Synthesis of Multifunctionalized Furans from Diazoallenes: Rearrangement of 6-Methylenebicyclo[3.1.0]hexanes

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Dedicated to Professor Martin F. Semmelhack on the occasion of his 65th birthday

Abstract: The synthesis of annulated tetrasubstituted furans using diazoallene precursors is described. This reaction provides efficient access to synthetically useful furan intermediates, which are otherwise difficult to obtain.

Key words: diazoallene, [3+2] cycloaddition, multifunctionalized furans

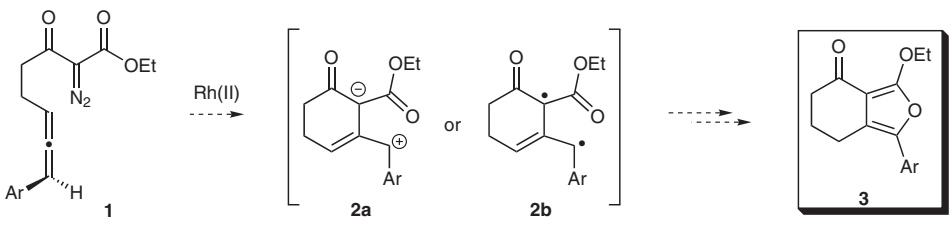
Substituted furans are found in a wide range of natural products and also serve as important synthetic intermediates.[1] As a result of the ubiquitous nature of furans, many strategies have emerged to address their installation. For example, the Feist–Bénary[2] and Paal–Knorr[3] furan syntheses are readily applied to the synthesis of annulated furans. However, tetrasubstituted annulated furans have been especially challenging to access, and often require multiple functionalizations of an initially installed furan core. As part of a general program to define new strategies for annulating five-membered carbo- and heterocycles to other rings,[4] we envisioned a sequence that would accomplish both the construction and annulation of tetrasubstituted furans. As a starting point for our studies, we targeted the synthesis of bicycles such as **3** (Scheme 1), which could be directly applied to the synthesis of a variety of natural products.

We envisaged that diazoallenes such as **1** could serve as precursors to **3** via a formal [3+2] cycloaddition/isomerization sequence initiated by rhodium complexes. This would presumably begin with decomposition of the diazo group to yield a rhodacarbenoid, which upon interaction with the allene (via a heterolytic or homolytic process) would yield either **2a** or **2b**, respectively, reminiscent of trimethylenemethane (TMM) intermediates.[5] At this stage, valence recombination of **2** followed by alkene isomerization was expected to give aromatic tetrasubstituted furan **3**.

To test this hypothesis, we embarked on a synthesis of diazoallenes **1**, which began with the synthesis of alcohol **7** as outlined in Scheme 2.

The synthesis of **7** commenced with the addition of the lithium acetylide generated from alkyne **4** to 4-*tert*-butyldimethylsilyloxybutanal to provide propargylic alcohol **5** in excellent yield. Sequential treatment of **5** with *o*-nitrobenzenesulfonyl hydrazide (*o*-NBSH), diethyl azodicarboxylate (DEAD) and PPh_3, following the Myers protocol,[6] gave allenol **7** after deprotection of the primary hydroxyl group. A Swern oxidation of alcohol **7** (Scheme 3) yielded an intermediate aldehyde, which was reacted with ethyl diazoacetate in the presence of DBU to provide **8**. Direct oxidation of alcohol **8** to the corresponding ketone proved to be difficult, consistent with the observations of others.[7] This unanticipated hurdle was circumvented by the treatment of **8** with $Rh_2(OAc)_4$ to afford β-keto ester **9**. At this stage, diazo installation using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) furnished **10** in good yield.

Access to **10** set the stage for the key annulation/cyclization sequence to access tetrasubstituted furans such as **13**. In the event, dropwise addition of **10** into a CH_2Cl_2 solution of $Rh_2(OAc)_4$ (3 mol%) at 23 °C yielded methylenecyclopropane **11** as an inconsequential mixture of isomers in 73% yield after stirring for 4 hours. Upon heating at 120 °C for 12 hours in toluene, **11** was smoothly converted to furan **13** in excellent yield, presumably via the intermediacy of **12** (Scheme 4).



