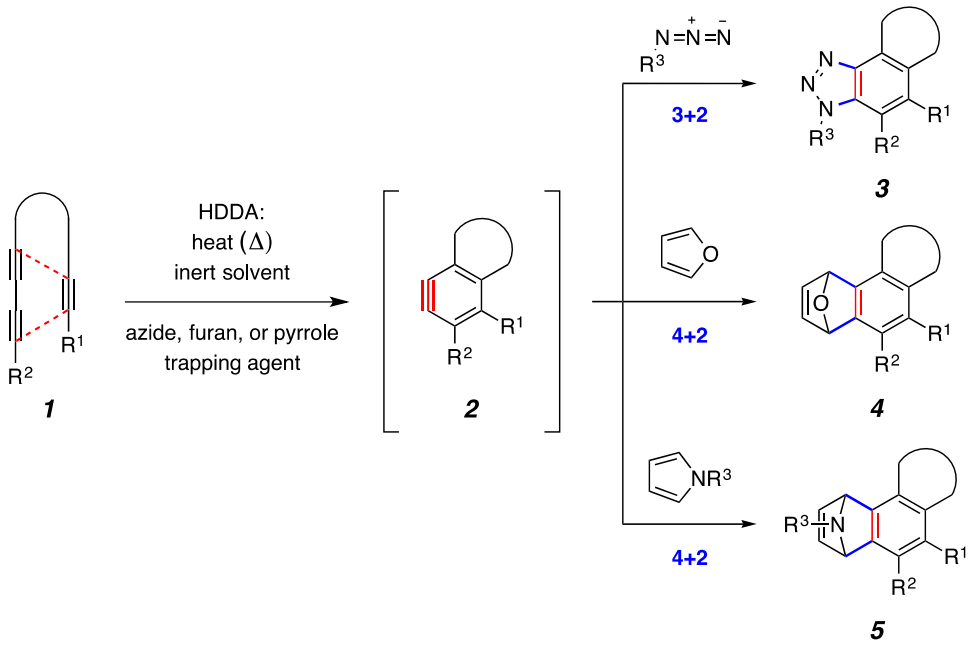
Abstract – Benzynes can be generated by the intramolecular thermal cycloisomerization of triynes–the title HDDA reaction. We report here that these can be trapped by cycloaddition reaction with trimethylsilyl azide (1,3-dipolar) or a furan or pyrrole (4+2 Diels–Alder).

INTRODUCTION

Reactions of *o*-benzyne (1,2-dehydrobenzene) and its derivatives have intrigued chemists for decades.[1] Cycloaddition of the 4+2 sense was identified at an early stage as one important mode of benzyne reactivity.[2] The use of competitive Diels-Alder trapping of 1,3-cyclohexadiene vs. furan was instrumental in establishing that benzynes prepared by different methods had, in fact, the same structure and reactivity.[3] More generally and of interest to the readership here, numerous methods of trapping benzynes to make heterocyclic compounds are known.[4] By now, many ways to produce benzynes or arynes are known,[5] but the most widely used method (and the last general one to be developed) is that of Kobayashi[6] in which an *o*-silylated aryl triflate is cleaved by fluoride ion to generate the highly reactive aryne.

We recently reported the generality of an intramolecular, formal 4+2 cycloaddition reaction of a triyne (**1**, Scheme 1) to produce a benzyne derivative (**2**).[7,8] This type of reaction process had been observed earlier, as described in reports from the research groups of Ueda,[9] Johnson,[10] and Sterenberg.[11] We now call this type of transformation a hexadehydro-Diels–Alder (HDDA) reaction,[7] a name that emphasizes the unique oxidation state of the substrate (a triyne) and the six-membered carbocyclic product (a benzyne) in

