A facile enediyne→fulvene→indene transformation provides a route to all possible isotopomers of substituted fulvenes and indenes.

Introduction

Interest in substituted fulvenes and benzofulvenes stems from their potential as building blocks for the preparation of metallocene catalysts, and from the application of fulvenes as electron acceptors in material science and molecular electronics. Fulvenes and benzofulvenes have also been used as key intermediates in the total synthesis of several natural products and patented as anti-inflammatory agents having antipyretic and analgesic activity. Deuterated indenes have received significant attention as mechanistic probes, e.g., in Clemmensen reduction, photochemistry of alkylindenes, hydrogenolysis, ruthenium-mediated cycloaromatization, etc.

Recently, we discovered a photochemical transformation of enediynes to indenes, which is accompanied by four formal hydrogen abstractions from the environment. In order to determine whether these hydrogens are transferred as H-atoms or protons, an important aspect in understanding the DNA-cleaving properties of these molecules, we carried out this reaction in the presence of CH₃OD and found that it results in a mixture of indene isotopomers, with varying extent of D incorporation at both of the methylene positions (Scheme 1).

In order to understand the details of D-incorporation in the individual steps of the enediynes–indene cascade, we needed to prepare the fulvene and indene isotopomers. Since they were not available through literature routes, we developed a new approach to selectively deuterated fulvenes and indenes, which we report in this paper.

Results and discussion

In this approach, the fulvene moiety is assembled through a 5-exo-dig radical cyclization initiated by Bu₃Sn radical addition to diaryl enediynes (Scheme 1) – the first synthetically useful application of reaction of an enediyne moiety with radical reagents, a process which has been only briefly studied so far. This process lends itself to the preparation of selectively deuterated fulvene isotopomers because the whole sequence introduces two hydrogen atoms into the fulvene moiety in two mechanistically separate and synthetically orthogonal steps (Scheme 2). In the first stage, either H or D is introduced at the exocyclic double bond depending on the choice of the tin reagent (Bu₃SnH or Bu₃SnD). Subsequent destannylation can be achieved using a source of either protons or deuterons (HCl or DCl), thus introducing either H or D at the endocyclic benzofulvene position.

D-incorporation at the endocyclic position through hydrolytic deuteriodestannylation proceeds with excellent efficiency (see the Supporting Information for the details). On the other hand, reaction of bis-TFP substituted enediyne 1 with Bu₃SnD in toluene, which is the most common solvent for such processes,

Scheme 1  Photochemical reactions leading to indene isotopomers (top) and tin-promoted radical cyclization leading to fulvene (bottom); TFP = tetrafluoropyridine.
resulted in only ~50% D-incorporation at the exocyclic double bond for the (E)-isomer, and ~56% D-incorporation for the (Z)-isomer. At a higher Bu3SnD concentration,17 deuterium incorporation increases (~69%) for the (Z)-isomer, 66% for the (E)-isomer) but still remains incomplete. These results point to H-atom abstraction from the benzylic position of toluene solvent as a competing process (commercial Bu3SnD is 96% deuterated). Despite the much higher concentration of toluene compared to the tin reagent (PhCH3) ~ 0.3 M, [Bu3SnD] ~ 3 × 10−4 M) and the contribution from the primary H/D isotope effect, the dramatic differences in the X–H bond dissociation energies (94 kcal mol−1) for Bu3SnH (74 kcal mol−1) and toluene (88 kcal mol−1).17 However, when the difference in reaction energies is translated into the H-abstraction barriers using Marcus theory,18 one would expect H-abstraction from toluene to proceed only ~105 times more slowly. A possible explanation for the small but consistent difference in the extent of deuteration between the (E)- and (Z)-isomers involves a weak non-covalent interaction between toluene and the electron-deficient TFP moiety leading to precoordination of toluene next to the radical center. This interaction may be more important in formation of the (E)-isomer where the toluene molecule can be associated with both TFP moieties. Such interactions should also contribute to the considerable degree of H-atom abstraction from the solvent – a hypothesis which is consistent with the higher amount of D-incorporation (~75%) in the case of R = phenyl even at lower Bu3SnH concentrations.