Scheme 1

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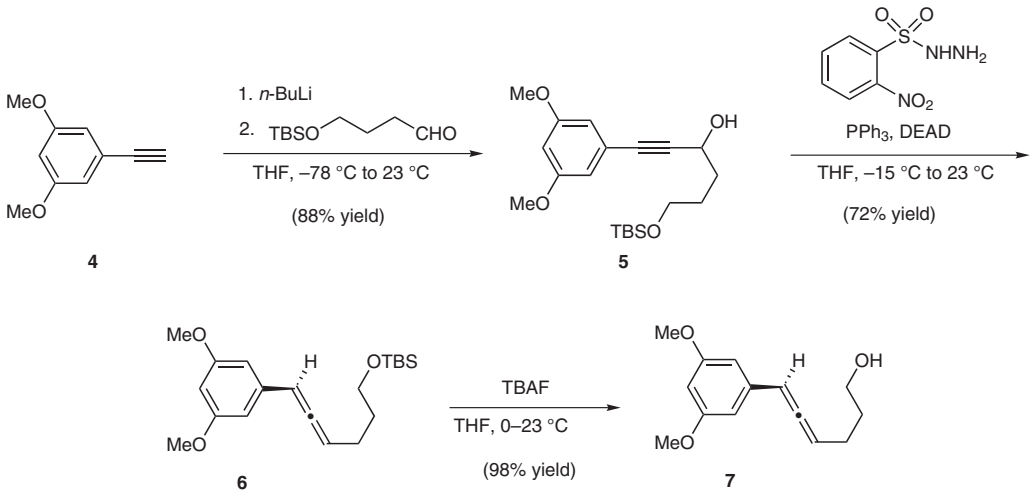
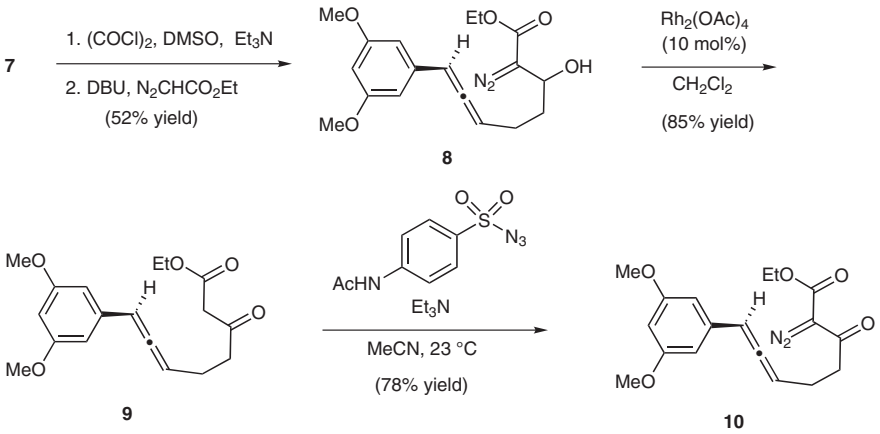
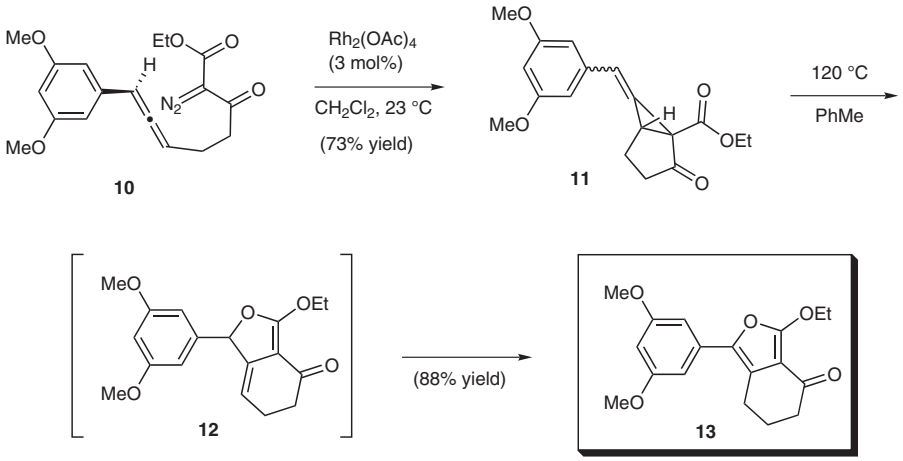


Scheme 2



Scheme 3



Scheme 4

Tetrasubstituted furan **13** provided crystals suitable for X-ray crystallography. The ORTEP depiction of **13**, shown in Figure 1 corroborates the assigned structure.

