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A novel stereoselective [8+2] double cycloaddition route to hydronaphthalene ring systems

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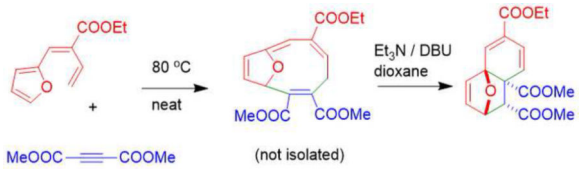
Abstract

Substituted hydronaphthalenes where each of the ten carbons of the two-ring system contains functionality were obtained through a tandem [8+2] cycloaddition and base-catalyzed rearrangement process using dienylfurans and electron-deficient alkynes. If the [8+2] process is conducted under solvent-free conditions the process could be conducted in a single reaction flask without isolation of the chromatographically sensitive [8+2] cycloadducts. A mechanism involving base catalysed alkene positional isomerization followed by disrotatory electrocyclic ring closure was proposed for the key reaction step that converts [8+2] cycloadducts to hydronaphthalenes. The products undergo selective ring opening-isomerization processes upon treatment with Lewis acids.

Graphical Abstract



Introduction

Furan-bridged ten-membered ring systems (*e.g.* **3a**, Scheme 1) are readily accessed through [8+2]-cycloaddition of electron-deficient alkynes [*e.g.* dimethylacetylene dicarboxylate (DMAD), **2**] and dienylfurans[1] (*e.g.* **1a**) or their isobenzofuran analogs.[2] Although that process proceeds in relatively high yield, the products are somewhat acid-sensitive and require tremendous care in their purification. The preferred purification method was silica gel chromatography using triethylamine-treated silica gel. In some experimental runs, an unanticipated minor compound, assigned as the fused oxanorbornene **4a,** was obtained in

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Supplementary Material

Complete experimental procedures, spectral characterization, and X-ray crystallography data.

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addition to the [8+2]-cycloadduct **3a**. Compound **4a** was never observed in the crude reaction mixture, thus suggesting that its formation is an artifact of the chromatographic purification process. This product could be eliminated by performing the chromatography purification quickly and avoiding excess triethylamine in the column preparation. In this manuscript the scope, limit, and mechanism for the formation of compound **4a** in a single pot from the coupling of dienylfurans and electron-deficient alkynes is discussed. This process represents a novel and unconventional stereoselective construction of densely functionalized hydronaphthalenes in a formal [8+2]-double cycloaddition process. Densely functionalized cyclohexadiene and hydronaphthalene derivatives are highly useful building blocks for preparation of medicinally-important derivatives featuring these ring systems and their preparation has been the focus of numerous recent investigations.[3] This ring system is most unusual in that it contains a bicyclo[4.4.0]decatriene ring system where every carbon atom is functionalized yet neither of the rings is aromatic.

Results and Discussion

Initially the transformation of isolated [8+2]-cycloadduct **3a** to compound **4a** was investigated under the assumption that triethylamine was causing the isomerization process. A reasonable mechanistic pathway is base-catalyzed alkene isomerization to conjugated hexatriene derivative **5a** followed by disrotatory 6 electrocyclic ring closure,[4] which establishes the relative stereochemistry at the junction of the oxanorbornene and cyclohexadiene rings. The stereochemistry of the other ester group was assigned based on the 4 Hz coupling constant between the bridgehead H and the H alpha to the ester group, which is consistent with only the indicated isomer. The alternative isomer is expected to exhibit nearly a 0 Hz coupling constant due to the nearly 90° dihedral angle.[5] This stereochemistry can result from protonation of the intermediate anion from the less hindered side prior to rearrangement of the resulting hexatriene ring system.

