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Synthesis and Diels–Alder Reactions of a Benzo[5]radialene Derivative

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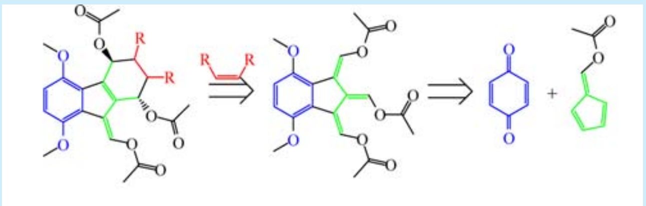
Supporting Information

ABSTRACT: Apart from their exotic structure, radialenes have been employed as precursors of more complex polycyclic molecules. In this work we report the synthesis of the first compound having the benzo[5]radialene substructure, starting from simple materials. Such a compound proved to be a convenient diene in Diels–Alder reactions, for the preparation of highly functionalized fluorenes and benzo[b]fluorenes in a quimio- and stereocontrolled fashion.



Fluorenes and benzo[b]fluorenes via benzo[5]radialenes: all C-C bonds from Diels-Alder reactions

Radialenes are cross conjugated cyclic compounds in which all ring carbons are sp^2 hybridized and contain the maximum possible number of exocyclic double bonds.[1] Initially considered as an academic curiosity due to their aesthetically interesting structure, these compounds are finding their way into some applications such as building blocks for organic conductors,[2] optic materials,[3] charge transfer complexes,[4] and precursors of more complex polycyclic molecules by cycloadditions.[5] Since the publication on the first of such compounds,[6] numerous reports concerning their synthesis,[7a] aromaticity,[7b] conformation,[7c] and reactivity[7d,e,f] emerged. Although the parent compounds are quite reactive, the [3]-, [4]-, and [6]radialenes (Figure 1; **I**, **II**, and **IV**, respectively) were synthesized.[8] However, [5]radialene (**III**) is yet to be fully described, in spite of serious efforts for this.[9] In this sense we planned the synthesis of a derivative of the yet unknown benzo[5]radialene (**V**),[10] to be used in Diels–Alder (DA) reactions for the preparation of fluorenes and benzo[b]-fluorenes, compounds of increased interest in natural products,[11] medicinal chemistry,[12] and optic materials.[13]

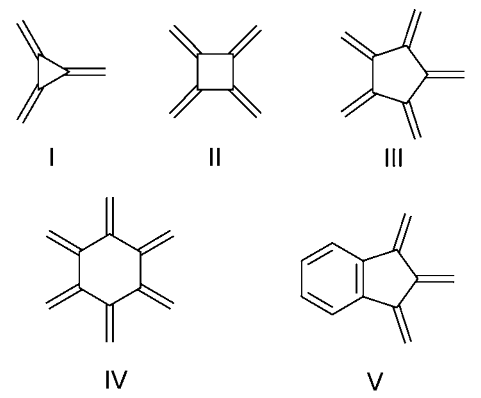
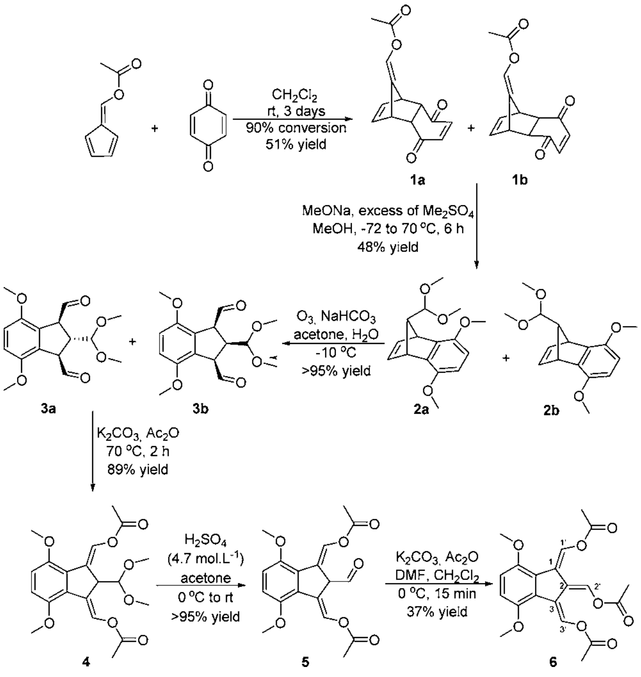


Figure 1. [3]-, [4]-, [5]-, [6]radialenes, and benzo[5]radialene.