A preliminary survey has revealed this conversion of diazoallenes to annulated furans to be quite general for a range of substrates as shown in Table 1. A series of aromatic groups are readily tolerated at the terminus of the allene (entries 1–3) as are alkyl substituents (entries 4 and 5). Additionally, sensitive groups such as acetonides and activated allylic ethers (entry 5) easily participate in this

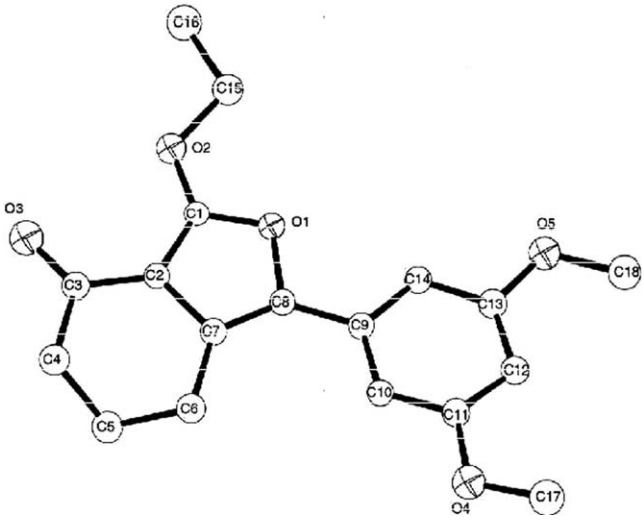
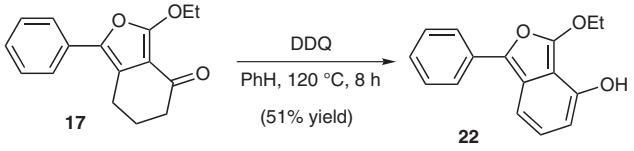


Figure 1 ORTEP illustration of furan 13 with thermal ellipsoids drawn at 50% probability (hydrogens are omitted for clarity).



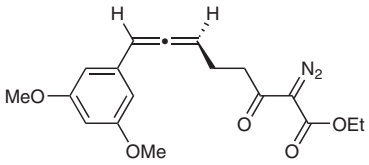
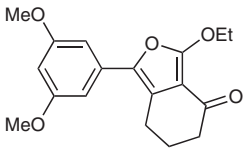
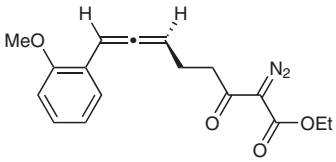
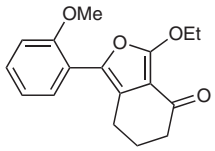
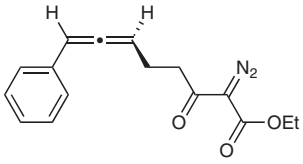
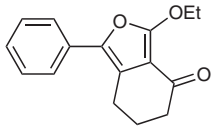
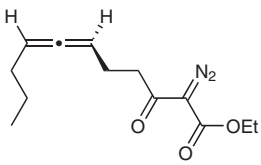
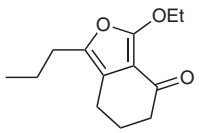
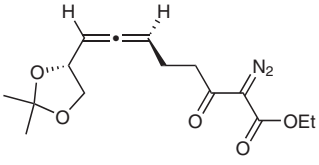
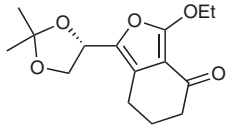
Scheme 5

transformation to provide products poised for further manipulation.

The furan products (e.g. **17**, Scheme 5) can be further elaborated to isobenzofurans via DDQ-promoted dehydrogenation in preparation for further functionalization (e.g. cycloaddition reactions).

In conclusion, we have developed an efficient strategy for the synthesis of annulated tetrasubstituted furans, which possess functionality that should allow for further synthetic operations. The synthesis strategy relies on a formal [3+2] cycloaddition/isomerization sequence of allenyl rhodacarbenoids that are generated from diazoallene precursors.[8] The Myers protocol for allene formation provides a powerful entry to the diazoallene substrates.