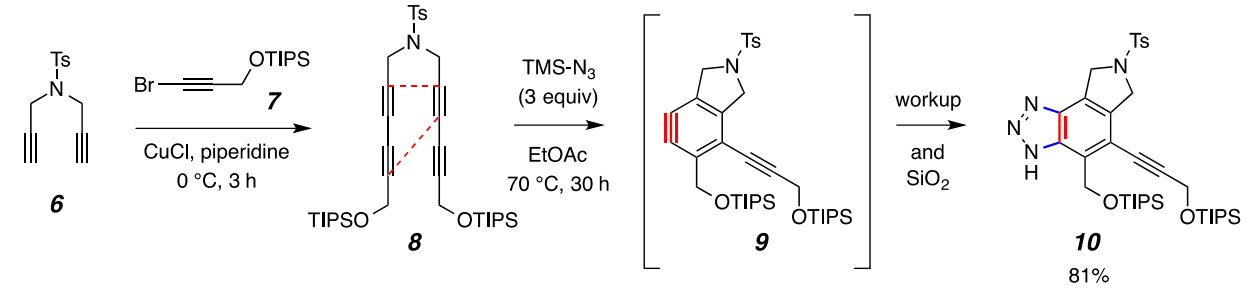
juxtaposition with the prototypical Diels–Alder cycloaddition (most commonly, between a 1,3-diene and an alkene dienophile to provide a cyclohexene product). Because of the purely thermal nature of this cycloisomerization process, the HDDA reaction uniquely produces the benzyne intermediate in the absence of the other reagents and byproducts that necessarily accompany all other methods of aryne generation.[5,12,13] One particularly captivating fact associated with this transformation is that the product benzyne is computed to be ca. 50 kcal•mol^{-1} more stable than the triyne precursor (!),[7,14] yet this intermediate, albeit aromatic, is rendered quite reactive because of its large strain energy (ca. 54 kcal•mol^{-1} [15]). We have probed the reactivity of several HDDA-generated benzynes with several types of cycloaddition addends (azide to **3**, furan to **4**, and pyrrole to **5**, Scheme 1) and report our observations here.



Scheme 1. Hexadehydro-Diels–Alder (HDDA) reaction: Triynes (cf. **1**) thermally cycloisomerize to benzynes (cf. **2**), which can be trapped, *in situ*, by cycloaddition partners like an azide (to **3**), furan (to **4**), or pyrrole (to **5**).