In summary, we sought a stable derivative of **V**, but reactive enough to participate in DA reactions. These conditions were fulfilled by compound **6**, which was prepared in six steps starting from 1,4-benzoquinone and 6-acetoxyfulvene[14] (Scheme 1). In this DA reaction,[15] a 8:1 mixture of *endo* (**1a**) and *exo* (**1b**) diastereoisomers was obtained and subsequently treated with sodium methoxide and an excess of dimethyl sulfate,[16] affording dimethylacetals **2a** and **2b**,[17] in a 6:1 mixture.[18] By applying the Schiaffo's solvent active

Scheme 1. Synthesis of Benzo[5]radialene 6



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ozonolytic procedure[19] to the crude mixture of **2a** and **2b**, epimeric aldehydes **3a** and **3b** were obtained, without any reductive workup. The crude mixture was directly used in the enolization/acetylation step, resulting in **4**, as a single isomer,[20] for which we could anticipate an *E,E* or *Z,Z* configuration based on the simplicity of its ^{1}H and ^{13}C NMR spectra. However, the configuration depicted for this compound, in Scheme 1, was only indirectly deduced from NOESY studies on compound **6**. Acetal selective acidic hydrolysis was easily achieved leading to aldehyde **5**, in good yield. Finally, formyl group conversion into enolacetate yielded the desired benzo[5]radialene derivative **6**.

For this last compound, the substitution pattern around the C−C double bonds was determined based on the observed NOE effects between the hydrogen atoms attached to C1′ and C3′ and those at the corresponding proximal methoxy groups.

Seeking the synthesis of fluorenes and benzo[*b*]fluorenes, we investigated the behavior of **6** in some DA reactions. Reactions with dienophiles such as 1,4-benzoquinone, 2,3-dichloro-1,4-benzoquinone, and *N*-methylmaleimide in refluxing toluene were fast and highly diastereoselective resulting in adducts **7**, **8**, and **9**, respectively (Table 1).

The relative *endo* configuration of the major adducts **7** and **8**, with the acetoxy groups lying in a *trans* relationship, was established based on NOESY experiments. These arrangements derive from the preferential approach of the dienophiles to the more planar and less crowded C1′−C1−C2−C2′ diene moiety of **6** as compared to C2′−C2−C3−C3′. This proposal was reinforced by theoretical calculations,[21] where the optimized geometry of diene at the SMD(toluene)-M06-2X/6-31+G(d) level of theory shows dihedral angle values of 21.0° and 32.0° for C1′−C1−C2−C2′ and C2′−C2−C3−C3′, respectively.[22,23]

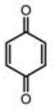
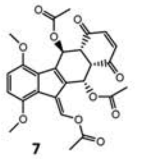
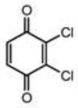
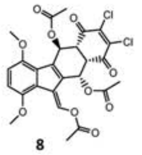
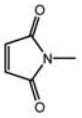
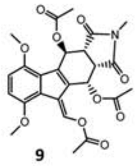
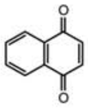
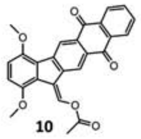
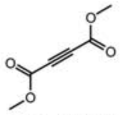
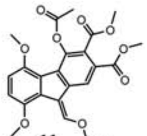
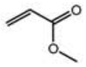
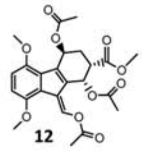
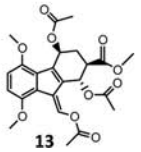
When **6** was mixed with 1,4-naphthoquinone, the initially formed DA adduct underwent the loss of two acetic acid molecules leading to compound **10** (Table 1).[24]

As for the DA reaction with dimethyl acetylenedicarboxylate as a dienophile, compound **11** was obtained (Table 1), as the result of elimination of only one acetic acid molecule from the initially formed adduct.