Thorough examination of the conditions for the [8+2]-cycloaddition between dienylfuran **1a** and DMAD employing a variety of solvent systems, temperatures, and reactant ratios revealed that this process is most efficient when performed as a neat process[6] using a 2:1 molar ratio of DMAD and dienylfuran. If lesser amounts of DMAD were employed, several unidentified byproducts were observed in the crude reaction mixtures and substantially lower yields were observed. A convenient procedure was desired where the neat reactants would be heated to the appropriate temperature for [8+2] cycloadduct formation and then a base solution would be added to effect the rearrangement. Treatment of the crude [8+2] adduct/unreacted DMAD mixture with triethylamine in dioxane at room temperature afforded mixtures of rearrangement products **4a** and double bond shift product **6a**[7] in moderate yield. None of the simple double bond shift isomer **5a** was ever observed in the reaction mixture. Vinylogous carbonate **6a** is an alternative base-catalyzed alkene isomerization product, which is more stable than the starting material due to the vinylogous carbonate linkage and the furan resonance contribution. Next a determined effort to optimize the rearrangement process of **3a** to **4a** was attempted using variety of basic substances. Diisopropyl ethylamine and potassium *t*-butoxide were ineffective at promoting the reaction. Use of DBU in THF or methanol afforded lower yields of rearrangement products. The best

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yield of product was obtained using a dual base system of DBU and triethylamine in dioxane at room temperature.

The relative energetics of the observed isomerization products were examined computationally in the simplest system **3–6h** (Scheme 2). The vinylogous carbonate **6h** is more stable than the alternative isomerization product **5h** or the starting material **3h**. Although alkene isomerization product **5h** is higher in energy that [8+2] cycloadduct **3h**, its pericyclic rearrangement product **4h** is the most stable of the products observed. Both of the enolate precursors (**8h** and **9h**) to **5h** and **6h** are equal in energy, which implies that the major reaction pathway is the result of a kinetically controlled deprotonation followed by reprotonation and rapid electrocyclic ring closure. The unobserved furan isomerization product **7h**, the result of a formal 1,7 hydride shift, is the true thermodynamic product however this compound was never observed.

Next the reaction was tested on a variety of dienylfuran substrates (see Table 1). The compound with deuterium in place of hydrogen at C-2 of the dienylfuran (see entry 2) was far more selective for the formation of rearrangement product **4a**-d_1 (65 % yield) with minimal formation of **6a**, indicating a strong kinetic isotope effect in the deprotonation event. As expected, the rearrangement product (**4b**, entry 3) using the methylfuran substrate was the exclusive product since the competing pathway is blocked. Adduct **4b** was a solid and after growing suitable crystals, X-ray analysis confirmed the proposed structure. The reaction proceeded similarly for the larger ring system (entry 5), however the smaller ring system (entry 4) was much less efficient. In this case the crude [8+2]-product was especially prone to decomposition, which could account for the lowered yield. In cases using substrates where the distal alkene group of the dienylfuran is within a ring system (entries 6–7) the final product was the simple [8+2] cycloadducts (**3e, 3f**), indicating that the [8+2] cycloaddition process was successful but the product does not undergo base-catalyzed rearrangement, and may reflect steric hindrance in the deprotonation step or conformational changes in the orientation of C-H bonds forced by the ring system. The highest yield for formation of **4** was observed with ester-substituted dienylfuran substrate in entry 8, which directs the deprotonation process to the correct position and lacks the ring structure detrimental to the isomerization as in entries 6–7. The minimally-substituted dienylfuran in entry 9 similarly afforded primarily the rearranged compound **4h**, however in this case the [8+2] event was not efficient using the neat solvent conditions. The yield noted is only for the rearrangement step. The monosubstituted dienylfuran of entry 10 afforded only rearrangement product **4i** however the analogous *t*-butyl substrate in entry 11 afforded only the [8+2] cycloadducts **3j**. This later case likely fails to rearrange due to severe eclipsing interactions between the furan ring hydrogens and the *t*-butyl group, and the resulting conformation is unable to participate in the rearrangement. The reaction using the unsymmetrical alkyne in entry 12 afforded the analogous rearrangement product **4k**. This latter reaction was performed on the isolated major isomer (depicted) from the [8+2] cycloaddition.[8]

A brief survey of the reactivity of these intermediates was conducted. The reaction with Lewis acids led to the ring opening product **10**. Surprisingly, the exact same product was obtained from the attempted copper-catalyzed nucleophilic addition to the oxanorbornene

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linkage.[9] In this system the dominant pathway for the intermediate allylic carbocation is the observed selective deprotonation product **10** and not the -deprotonation product **11** typically observed in oxanorbornenes that can aromatize (after conversion to the phenol).[10] A conjugate deprotonation pathway was also observed in the copper-catalyzed nucleophilic addition process as well.