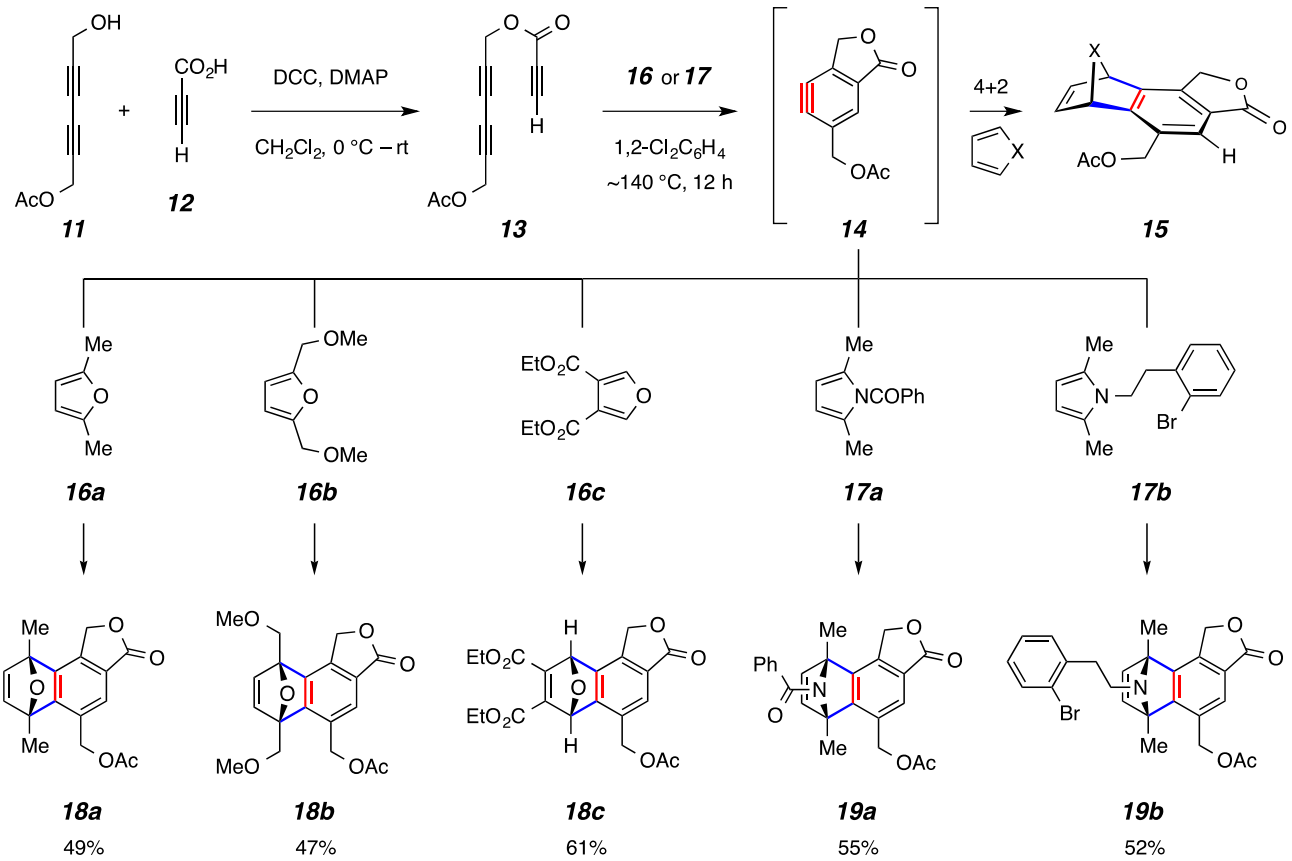
RESULTS AND DISCUSSION

We first studied the generation and trapping of benzyne **9** from the symmetrical, and therefore readily available, tetrayne substrate **8**. The latter was prepared by a cross-coupling of the known diyne **6**[16] and bromoalkyne **7**. When **8** was heated in the presence of the 1,3-dipole trimethylsilyl azide (3 equivalents) in the inert (i.e., non-participating) solvent ethyl acetate, the desilylated benzotriazole **10** was isolated in 81% yield following chromatographic purification.



Scheme 2. Dipolar cycloaddition (3+2) trapping reaction of benzyne **9**, derived from tetrayne **8** (0.022 M in ethyl acetate), with trimethylsilyl azide (3 equiv) provides the tricyclic benzotriazole adduct **10**.

We then explored trapping of benzyne **14** in a 4+2 sense by heterocyclic aromatic dienes. That is, triyne **13**, readily accessible by propiolate ester formation from the known alcohol **11**,[17] was heated in the presence of various furans (**16**) or pyrroles (**17**) to give adducts having the generic structure **15**. Both electron rich and poor furans (cf. **16a** vs. **16c**) are competent dienes, leading to adducts **18a** and **18c**, respectively. Substitution may or may not be present at C2 and C5 of the furans (cf. **18a** and **18b** vs. **18c**).[18] Pyrroles are also effective dienes for trapping **14**. Again, both electron withdrawing (**17a**) and donating (**17b**) substituents are tolerated on the pyrrole ring, resulting in formation of **19a** and **19b**, respectively, with comparable efficiency.



Scheme 3. Diels–Alder (4+2) trapping reactions of the benzyne **14** derived from triyne **13** (0.01 M in 1,2-dichlorobenzene) in the presence of 5-10 equiv (see Experimental) of furans **16** or pyrroles **17** provides the tetracycles **18** or **19**, respectively.

The results given in Scheme 3 are from trapping experiments in which a substantial excess of the diene was used (5-10 equiv). The unreacted diene **16b**, **17a**, or **17b** could be recovered during the chromatographic purification of the product with efficiencies of 51%, 95%, or 99%, respectively. We have also carried out one of the reactions using only a small excess of the heterocyclic diene. Namely, when **13** was heated in the presence of only 1.5 equivalents of the *N*-benzoylated pyrrole **17a**, adduct **19a** was isolated in a comparable, 53% yield, suggesting that this diene is a reasonably efficient trapping agent.

CONCLUSION

In summary, we have established that readily available classes of cycloaddition partners—namely, a 1,3-dipole and heterocyclic dienes–can serve as trapping agents for benzynes produced by the HDDA reaction of triynes. This conjunctive operation quickly establishes a relatively high degree of structural complexity. Among other things, the products of these reactions hold the potential for development as scaffolds for further elaboration, using orthogonal chemistries, into candidate ligand structures in drug discovery efforts.

EXPERIMENTAL

General Protocols

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Varian Inova or Bruker Avance spectrometer. ^{1}H NMR chemical shifts in $CDCl_3$ are referenced to TMS (δ 0.00 ppm). "nfom" refers to non-first order multiplets. ^{13}C NMR chemical shifts recorded in $CDCl_3$ are referenced to the chloroform resonance at δ 77.16 ppm. TMS is present in some of the ^{13}C NMR samples (δ ca. 0.0 ppm). ^{1}H resonances are reported in the following format: chemical shift in ppm [# of protons, multiplicity, coupling constant(s) in Hz, and assignment]. ^{1}H NMR assignments are indicated by italics and unique structure environment (e.g., C*H*$_2$Ar). Infrared spectra were determined with a Midac Corporation Prospect 4000 FT-IR spectrometer. Spectra were collected as thin films in attenuated total reflectance (ATR) mode on a 45° germanium window. High-resolution mass spectrometry (HRMS) measurements were made on samples ionized via electrospray ionization (ESI) on a Bruker BioTOF II (ESI-TOF) instrument using PEG as an internal standard/calibrant. Samples were introduced as solutions in methanol. Low resolution mass spectrometry (LRMS) measurements were made on samples ionized via electron impact (EI, 70 eV) on an Agilent 5975 mass selective detector during gas chromatography-mass spectrometry (GC-MS) analysis. Flash column chromatography was performed on silica gel (230-400 mesh). Thin layer chromatography was performed on plastic-backed plates coated with silica gel and visualized using a solution of phosphomolybdic acid or potassium permanganate and/or by UV detection. Piperidine was