Table 1 Preparation of Tetrasubstituted Furans from Diazoallenes

Entry	Diazoallene	Product	Yield (%)
1	 **10**	 **13**	64
2	 14	 **15**	56
3	 **16**	 **17**	47
4	 **18**	 **19**	55
5	 **20**	 **21**	52

All air- or moisture-sensitive reactions were conducted in flame-dried glassware under N_2 using anhydrous, deoxygenated solvents. Toluene, MeCN, CH_2Cl_2, and Et_3N were distilled under N_2 from CaH_2 immediately prior to use and THF was distilled under N_2 from sodium benzophenone ketyl. All other reagents were purchased from Aldrich or Lancaster and used without further purification. Melting points were measured on a Büchi melting point apparatus and are corrected using vanillin (mp 80–81 °C) as a standard. Reaction temperatures were controlled by an IKAmag temperature modulator. TLC was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV and anisaldehyde stain. Fisher silica gel 240–400 mesh (particle size 0.032–0.063) was used for flash chromatography. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 (at 500 MHz and 125 MHz, respectively), on a Bruker AVB-400 (at 400 MHz and 100 MHz, respectively) and AV-300 (at 300 MHz and 75 MHz, respectively) in $CDCl_3$ at 23 °C, unless otherwise stated. Chemical shifts were referenced to the residual solvent peak, which was set at 7.26 ppm for ^1H and 77.23 ppm (center peak) for ^{13}C spectra. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in cm^{-1}. High-resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility.

6-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(3,5-dimethoxyphenyl)hex-1-yn-3-ol (5); Typical Procedure

A flame-dried, round-bottom flask was charged with anhyd THF (23 mL) and 1-ethynyl-3,5-dimethoxybenzene (1.15 g, 7.09 mmol). The solution was cooled to –78 °C and *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M in hexanes) was added slowly over 20 min. The solution was allowed to stir for 15 min at –78 °C and slowly warmed to 0 °C. After stirring at 0 °C for 20 min, the solution was cooled down again to –78 °C. 4-*tert*-Butyldimethylsilyloxybutanal (1.474 g, 7.80 mmol) was added slowly over 20 min. The mixture was stirred for an additional 15 min at –78 °C, then the acetone bath was removed and the mixture was allowed to warm to 23 °C. After 1 h, sat. aq NH_4Cl solution (30 mL) was added slowly and stirring continued for 15 min. The mixture was diluted with EtOAc (40 mL) and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the concentrate was purified by flash column chromatography (2:1 hexanes–EtOAc) to obtain the pure propargylic alcohol **5**; yield: 2.14 g (86%); dense liquid; R_f 0.37 (2:1 hexanes–EtOAc).

IR (neat): 3386, 2954, 1597, 1421, 1254 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.87 (s, 9 H), 1.64–1.99 (m, 4 H), 3.60–3.70 (m, 9 H), 4.60 (t, *J* = 6.0 Hz, 1 H), 6.38 (t, *J* = 2.4 Hz, 1 H), 6.53 (t, *J* = 2.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 124.3, 109.5, 101.7, 90.0, 84.6, 63.3, 62.5, 55.4, 35.4, 28.7, 26.0, 18.4, –5.2.

***tert*-Butyl{[6-(3,5-dimethoxyphenyl)hexa-4,5-dienyl]oxy}dimethylsilane (6); Typical Procedure**

DEAD (0.69 mL, 4.5 mmol) was added to a solution of Ph_3P (1.18 g, 4.5 mmol) in THF (12 mL) at –15 °C. After 8 min, a solution of propargylic alcohol **5** (1.09 g, 3.0 mmol) in THF (9 mL) was added to the yellow mixture, followed 30 min later by a solution of NBSH (0.97 g, 4.5 mmol) in THF (12 mL). The resulting suspension was held at –15 °C for 1 h, after which time TLC analysis indicated complete consumption of the starting alcohol **5**. The mixture was warmed to 23 °C and allowed to stand for 4 h. Concentration of the mixture and purification of the residue by flash column chromatography (20:1 hexanes–EtOAc) afforded allene **6** as yellow oil; yield: 0.749 g (72%); dense liquid; R_f 0.38 (9:1 hexanes–EtOAc).