Summary and Conclusions

In summary, a novel single step synthesis of highly functionalized hydronaphthalene systems has been presented employing readily available dienylfurans and electron-deficient acetylenes as starting materials. The reaction proceeds through [8+2] cycloaddition followed by base catalyzed olefin isomerization followed by transannular 1,3,5-hexatriene ring closure. The simple procedure requires heating the neat reacts followed by addition of base and solvent to afford the final products without requirement to isolate the hydrolytically sensitive [8+2] cycloadducts. The products undergo a selective ring opening deprotonation upon treatment with various transition metal catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

One-step formation of densely functionalized naphthalenes in one reaction flask

Novel rearrangement of [8+2] cycloaddition products via transannular 1,3,5-hexatriene ring closure

Selective isomerization to triene-alcohols upon treatment with Lewis acids

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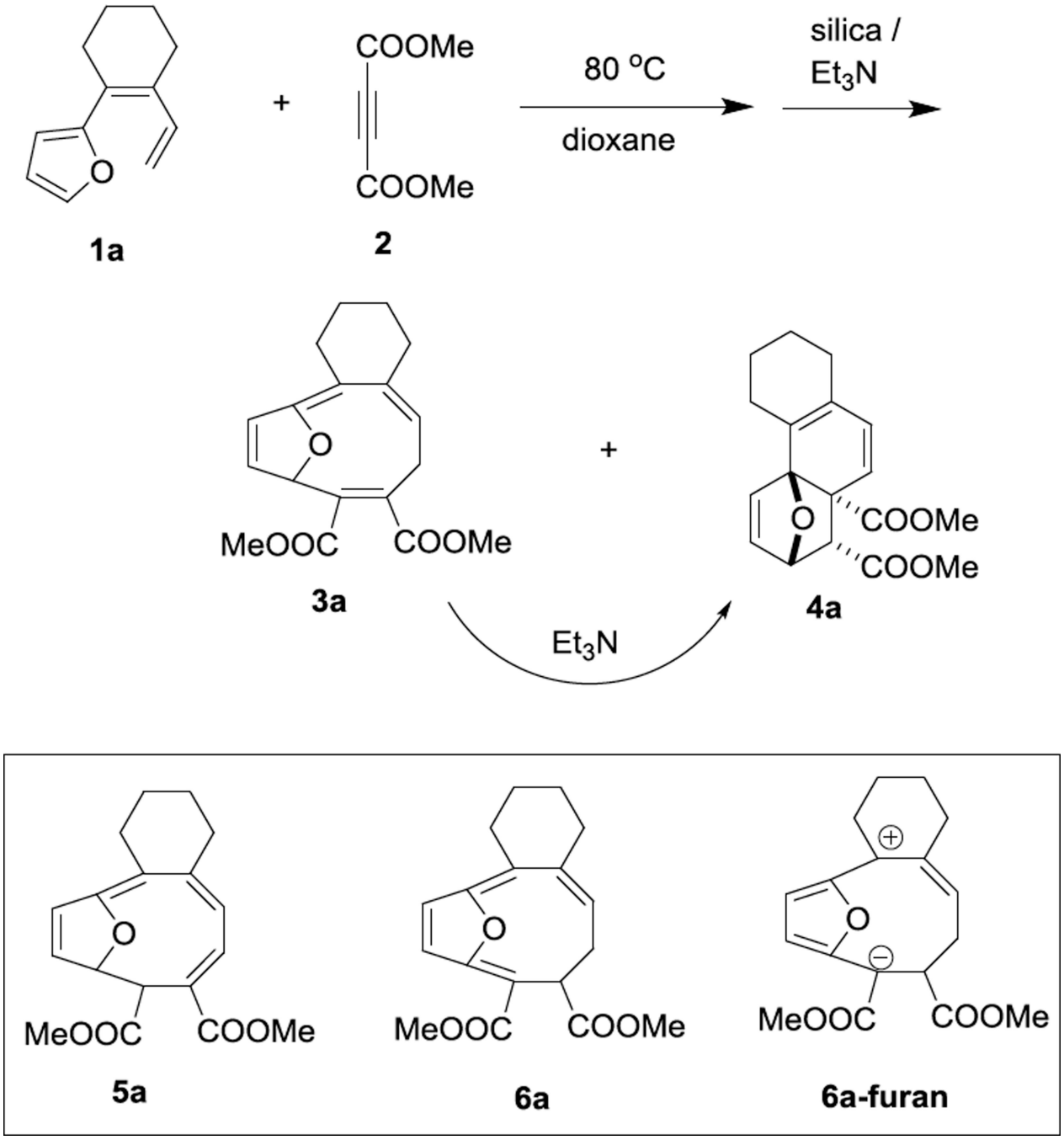

Scheme 1.