degassed by purging with N_2 gas immediately prior to use in cross-coupling reactions. Anhydrous methylene chloride was taken from a column of activated alumina immediately prior to use. Reaction temperatures listed are the temperature of the external heating (or cooling) bath. HDDA reactions were typically performed in a screw-capped vial or culture tube fitted with an inert, teflon-lined cap, including those that were carried out at temperatures greater than the boiling point of the solvent.

[(3-Bromoprop-2-yn-1-yl)oxy]triisopropylsilane (7)

TIPSCl (1.27 g, 6.6 mmol) was added to a solution of imidazole (449 mg, 6.6 mmol), DMAP (81 mg, 0.66 mmol), and 3-bromo-2-propyn-1-ol[19] (804 mg, 6.0 mmol) in dichloromethane (DCM, 20 mL) at 0 °C with stirring. After 2 h the reaction mixture was diluted with water (30 mL) and extracted with DCM (2x20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (19:1, hexanes:EtOAc) gave the silyl ether **7** (1.57 g, 5.4 mmol, 90%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.40 (2H, s, CH_2OTIPS), 1.17-1.05 (3H, m, J = 5.5 Hz, Si(C*H*$(CH_3)_2)_3$), and 1.08 [18H, d, J = 5.5 Hz, Si(CH(C*H*$_3)_2)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.7 (*C*-CH_2OTIPS), 52.9 (*C*H_2OTIPS), 44.4 (C-Br), 17.9 [SiCH(*C*$H_3)_2$], and 12.0 [Si*C*H$(CH_3)_2$]. IR (neat): 2943, 2866, 2220, 1463, 1368, 1260, 1102, 1093, 1070, 1014, 997, 919, 882, 748, 688, 671, and 648 cm^{-1}. LRMS: (EI, 70 eV, *m/z*): 290/292, 247/249, and 205/207. TLC: R_f = 0.6 (19:1 hexanes:EtOAc).

4-Methyl-*N*,*N*-bis{6-[(triisopropylsilyl)oxy]hexa-2,4-diyn-1-yl}benzenesulfonamide (8)

The preparation of and characterization data for this compound have recently been reported: "CuCl (40 mg, 0.4 mmol) was added to a solution of 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)-benzenesulfonamide (**6**)[16] (494 mg, 2.0 mmol) and [(3-bromoprop-2-yn-1-yl)oxy]triisopropylsilane (**7**) (1.3 g, 4.4 mmol) in freshly deaerated piperidine (8 mL, 0.4 M) at 0 °C. After 3 h the reaction mixture was partitioned between EtOAc (20 mL) and saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted twice with EtOAc (2x15 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (19:1, hexanes:EtOAc) gave tetrayne **8** (1.08 g, 1.62 mmol, 81%). On some occasions following nominally this same procedure resulted in considerably reduced yields. There likely is an important unidentified variable that is important to control. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (2H, d, J = 8.0 Hz, Ar-H), 7.31 (2H, d, J = 8.0 Hz, Ar-H), 4.41 (4H, s, CH_2OTIPS), 4.20 (4H, s, N-CH_2), 2.43 (3H, s, Ar-CH_3), 1.16-1.04 (6H, m, J = 5.5 Hz, OSi[C*H*$(CH_3)_2]_3$), and 1.07 (36H, d, J = 5.5 Hz, OSi[CH(C*H*$_3)_2]_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 134.6, 129.8, 127.8, 77.6, 71.3, 70.3, 68.3, 52.2, 37.3, 21.6, 17.9, and 11.9 ppm. IR (neat): 2943, 2866, 1463, 1356, 1165, 1093, 1069, 996, 884, 748, and 685 cm^{-1}. HR ESI-MS: $[C_{37}H_{57}NNaO_4SSi_2]^+$ requires 690.3439; found 690.3446. TLC: R_f = 0.35 (9:1 hexanes:EtOAc).[20]