The efficiency of deuteriation can be dramatically increased by using a solvent incapable of hydrogen atom donation. We found that in benzene or a,a,a-trifluorotoluene, the observed amount of H-incorporation can be explained by the 4% of residual Bu3SnH in Bu3SnD. The fulvene isotopomers can be further transformed to a variety of indenes with the selective introduction of either proton or deuteron to the cyclopentadienyl moiety. Nucleophilic attack at the exocyclic double bond by an organolithium compound leads to formation of the cyclopentadienyl anion lithium salt. Subsequent addition of either a proton or deuteron to the cyclopentadienyl moiety during workup with either H2O or D2O provides substituted indenes 7–9 (Scheme 3). This procedure combined with the appropriate deuterated fulvene provides a synthetic route to any of the possible indenes illustrated in Scheme 3. Although the initial radical cyclization results in a mixture of (E/Z)-isomers, their subsequent transformation to indene converges to a single isomer.

The reaction of LiAlH4 or LiAlD4 proceeds in a similar fashion with the nucleophile (hydride or deuteride) attacking the exocyclic double bond to form a substituted cyclopentadienyl anion. The cyclopentadienyl anion can then be trapped selectively using either H2O or D2O to form selectively deuterated indenes 10–13 (Scheme 4). In principle, trapping by other electrophiles, e.g., ferrous chloride, to directly form a metallocene complex20 or by Me3Sc19 should also be possible.

### Conclusion

The enediyne → fulvene → indene sequence provides a choice for selective introduction of hydrogen isotopes through a radical, electrophilic, or nucleophilic form at either of two positions of an indene or a fulvene moiety. Applications of this method for mechanistic studies of photochemical enediyne → indene transformations and of metalloocene catalysis will be reported in due course.

### Experimental

#### General

NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer at 300 MHz (1H NMR) and 75.4 MHz (13C NMR), respectively, in CDCl3, unless otherwise noted.19F NMR was performed on a Bruker 300 MHz spectrometer. Mass spectra were measured on a Jeol JMS-600H. GC analyses were conducted on a Varian CP-3800 GC. 1,2-Diodobenzene was synthesized according to the reported method.21 The synthetic procedures for I and compounds derived from it are given below. For synthesis of remaining compounds, as well as spectral data, please refer to the Supporting Information.†

#### 1,2-Bis(phenylethynyl)benzene (1)

A mixture of 1,2-diiodobenzene (3.00 g, 9.09 mmol), bis(triphosphine)palladium(II) dichloride (0.7 g, 1.00 mmol), and copper(i) iodide (0.39 g, 2.02 mmol) in Et,N (75 ml) was degassed by the freeze–pump–thaw method. The solution was brought to reflux with phosphacyclene (2.05 g, 20.0 mmol) was added. The reaction mixture was allowed to reflux overnight. The reaction mixture was filtered through Celite, washed with saturated ammonium chloride solution, water, and dried over MgSO4. Column chromatography (silica gel, hexanes) provided 1.95 g (77%) of 1 as an off-white solid, mp 51–52 °C (lit.8 51–52 °C). 1H NMR: δ 7.57 (m, 6H), 7.32 (m, 8H);13C NMR: δ 131.8, 131.6, 128.4, 128.3, 128.0, 125.8, 123.3, 93.6, 8.83; HRMS (EI, 70 eV) calcld. for C25H14 (M+) = 378.10955, found 378.10944.

#### 2-Phenyl-1-(phenylmethylenyl)-1H-indene (3)

A solution of diyne 1 (94 mg, 0.336 mmol) in anhydrous toluene (5 ml) was brought to reflux in a dry three-neck flask. A solution of tributyltin hydride (120 mg, 0.412 mmol) and AIBN (6 mg, 0.037 mmol) in anhydrous toluene (5 ml) was added by
syringe pump over 1 h and the reaction mixture was allowed to reflux for 2 h. The toluene was evaporated in vacuo and the reaction mixture was redissolved in dichloromethane (5 ml). Concentrated HCl (5 ml) was added and the reaction was stirred vigorously for 1 h. The organic layer was washed with water, and dried over MgSO₄. Flash chromatography (40 g silica gel, hexanes) afforded 77 mg (82%) of (+)-3 as a yellow oil. NMR and GC data provided a 6:1 E:Z ratio. 10 mg of pure (E)-isomer was isolated in the first few fractions of the separation. ¹H NMR: δ 7.47 (m, 1H), 7.32 (s, 1H), 7.29 (m, 1H), 7.22 (td, J = 0.9 Hz, 1H), 6.96 (td, J = 7.5 Hz, J = 1.3 Hz, 1H), 6.88 (s, 1H); ¹³C NMR: δ 144.3, 143.2, 140.3, 136.8, 136.0, 134.7, 134.7, 129.6, 129.6, 129.3, 128.4, 128.3, 128.2, 128.2, 127.4, 124.9, 123.3, 120.7; HRMS (EI, 70 eV) calcd. for C₂₂H₁₁D₃ (M⁺) 321.13418, found 321.13244.