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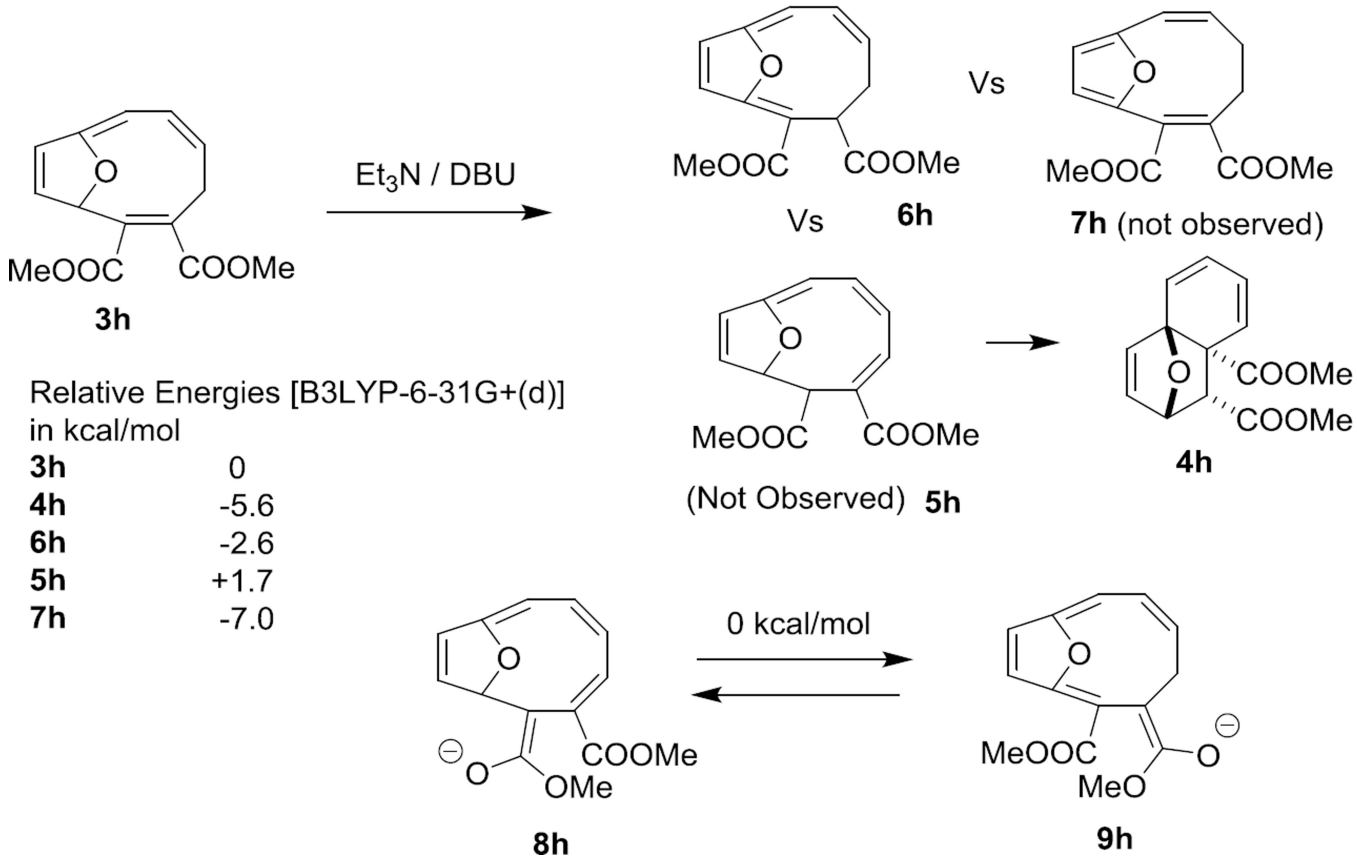
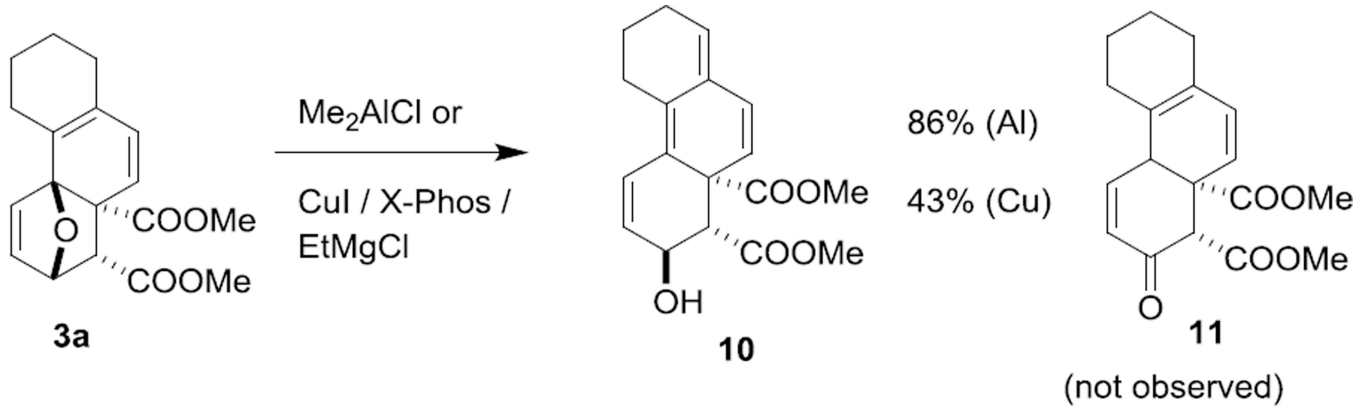