7-Tosyl-4-{[(triisopropylsilyl)oxy]methyl}-5-{3-[(triisopropylsilyl)oxy]prop-1-yn-1-yl}-1,6,7,8-tetrahydro-[1,2,3]triazolo[4,5-e]isoindole (10)

A solution of tetrayne **8** (30 mg, 0.045 mmol) and Me_3SiN_3 (16 mg, 0.135 mmol) in EtOAc (2 mL, 0.022 *M*) was kept at 70 °C in a screw-capped vial. After 30 h the reaction mixture was concentrated. Purification of the residue by flash column chromatography (3:2, hexanes:EtOAc) yielded the benzotriazole **10** (26 mg, 0.036 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* = 8.5 Hz, Ar-H), 7.32 (2H, d, *J* = 8.5 Hz, Ar-H), 5.23 (2H, s, C*H*$_2$OAr), 5.01 (2H, br s, N-C*H*$_2$), 4.77 (2H, br t, *J* = 3.0 Hz, N-C'*H*$_2$), 4.68 (2H, s, C*H*$_2$OTIPS), 2.40 (3H, s, Ar-C*H*$_3$), 1.31-1.10 [6H, nfom, SiC*H*(CH$_3$)$_2$], 1.13 [18H, d, *J* = 6.0 Hz, SiCH(C*H*$_3$)$_2$], and 1.10 [18H, d, *J* = 6.0 Hz, SiCH(C*H*$_3$)$_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 139.8, 134.8, 133.8, 132.1, 130.0, 127.6, 127.3, 124.6, 112.6, 98.8, 78.0, 63.6, 54.2, 53.1, 52.4, 21.5, 18.0, 17.9, 12.0, and 11.9. IR (neat): 3263, 2944, 2866, 1463, 1351, 1252, 1165, 1095, 1066, 1015, 996, 919, 882, 815, and 767 cm^{-1}. HR ESI-MS: $[C_{37}H_{58}N_4NaO_4SSi_2]^+$ requires 733.3610; found 733.3627. TLC: R_f = 0.35 (3:2 hexanes:EtOAc).

6-Acetoxyhexa-2,4-diyn-1-yl Propiolate (13)

To a solution of diyne alcohol **11**[17] (1.38 g, 9.1 mmol) and DMAP (0.11 g, 0.91 mmol) in 45 mL of DCM was added propiolic acid (**12**, 1.2 mL, 19.4 mmol) dropwise. The solution was cooled to 0 ºC and DCC (2.8 g, 13.6 mmol; CAUTION: sensitizer) was added in one portion. The reaction mixture, which turned brown quickly, was stirred at 0 °C for 2 h. The solvent was removed *in vacuo* and EtOAc (20 mL) was added to the residue. The precipitate (*N,N*'-dicyclohexylurea) was removed by vacuum filtration and thoroughly washed with additional EtOAc (15 mL). The filtrate was washed with 1M HCl (20 mL), satd $NaHCO_3$ (20 mL), and brine; dried over Na_2SO_4; and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (5:1, hexanes:EtOAc) provided the ester **13** (1.02 g, 55%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.85 (2H, s, OC*H*$_2$), 4.74 (2H, s, OC*H*$_2$), 2.98 (1H, s, CC*H*), and 2.11 (3H, s, OAc); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 151.7, 76.4, 74.4, 73.8, 72.1, 71.5, 70.2, 53.8, 52.3, and 20.7; IR (neat): 3281, 3261, 2992, 2940, 2122, 1746, 1723, 1430, 1378, 1358, 1261, 1209, 1031, and 763 cm^{-1}; HR ESI-MS: $[C_{11}H_8NaO_4]^+$ (M+Na$^+$) requires 227.0315; found 227.0332; TLC: R_f = 0.24 (3:1 hexanes:EtOAc).