IR (neat): 2954, 1604, 1472, 1205, 1155 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.87 (s, 9 H), 1.61–1.73 (m, 2 H), 2.14–2.22 (m, 2 H), 3.65 (t, *J* = 6.3 Hz, 2 H), 3.76 (s, 6 H), 5.58 (dt, *J* = 6.6, 6.3 Hz, 1 H), 6.05 (dt, *J* = 6.6, 3.0 Hz, 1 H), 6.30 (t, *J* = 2.1 Hz, 1 H), 6.44 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4, 161.1, 137.4, 104.8, 99.2, 95.3, 95.1, 62.7, 55.5, 32.3, 26.2, 25.2, 18.5.

6-(3,5-Dimethoxyphenyl)hexa-4,5-dien-1-ol (7); Typical Procedure

A flame-dried, round-bottom flask was charged with anhyd THF (20 mL) and allene **6** (0.696 g, 2.0 mmol). The solution was cooled to 0 °C and TBAF (2.0 mL, 2.0 mmol, 1.0 M in THF) was added slowly over 30 min. The solution was allowed to stir for 15 min at 0 °C and slowly warmed up to 23 °C. After stirring at 23 °C for 4 h, sat. aq NH_4Cl solution (20 mL) was added slowly and stirring continued for 15 min. The mixture was diluted with EtOAc (40 mL) and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the concentrate was purified by flash column chromatography (1:1 hexanes–EtOAc) to obtain the pure alcohol **7**; yield: 0.460 g (98%); dense liquid; R_f 0.32 (1:1 hexanes–EtOAc).

IR (neat): 3362, 2937, 1604, 1473, 1204 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (tt, *J* = 6.6, 7.2 Hz, 2 H), 2.14–2.22 (m, 3 H), 3.65 (t, *J* = 6.6 Hz, 2 H), 3.75 (s, 6 H), 5.57 (q, *J* = 6.6 Hz, 1 H), 6.05 (dt, *J* = 6.3, 3.0 Hz, 1 H), 6.29 (t, *J* = 2.1 Hz, 1 H), 6.43 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4, 161.0, 137.1, 104.7, 99.2, 95.3, 94.8, 62.2, 55.4, 31.9, 25.0.

Ethyl 8-(3,5-Dimethoxyphenyl)-3-oxoocta-6,7-dienoate (9); Typical Procedure

To a solution of oxalyl chloride (0.33 mL, 3.84 mmol) in CH_2Cl_2 (5.5 mL) at –50 °C was added DMSO (0.53 mL, 3.65 mmol). After stirring for 15 min, alcohol **7** (0.45 g, 1.92 mmol) in CH_2Cl_2 (5.5 mL) was added and the mixture was stirred for 30 min. Et_3N (1.68 mL, 11.5 mmol) was then added and after stirring for 30 min, the reaction was warmed to 23 °C over 2 h and quenched with H_2O (15 mL) and aq sat. NH_4Cl (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The product was filtered through a plug of silica gel (66% EtOAc in hexanes) to furnish the corresponding aldehyde as a colorless oil, which was immediately taken on to the next step. To a solution of this aldehyde in MeCN (20 mL) was added ethyl diazoacetate (0.53 mL, 3.84 mmol) followed by DBU (53.8 μL, 0.37 mmol) dropwise via syringe. The mixture was stirred at 23 °C overnight and concentrated. The residue was purified by flash column chromatography (2:1 hexanes–EtOAc) to afford **8** as a light yellow oil in 52% overall yield (0.332 g). To a solution of alcohol **8** (320 mg, 0.97 mmol) in CH_2Cl_2 (28 mL) was added $Rh_2(OAc)_4$ (43 mg, 0.097 mmol). A gaseous evolution was observed from the green reaction mixture. After 30 min, the solution was concentrated and the crude material was filtered through a plug of silica gel (66% EtOAc in hexane) to give **9** as colorless oil; yield: 0.25 g (5%); dense liquid; R_f 0.2 (4:1 hexanes–EtOAc).