Scheme 2.



Scheme 3.

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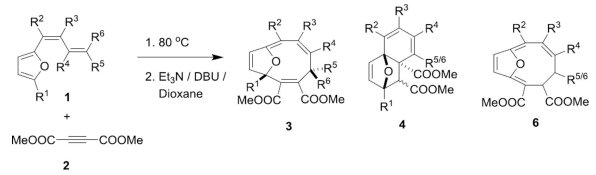
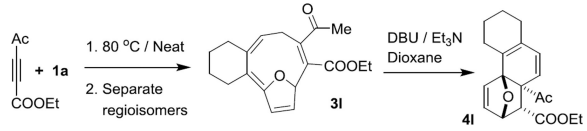
Table 1

Scope and limit for tandem [8+2] cycloaddition and base catalyzed rearrangement leading to hydronaphthalenes.



Entry[a]	R^1	R^2	R^3	R^4	R^5	R^6	Yield 4	Yield 3/6
1	H	$R^{2,3} = -(CH_2)_4-$		H	H	H	62% **4a**	11% **6a**
2	D	$R^{2,3} = -(CH_2)_4-$		H	H	H	65% **4a**-d_1	Trace **6a**
3	Me	$R^{2,3} = -(CH_2)_4-$		H	H	H	66% **4b**	N/A
4	H	$R^{2,3} = -(CH_2)_3-$		H	H	H	6% **4c**	0%
5	H	$R^{2,3} = -(CH_2)_6-$		H	H	H	63% **4d**	0%
6	H	H	CO_2Et	$R^{4,5} = -(CH_2)_4-$		H	0% **4e**	60% **3e**
7	H	H	CH_2OH	$R^{4,5} = -(CH_2)_4-$		H	0% **4f**	53% **3f**
8	H	H	CO_2Et	H	H	H	71% **4g**	0%
9[b,c]	H	H	H	H	H	H	62% **4h**	0%
10	H	Ph	H	H	H	H	67% **4i**	0%
11	H	*t*-Bu	H	H	H	H	0% **4j**	65% **3j**
12[c,d]							67% **4k**	0%

[a]Unless otherwise noted the [8+2]-segment of the reaction was conducted with no solvent.

[b]The [8+2]-segment of the reaction was conducted in dioxane solvent at 0.5 M concentration of the dienylfuran.

[c]Yield is based on isolated and previously prepared[1] **3** going to **4**, the yield does not include the formation of **3**.

[d]ethyl 4-oxopent-2-ynoate used instead of DMAD.