1-(2-Bromophenethyl)-2,5-dimethyl-1*H*-pyrrole (17b)

Acetic acid (0.6 mL, 10.5 mmol) was added to a solution of 2-(*o*-bromophenyl)ethylamine[21] (2.13 g, 10.7 mmol) and hexane-2,5-dione (1.46 g, 12.8 mmol) in toluene (55 mL). The resulting biphasic reaction mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography (10:1, hexanes:EtOAc) to give the pyrrole **17b** (2.46 g, 83%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (1H, dd, *J* = 8.0, 1.4 Hz, BrAr*H*$_o$), 7.22 (1H, ddd, *J* =

7.5, 7.5, 1.4 Hz, BrArH_p), 7.11 (1H, ddd, J = 7.7, 7.6, 1.8 Hz, BrArH_m'), 7.04 (1H, dd, J = 7.5, 1.9 Hz, BrArH_m), 5.76 [2H, s, $C_{pyrrole}H$ (2x)], 3.96 (2H, t, J = 7.7 Hz, NCH_2), 3.04 (2H, t, J = 7.8 Hz BrArCH_2), and 2.19 [6H, s, Me (2x)]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 133.0, 131.3, 128.6, 127.9, 127.6, 124.6, 105.4, 43.5, 37.9, and 12.5; IR (neat): 3099, 3054, 3007, 2973, 2931, 2863, 1739, 1718, 1568, 1519, 1472, 1440, 1407, 1357, 1300, 1021, and 750 cm^{-1}; LRMS: (EI, 70 eV, *m/z*): 279/277, 198, 183, 108; TLC: R_f = 0.56 (5:1 hexanes:EtOAc).

General procedure for the HDDA cascade reactions of triyne 13 with furans 16a-c and pyrroles 17a-b

A solution of triyne (~20 mg) in *o*-dichlorobenzene (~10 mL, 0.01 M in triyne substrate) was heated in the presence of 10 equiv of the furan **16a-c** or acylpyrrole **17a** (5 equiv in the case of pyrrole **17b**) under an atmosphere of nitrogen at 135–140 °C for 12 h. The reaction mixture was cooled and purified by flash column chromatography. The solvent was removed by initially eluting the column with hexanes. The excess trapping reagent was then recovered if desired (typically, 3:1, hexanes:EtOAc) and the more polar product was then eluted with a yet more polar solvent mixture (typically, 1:1, hexanes:EtOAc or pure EtOAc).

(6,9-Dimethyl-3-oxo-1,3,6,9-tetrahydro-6,9-epoxynaphtho[1,2-*c*]furan-5-yl)methyl Acetate (18a)

Product **18a** was isolated in 49% yield following chromatographic purification using 1:1 (hexanes:EtOAc) as the elution solvent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, s, ArH), 6.89 (1H, d, J = 5.3 Hz, CH_a=CH$_b$), 6.87 (1H, d, J = 5.3 Hz, CH$_a$=CH_b), 5.43 (1H, d, J = 14.8 Hz, CH_aH$_b$), 5.32 (1H, d, J = 13.1 Hz, CH_a'H$_b$'), 5.29 (1H, d, J = 15.1 Hz, CH$_a$$H_b$), 5.19 (1H, d, J = 12.6 Hz, CH$_a$'H_b'), 2.10 (3H, s, OAc), 2.06 (3H, s, Me), and 1.94 (3H, s, Me'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.0, 158.5, 148.5, 147.2, 147.0, 135.6, 130.0, 125.1, 123.6, 90.8, 87.8, 67.8, 62.4, 20.9, 17.2, and 16.0 ppm; IR (neat): 2982, 2937, 1762, 1742, 1450, 1381, 1358, 1308, 1228, 1136, 1106, 861, and 766 cm^{-1}; HR ESI-MS: $[C_{17}H_{16}NaO_5]^+$ (M+Na$^+$) requires 323.0890; found 323.0885; TLC: R_f = 0.3 (1:1 hexanes:EtOAc).

[6,9-bis(Methoxymethyl)-3-oxo-1,3,6,9-tetrahydro-6,9-epoxynaphtho[1,2-*c*]furan-5-yl]methyl Acetate (18b)

Product **18b** was isolated in 47% yield following chromatographic purification using 1:3 (hexanes:EtOAc) as the elution solvent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, s, ArH), 7.02 (1H, d, J = 5.4 Hz, CH_a=CH$_b$), 6.91 (1H, d, J = 5.4 Hz, CH$_a$=CH_b), 5.32 (1H, d, J = 12.7 Hz, CH_aH$_b$), 5.31 (1H, d, J = 15.4 Hz, CH_a'H$_b$'), 5.25 (1H, d, J = 15.4 Hz, CH$_a$'H_b'), 5.17 (1H, d, J = 12.7 Hz, CH$_a$$H_b$), 4.41 (1H, d, J = 11.3 Hz, MeOCH_aH$_b$), 4.20 (1H, d, J = 11.3 Hz, MeOCH$_a$$H_b$), 4.12 (1H, d, J = 10.1 Hz, MeOCH_a'H$_b$'), 4.11 (1H, d, J = 10.2 Hz, MeOCH$_a$'H_b'), 3.57 (3H, s, OMe), 3.52 (3H, s, OMe'), and 2.09 (3H, s, OAc);