2-Phenyl-1-(phenylmethylene)-3-deutero-1H-indene (5)

Synthesized analogously to 3, using DCl instead of HCl and yielding 73 mg (75%) of (+)-5 as a yellow oil. ¹H NMR: δ 7.47 (m, 1H), 7.32, (s, 0.15H), 7.29 (m, 1H), 7.22 (td, J = 7.4 Hz, J = 0.9 Hz, 1H), 6.96 (td, J = 7.5 Hz, J = 1.3 Hz, 1H), 6.88 (s, 1H); ¹³C NMR: δ 144.3, 143.2, 140.3, 136.8, 136.0, 134.7, 134.7, 129.6, 129.6, 129.3, 128.4, 128.3, 128.2, 128.2, 127.4, 124.9, 123.3, 120.7; HRMS (EI, 70 eV) calcd. for C₂₂H₁₁D₂ (M⁺) 282.12520, found 282.12520.

2-Phenyl-1-(phenylethynyl)methylene)-3-deutero-1H-indene (9)

A solution of I (200 mg, 0.719 mmol) in anhydrous toluene (10 ml) was brought to reflux in a dry three-neck flask. A solution of tributyltin deuteride instead of DCl in THF (3 ml) was added dropwise to a solution of fluorene (275 mg, 1.037 mmol) in anhydrous toluene and the solution was brought to 0 °C over 1 h and the reaction mixture was allowed to reflux for 2 h. The toluene was evaporated in vacuo and the reaction mixture was dissolved in dichloromethane (5 ml). 20% DCl in D₂O (5 ml) was added and the reaction was stirred vigorously for 1 h. The organic layer was washed with water and extracted with dichloromethane. The combined organic layer was dried over magnesium sulfate and concentrated to a residue that was dissolved in anhydrous THF (5 ml) at −78 °C and slowly brought to −30 °C over 2 h while stirring. The enediyne reaction mixture was added dropwise and the solution was brought to 0 °C over 2 h while stirring. D,O (5 ml) was added, the reaction mixture was brought to room temperature, and the product was extracted with diethyl ether. The combined organic layers were dried over MgSO₄ and concentrated to a residue that was purified by column chromatography (silica gel, 20 : 1 hexane-chloroform) and recrystallized from a mixture of ethanol and water to afford 209 mg (65%) of 9 as white crystals, mp 84-85 °C. ¹H NMR: δ 7.93 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.41 (m, 2H), 7.27 (m, 8H), 7.12 (m, 3H), 7.00 (t, J = 7.4 Hz, 1H), 6.90 (m, 2H), 6.69 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H); 5.22 (br s, 1H), 4.17 (d, J = 11.4 Hz, 0.32H), 3.66 (br a 0.08H), 3.55 (br a 0.08H); ¹³C NMR: δ 146.2, 145.7, 145.0, 144.2, 144.2, 143.1, 142.0, 142.0, 141.1, 140.9, 140.7, 137.7, 129.3, 128.4, 128.2, 128.1, 127.2, 127.0, 126.8, 126.6, 126.5, 126.1, 126.1, 126.0, 124.4, 123.9, 122.5, 119.5, 49.1, 48.1; HRMS (EI, 70 eV) calcd. for C₂₂H₁₁D₃ (M⁺) 449.22383, found 449.22380.

1-Benzyl-2-phenyl-1H-indene (10)

A solution of 3 (80 mg, 0.285 mmol) in THF (10 ml) was cooled to −30 °C. LiAlH₄ (16 mg, 0.421 mmol) was added and the mixture was warmed to room temperature over 2 h. The reaction mixture was cooled to 0 °C and H₂O (5 ml) was added dropwise. The product was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate and concentrated to a residue that was purified by column chromatography (silica gel, hexanes) to afford 55 mg (68%) of 10 as an opaque white oil. ¹H NMR: δ 7.50 (m, 1H), 7.45 (m, 2H), 7.37 (m, 2H), 7.22 (m, 9H), 4.14 (s, 2H), 3.87 (s, 2H); ¹³C NMR: δ 146.5, 142.8, 142.5, 139.5, 137.1, 136.6, 128.5, 128.5, 128.0, 128.0, 127.1, 126.4, 126.0, 124.7, 123.4, 120.2, 41.3 (t, J = 20.6 Hz) 32.4; HRMS (EI, 70 eV) calcd. for C₁₉H₁₃ (M⁺) 282.14085, found 282.14269.