IR (neat): 2938, 1742, 1716, 1593, 1205 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3 H), 2.23–2.48 (m, 2 H), 2.69 (dt, *J* = 1.6, 7.2, Hz, 2 H), 3.30–3.48 (m, 2 H), 3.78 (s, 6 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.59–5.66 (m, 1 H), 6.08 (dt, *J* = 6.4, 3.6 Hz, 1 H), 6.29 (t, *J* = 2.0 Hz, 1 H), 6.39 (d, *J* = 2.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 202.0, 167.2, 161.1, 136.7, 104.7, 99.5, 96.6, 94.2, 61.5, 55.5, 49.6, 41.4, 34.2, 22.3, 14.2.

HRMS (EI+): *m/z* calcd for $[C_{18}H_{22}O_5]^+$: 318.1467; found: 318.1469.

8-(3,5-Dimethoxyphenyl)-1-ethoxy-1,3-dioxoocta-6,7-diene-2-diazonium (10); Typical Procedure

To a solution of keto ester **9** (45.3 mg, 0.15 mmol) in MeCN (2.5 mL) at 0 °C was added Et_3N (64.5 μL, 0.45 mmol) followed by *p*-acetamidobenzenesufonyl azide (73.5 mg, 0.3 mmol). After 10 min at 0 °C, the solution was allowed to warm to r.t. over 4 h. The mixture was poured into H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. The product was purified by flash column chromatography (3:1 hexanes–EtOAc) to afford **10** as colorless oil in 70% overall yield (38.6 mg); dense liquid; R_f 0.32 (3:1 hexanes–EtOAc).

IR (neat): 2938, 1716, 1653, 1593 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 2.34–2.63 (m, 2 H), 2.89 (dt, *J* = 17.1, 6.6 Hz, 1 H), 3.16 (dt, *J* = 16.8, 6.9 Hz, 1 H), 3.76 (s, 6 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 5.63 (dt, *J* = 6.0, 6.0 Hz, 1 H), 6.07 (dt, *J* = 6.3, 3.3 Hz, 1 H), 6.28–6.30 (m, 1 H), 6.38–6.40 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4, 192.1, 161.5, 161.1, 137.0, 104.7, 99.6, 96.5, 94.5, 61.6, 55.5, 38.5, 23.4, 14.5.

The allenes **14**, **16** and **18** were prepared by the same sequence of reactions starting from appropriate alkynes (Table 1). The properties of the final products, allenes **14**, **16** and **18** are given below.

14

Dense liquid; R_f 0.47 (3:1 hexanes–EtOAc).

IR (neat): 3400, 1716, 1653, 1303 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 2.35–2.59 (m, 2 H), 2.92 (dt, *J* = 16.8, 6.6 Hz, 1 H), 3.11 (dt, *J* = 16.8, 7.2 Hz, 1 H), 3.80 (s, 3 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 5.59 (dt, *J* = 6.3, 6.3 Hz, 1 H), 6.55 (dt, *J* = 6.6, 3.3 Hz, 1 H), 6.80–6.90 (m, 2 H), 7.14 (dt, *J* = 1.5, 7.4 Hz, 1 H), 7.31 (dd, *J* = 1.5, 6.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6, 192.2, 161.5, 156.0, 128.1, 127.8, 123.1, 120.9, 111.0, 93.4, 90.1, 61.5, 55.7, 38.9, 23.6, 14.4.

16

Dense liquid; R_f 0.48 (3:1 hexanes–EtOAc).

IR (neat): 2982, 1723, 1711, 1658, 1304 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 2.36–2.64 (m, 2 H), 2.91 (dt, *J* = 16.8, 6.6 Hz, 1 H), 3.16 (dt, *J* = 16.8, 7.2 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 5.64 (dt, *J* = 6.3, 6.0 Hz, 1 H), 6.15 (dt, *J* = 6.3, 3.3 Hz, 1 H), 7.14–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.3, 192.1, 161.5, 134.9, 128.8, 127.1, 126.9, 96.4, 94.3, 76.7, 61.6, 38.7, 23.6, 14.5.

18

Dense liquid; R_f 0.51 (4:1 hexanes–EtOAc).

IR (neat): 2959, 1719, 1654, 1292 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3 H), 1.21–1.37 (m, 7 H), 1.87–1.96 (m, 2 H), 2.24–2.32 (m, 2 H), 2.93 (t, *J* = 7.2 Hz, 2 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 5.04–5.14 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 192.3, 161.5, 92.5, 89.8, 76.2, 61.5, 39.5, 31.5, 28.8, 23.5, 22.4, 14.5, 14.1.