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.5, 155.4, 146.2, 145.0, 143.8, 136.8, 130.6, 125.0, 124.2, 94.1, 90.7, 70.2, 70.1, 69.2, 63.3, 59.9, 59.8, and 21.1 ppm; IR (neat): 2973, 2938, 1762, 1742, 1471, 1456, 1380, 1374, 1231, 1176, 1110, 1019, and 765 cm^{-1}; HR ESI-MS: $[C_{19}H_{20}NaO_7]^+$ ($M+Na^+$) requires 383.1101; found 383.1110; TLC: R_f = 0.15 (1:1 hexanes:EtOAc).

Diethyl 5-(Acetoxymethyl)-3-oxo-1,3,6,9-tetrahydro-6,9-epoxynaphtho[1,2-*c*]furan-7,8-dicarboxylate (18c)

Product **18c** was isolated in 61% yield following chromatographic purification using 2:1 (hexanes:EtOAc) as the elution solvent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (1H, s, Ar*H*), 6.32 (1H, d, *J* = 1.2 Hz, bridgehead C*H*$_a$), 6.07 (1H, d, *J* = 1 Hz, bridgehead C*H*$_b$), 5.45 (1H, d, *J* = 15.2 Hz, C*H*$_a$H$_b$), 5.38 (1H, d, *J* = 13.0 Hz, C*H*$_a$'H$_b$'), 5.34 (1H, d, *J* = 15.2 Hz, CH$_a$*H*$_b$), 5.27 (1H, d, *J* = 13.0 Hz, CH$_a$'*H*$_b$'), 4.281 (1H, dq, *J* = 10.8, 7.2 Hz, CH$_3$C*H*$_a$H$_b$O), 4.274 (2H, q, *J* = 7.1 Hz, CH$_3$'C*H*$_2$'O), 4.272 (1H, dq, *J* = 11.0, 7.1 Hz, CH$_3$CH$_a$*H*$_b$O), 2.14 (3H, s, OAc), 1.34 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), and 1.33 (3H, t, *J* = 7.1 Hz, OCH$_2$'C*H*$_3$'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 169.9, 162.6, 162.0, 152.5, 150.3, 150.2, 141.8, 138.0, 131.6, 125.1, 124.8, 83.8, 83.2, 68.4, 62.7, 62.21, 62.18, 21.0, 14.3, and 14.2 ppm; IR (neat): 2985, 2940, 1767, 1741, 1636, 1447, 1372, 1303, 1225, 1106, 1015, 865, and 766 cm^{-1}; HR ESI-MS: $[C_{19}H_{20}NaO_7]^+$ ($M+Na^+$) requires 439.1000; found 439.1021; TLC: R_f = 0.4 (1:1 hexanes:EtOAc).

(10-Benzoyl-6,9-dimethyl-3-oxo-1,3,6,9-tetrahydro-6,9-epiminonaphtho[1,2-*c*]furan-5-yl)methyl Acetate (19a)

Product **19a** was isolated in 55% yield following chromatographic purification using 2:1 (hexanes:EtOAc) as the elution solvent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (1H, s, Ar*H*), 7.48-7.52 [3H, overlapping m, (O=C)Ar*H*$_p$ and (O=C)Ar*H*$_o$], 7.37 [2H, dd, *J* = 8.6, 7.3 Hz, (O=C)Ar*H*$_m$], 6.80 (1H, d, *J* = 5.5 Hz, C*H*$_a$=CH$_b$), 6.78 (1H, d, *J* = 5.5 Hz, CH$_a$=C*H*$_b$), 5.36 (1H, d, *J* = 12.8 Hz, C*H*$_a$H$_b$), 5.35 (1H, d, *J* = 14.9 Hz, C*H*$_a$'H$_b$'), 5.25 (1H, d, *J* = 14.5 Hz, CH$_a$'*H*$_b$'), 5.22 (1H, d, *J* = 12.4 Hz, CH$_a$*H*$_b$), 2.09 (3H, s, OAc), 2.04 (3H, s, NCMe), and 1.74 (3H, s, NCMe'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3, 170.5, 170.0, 158.2, 148.3, 147.8 (alkene), 147.2 (alkene'), 137.4, 136.4, 132.0 [(O=C)Ar*C*$_{o/p}$], 131.2, 129.0 [(O=C)Ar*C*$_{o/p}$], 128.4 [(O=C)Ar*C*$_m$], 125.4 (Ar*C*H), 123.7, 76.9, 74.1, 68.1 (*C*H$_2$O), 62.7 (*C*H$_2$O'), 21.1 (*C*H$_3$C=O), 17.7 (NC*C*H$_3$), and 16.5 (NC*C*H$_3$'), (assignments deduced from HMQC data); IR (neat): 3062, 2976, 2938, 1764, 1742, 1650, 1448, 1375, 1328, 1232, 1112, 1021, and 766 cm^{-1}; HR ESI-MS: $[C_{24}H_{21}NNaO_5]^+$ ($M+Na^+$) requires 426.1312; found 426.1274; TLC: R_f = 0.36 (1:1 hexanes:EtOAc).