1-Benzyl-2-phenyl-1H-indene (11)

Synthesized analogously to 10, using D₂O instead of H₂O and yielding 53 mg (66%) of 11 as an opaque white oil. ¹H NMR: δ 7.50 (m, 1H), 7.45 (m, 2H), 7.37 (m, 2H), 7.22 (m, 9H), 4.15 (s, 2H), 3.87 (s, 2H); ¹³C NMR: δ 146.5, 142.8, 142.5, 139.5, 137.1, 136.6, 128.5, 128.5, 128.0, 128.0, 127.1, 126.4, 126.0, 124.7, 123.4, 120.2, 41.3 (t, J = 20.6 Hz) 32.4; HRMS (EI, 70 eV) calcd. for C₁₉H₁₃D (M⁺) 299.20973, found 299.2097.
123.4, 120.2, 41.3 (t, \(J = 20.6\) Hz) 32.4; HRMS (EI, 70 eV) calcd. for \(\text{C}_{22}\text{H}_{16}\text{D}_{2}\) (M\(^+\)) 283.14713, found 283.14597.

1-Benzyl-2-phenyl-1H-indene (12)

Synthesized analogously to 10, using LiAlD\(_3\) instead of LiAlH\(_3\), \(\text{D}_2\)O instead of \(\text{H}_2\)O, and yielding 52 mg (64\%) of 13 as an opaque white oil. 'H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.50 (m, 1H), 7.45 (m, 1H), 7.37 (m, 2H), 7.22 (m, 9H), 4.12 (m, 1H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.50 (m, 1H), 7.45 (m, 2H), 7.22 (m, 9H), 4.12 (m, 1H), 3.87 (s, 2H); \(^{13}\)C NMR: \(\delta\) 146.5, 142.8, 142.6, 139.4, 137.1, 136.5, 128.5, 128.3, 128.0, 127.1, 126.4, 126.0, 124.7, 123.4, 120.2, 41.4, 31.8 (t, \(J = 19.1\) Hz); HRMS (EI, 70 eV) calcd. for \(\text{C}_{22}\text{H}_{17}\text{D}\) (M\(^+\)) 283.14713, found 283.14597.

1-Benzyl-2-phenyl-1H-indene (13)

Synthesized analogously to 10, using LiAlD\(_3\) instead of LiAlH\(_3\), and yielding 54 mg (67\%) of 13 as an opaque white oil. 'H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.50 (m, 1H), 7.45 (m, 1H), 7.37 (m, 1H), 7.22 (m, 9H), 4.12 (m, 1H), 3.87 (s, 2H); \(^{13}\)C NMR: \(\delta\) 146.5, 142.8, 142.6, 139.4, 137.1, 136.5, 128.5, 128.3, 128.0, 127.1, 126.4, 126.1, 124.7, 123.4, 120.2, 41.1 (t, \(J = 19.8\)), 31.8 (t, \(J = 19.1\)) \(\delta\) 7.50 (m, 1H), 7.45 (m, 1H), 7.37 (m, 1H), 7.22 (m, 9H), 4.12 (m, 1H), 3.87 (s, 2H); \(^{13}\)C NMR: \(\delta\) 146.5, 142.8, 142.6, 139.4, 137.1, 136.5, 128.5, 128.3, 128.0, 127.1, 126.4, 126.1, 124.7, 123.4, 120.2, 41.1 (t, \(J = 19.8\)), 31.8 (t, \(J = 19.1\)); HRMS (EI, 70 eV) calcd. for \(\text{C}_{22}\text{H}_{17}\text{D}\) (M\(^+\)) 284.15340, found 284.15255.

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References

15 A solution of BuSnD was added to a solution of other reagents using a syringe pump to minimize the formation of acyclic addition products. “Low concentration” refers to a total toluene volume of 33 ml, while “high concentration” refers to 3 ml of toluene. The H/D ratios from 'H NMR and high-resolution MS are in perfect agreement with each other. See Supplementary Information† for details.
18 (a) For the interconnection of reaction and activation energies in hydrogen transfer reactions, see: J. P. Roth, J. C. Yoder, T.-J. Won and J. M. Mayer, Science, 2002, 294, 2524; (b) I. V. Alabugin, M. Manoharan, B. Breiner and F. Lewis, J. Am. Chem. Soc., 2003, 125, 9329; (c) for the seminal theoretical treatment, see: R. A. Marcus, J. Phys. Chem., 1968, 72, 891.
19 From a practical point of view, it is important to work up the reaction mixtures expeditiously since prolonged exposure to base leads to facile hydrogen exchange at the endocyclic methylene group. This exchange is especially fast in bis-TPF indenes where it can be used for selective D-labeling at this position.