20

Mixture of diastereomers (dr = 4.5:1); dense liquid; R_f 0.52 (2:1 hexanes–EtOAc).

IR (neat): 2985, 1717, 1655, 1372 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (major diastereomer) = 1.20–1.39 (m, 9 H), 2.29–2.37 (m, 2 H), 2.84–3.09 (m, 2 H), 3.57–3.68 (m, 1 H), 4.04–4.10 (m, 1 H), 4.27 (q, *J* = 9.0 Hz, 2 H), 4.44–4.54 (m, 1 H), 5.15–5.21 (m, 1 H), 5.27–5.38 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major diastereomer) = 204.9, 191.9, 109.6, 92.4, 92.1, 75.0, 69.6, 61.6, 39.3, 26.9, 26.1, 23.0, 14.6.

Tetrasubstituted Furans from Diazoallenes; 1-(3,5-Dimethoxyphenyl)-3-ethoxy-6,7-dihydro-2-benzofuran-4(5*H*)-one (13); Typical Procedure

A flame-dried, round-bottom flask was charged with CH_2Cl_2 (12 mL) and $Rh_2(OAc)_4$ (1.49 mg, 0.0036 mmol). Allene **10** (38.6 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added over 2 h via syringe pump. After stirring at rt for 4 h, the solution was concentrated and the crude material was filtered through a plug of florisil (66% EtOAc in hexane) to give the corresponding 6-methylenebicyclo[3.1.0]hexane **11** (*E*/*Z* = 7.6:1) as a colorless oil. A flame-dried 25 mL Schlenk flask equipped with a Teflon screw-top cap was charged with **11** (as obtained above) in anhyd toluene (0.038 M). The mixture was flushed with N_2 by sparging over 1 min and capped tightly. The flask was placed in an oil bath which was heated to 120 °C (ca. 20 min) and held at this temperature overnight. At the completion of the reaction (determined by TLC analysis), the solvent was removed by evaporation under reduced pressure and the concentrate was purified by flash chromatography (1:1 hexanes–EtOAc) to afford furan **13** in 64% overall yield (23 mg); white solid; mp 104–105 °C; R_f 0.33 (1:1 hexanes–EtOAc).

IR (neat): 2941, 1741, 1679, 1576, 1205, 1157 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (t, *J* = 7.1 Hz, 3 H), 2.02 (tt, *J* = 6.6, 6.0 Hz, 2 H), 2.44 (t, *J* = 6.3 Hz, 2 H), 2.85 (t, *J* = 6.3 Hz, 2 H), 3.81 (s, 6 H), 4.60 (q, *J* = 7.1 Hz, 2 H), 6.34 (t, *J* = 2.4 Hz, 1 H), 6.61 (*J* = 2.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.4, 161.2, 159.6, 136.9, 132.4, 122.2, 102.6, 100.4, 98.5, 68.2, 55.6, 39.4, 23.9, 22.6, 15.2.

HRMS (EI+): *m/z* calcd for $[C_{18}H_{20}O_5]^+$: 316.1311; found: 316.1304.

15

Colorless oil; R_f 0.29 (1:1 hexanes–EtOAc).

IR (neat): 3391, 294, 1678, 1580, 1247 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 6.9 Hz, 3 H), 1.97 (tt, *J* = 6.3, 6.0 Hz, 2 H), 2.43 (t, *J* = 6.3 Hz, 2 H), 2.64 (t, *J* = 6.3 Hz, 2 H), 3.85 (s, 3 H), 4.56 (q, *J* = 6.9 Hz, 2 H), 6.92–7.01 (m, 2 H), 7.24–7.31 (m, 1 H), 7.35 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.8, 160.1, 156.2, 134.7, 129.2, 123.4, 120.8, 119.6, 111.5, 100, 67.9, 55.6, 39.7, 24.1, 22.8, 15.3.

HRMS (EI+): *m/z* calcd for $[C_{17}H_{18}O_4]^+$: 286.1205; found: 286.1201.

17

White solid; mp 98–99 °C; R_f 0.18 (2:1 hexanes–EtOAc).