{10-(2-Bromophenethyl)-6,9-dimethyl-3-oxo-1,3,6,9-tetrahydro-6,9-epiminonaphtho[1,2-*c*]furan-5-yl}methyl Acetate (19b)

Product **19b** was isolated in 52% yield following chromatographic purification using EtOAc as the elution solvent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 [1H, s, $(AcOCH_2)ArH$], 7.48 (1H, dd, J = 8.0, 1.2 Hz, $BrArH_o$), 7.20 (1H, ddd, J = 7.5, 6.9, 1.2 Hz, $BrArH_p$), 7.18 (1H, dd, J = 7.6, 2.1 Hz, $BrArH_{m'}$), 7.04 (1H, ddd, J = 8.0, 7.0, 2.1 Hz, $BrArH_m$), 6.77 (1H, d, J = 5.6 Hz, CH_a=CH_b), 6.76 (1H, d, J = 5.6 Hz, CH_a=CH_b), 5.41 (1H, d, J = 14.8 Hz, CH_aH_b), 5.29 (1H, d, J = 14.8 Hz, CH_aH_b), 5.27 (1H, d, J = 12.7 Hz, CH_a'H_b'), 5.20 (1H, d, J = 12.7 Hz, CH_a'H_b'), 2.96 (1H, ddd, J = 13.0, 10.0, 6.7 Hz, $ArCH_aH_b$), 2.94 (1H, ddd, J = 13.1, 9.9, 6.7 Hz, $ArCH_aH_b$), 2.40 (1H, ddd, J = 14.0, 9.9, 7.1 Hz, NCH_aH_b), 2.33 (1H, ddd, J = 13.9, 10.1, 6.9 Hz, NCH_aH_b), 2.10 (3H, s, OAc), 1.98 [3H, s, $CH_3C(N)C_{Ar}C_{Ar}CH_2OAc$], and 1.83 [3H, s, $CH_3C(N)C_{Ar}C_{Ar}CH_2OC(O)Ar$]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (Me*C*=O), 170.2 (Ar*C*=O), 158.5 [$MeC(N)C_{Ar}C_{Ar}CH_2OAc$], 148.7, 147.5 (2x, alkenes), 139.5 (BrC=CCH_2), 137.9, 133.0, 132.2, 131.1 (BrC=*C*H), 128.2, 127.7, 125.3 (Ar*C*H), 124.4 (Br*C*), 123.7, 78.8 (Me*C*N), 75.7 (Me*C*′N), 68.2 [$ArCH_2OC(O)Ar$], 62.8 (CH_2OAc), 45.3, 38.7, 21.1 (CH_3C=O), 16.4 [$CH_3C(N)C_{Ar}C_{Ar}CH_2OAc$], and 14.9 [$CH_3C(N)C_{Ar}C_{Ar}CH_2OC(O)Ar$], (assignments deduced from HSQC and HMBC data); IR (neat): 2989, 2934, 2889, 2818, 1762, 1747, 1638, 1452, 1373, 1230, 1104, 1021, 868, and 768 cm^{-1}; HR ESI-MS: $[C_{25}H_{24}BrNNaO_4]^+$ ($M+Na^+$) requires 504.0781, 506.0761; found 504.0807, 506.0793; TLC: R_f = 0.12 (EtOAc).

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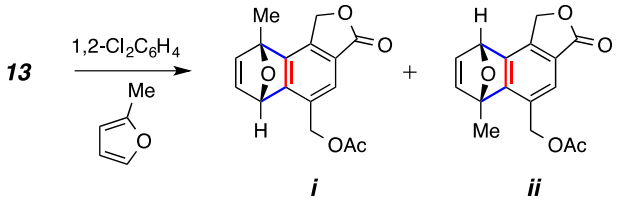

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