IR (neat): 2940, 1678, 1612, 1580, 1264 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (t, *J* = 7.2 Hz, 3 H), 1.97 (tt, *J* = 6.4, 6.0 Hz, 2 H), 2.45 (t, *J* = 6.4 Hz, 2 H), 2.86 (t, *J* = 6.0 Hz, 2 H), 4.61 (q, *J* = 6.8 Hz, 2 H), 7.19–7.24 (m, 1 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$). δ = 193.5, 159.7, 137.1, 130.8, 128.9, 126.6, 124.1, 121.6, 100.3, 68.1, 39.4, 23.9, 22.5, 15.2.

HRMS (EI+): *m/z* calcd for $[C_{16}H_{16}O_3]^+$: 256.1099; found: 256.1102.

19

Colorless oil; R_f 0.25 (3:1 hexanes–EtOAc).

IR (neat): 2934, 2871, 1680, 1582, 1068 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3 H), 1.18–1.35 (m, 2 H), 1.41 (t, *J* = 6.9 Hz, 2 H), 1.51 (tt, *J* = 7.2, 7.5 Hz, 2 H), 1.91 (tt, *J* = 6.6, 6.3 Hz, 2 H), 2.35 (t, *J* = 6.6 Hz, 2 H), 2.41–2.61 (m, 2 H), 4.47 (q, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 159.1, 139.3, 119.0, 67.8, 39.7, 30.5, 257, 24.1, 22.3, 20.6, 15.2, 14.0.

21

Colorless oil; R_f 0.29 (1:1 hexanes–EtOAc).

IR (neat): 2985, 1683, 1580, 1061 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.47 (m, 9 H), 1.95 (tt, *J* = 6.3, 6.0 Hz, 2 H), 2.37 (t, *J* = 6.6 Hz, 2 H), 2.51–2.70 (m, 2 H), 4.04 (t, *J* = 8.1 Hz, 1 H), 4.14 (t, *J* = 7.5 Hz, 1 H), 4.51 (q, *J* = 6.9 Hz, 2 H), 4.98 (t, *J* = 4.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.1, 160.1, 133.4, 125.6, 109.8, 99.0, 69.7, 68.1, 66.9, 39.6, 26.3, 26.1, 23.8, 20.5, 15.2.

3-Ethoxy-1-phenyl-2-benzofuran-4-ol (22)

A flame-dried 25 mL Schlenk flask equipped with a Teflon screw-top cap was charged with **17** (12 mg, 0.0468 mmol) and DDQ (22 mg, 0.097 mmol) in anhyd benzene (0.024 M). The mixture was flushed with N_2 by sparging over 1 min and capped tightly. The flask was placed in an oil bath which was heated to 120 °C (ca. 20 min) and held at this temperature overnight. At the completion of the reaction (determined by TLC analysis), the solvent was removed by evaporation under reduced pressure and the concentrate was purified by preparative TLC (3:1 hexanes–EtOAc) to afford **22**; yield: 6.1 mg (51%); white solid; mp 72–73 °C; R_f 0.47 (3:1 hexanes–EtOAc).

IR (neat): 2984, 1674, 1599, 1275, 1193 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.2 Hz, 3 H), 4.03 (q, *J* = 7.2 Hz, 2 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 7.10 (d, *J* = 8.5 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.48–7.56 (m, 2 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 11.1 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 169.4, 162.0, 137.3, 135.2, 133.4, 129.6, 128.7, 119.2, 118.7, 62.3, 13.2.

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References

(1) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; 4th ed., Blackwell: Oxford, **2000**, 296.
(2) For an application to annulated furan synthesis, see: Zambias, R.; Caldwell, C.; Kopka, I.; Hammond, M. *J. Org. Chem.* **1988**, *53*, 4135.
(3) Koenig, B. *In Science of Synthesis*, Vol. 9; Maas, G., Ed.; Thieme: Stuttgart, **2002**, 183.
(4) For recent reports from our group in this regard, see: (a) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468. (b) Pujanauski B. G., Bhanu Prasad B. A., Sarpong R.; *J. Am. Chem. Soc.*; **2006**, *128*: 6786.
(5) For a pertinent, recent review on the trimethylmethylene-methane diyl, see: Allan, A. K.; Carroll, G. L.; Little, R. D. *Eur. J. Org. Chem.* **1998**, 1.
(6) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.
(7) See, for example: Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113.
(8) The diazoallene compounds were found to be unstable using EI techniques for mass spectrometry measurements.