The regioselectivity of this last elimination reaction is noteworthy and can be rationalized considering that, after the initial C−OAc bond heterolysis, the incipient positive charge in **A** is fully stabilized by the electron-rich aromatic ring, a situation that cannot be achieved for the positive charge in **B** (Scheme 2). In order to study the thermochemistry of the elimination reaction occurring by C−OAc bond heterolysis, the reaction paths a and b were considered. Relative Gibbs free energies at the SMD(toluene)-M06-2X/6-31+G(d) level of theory showed a slightly more stable species for reaction path a, which corroborates the assumption that the positive charge in **A** is fully stabilized by the electron-rich aromatic ring, leading to the thermodynamic product **11**.

In order to address regioselectivity issues for cycloadditions of **6**, at the C1′−C1−C2−C2′ moiety, we used the unsymmetrical dienophile methyl acrylate and obtained a 1:1 mixture of *endo* **12** and *exo* **13** adducts (Table 1). The remarkably high regioselectivity observed for this cycloaddition can be explained if we consider that for **6** the calculated p_z atomic orbital coefficient of the HOMO is higher at C1′ (0.26438/0.19207)[25] and that of the LUMO of methyl acrylate (−0.34789/0.57171) is higher at C3, as obtained at the SMD(toluene)-M06-2X/6-31+G(d) level of theory.

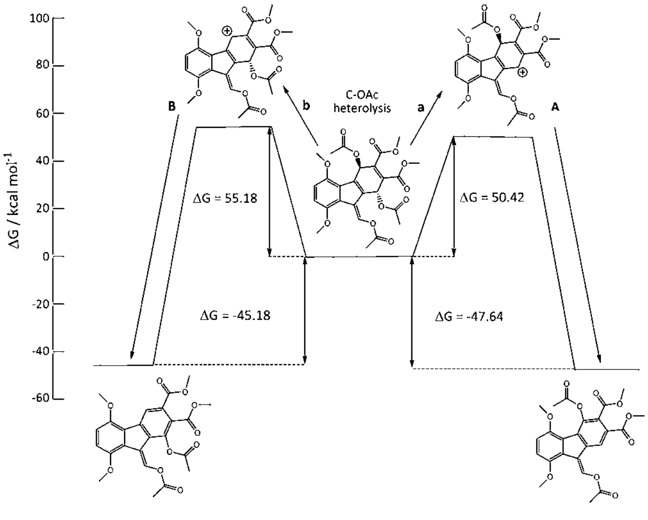
Table 1. DA Products Starting from 6 and Dienophiles

entry	dienophile[a]	conditions	products	yield(%)[b]
1		toluene reflux 2 h	 **7**	76
2		toluene reflux 30 min	 **8**	56
3		toluene reflux 6 h	 **9**	58
4		toluene reflux 6 h	 **10**	54
5	 used in 20 fold excess	toluene reflux 20 h	 **11**	44
6	 used as solvent	rt 3 days	 **12**  **13**	57 (1:1 mixture[c])

[a]Dienophiles used in equimolar quantities, unless otherwise noted. [b]Yields of products after crystallization. [c]Separated by column chromatography.

In summary, we reported the first synthesis of **6**, a benzo[5]radialene derivative, and some of its DA reactions. These reactions proceeded smoothly at the C1′−C1−C2−C2′ diene moiety with high *endo* selectivity, except for methyl acrylate, although, in this case, very good regioselectivity was observed. For 1,4-naphthoquinone and dimethyl acetylenedicarboxylate adducts, loss of acetic acid precluded the assignment of their configurations. However, all these results paved the way for using the yet neglected benzo[5]radialenes in a diversity oriented approach to highly functionalized fluorenes and benzo[*b*]fluorenes.

Scheme 2. Energy Profile for AcOH Elimination from the DA Adduct between 6 and Dimethyl Acetylenedicarboxylate



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■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures and spectra, including NOESY experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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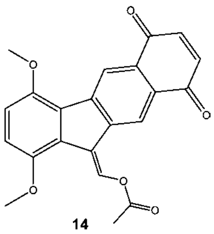
(24) During the attempts of purification of **7** by silica-gel column chromatography, compound **14**, similar to **10**, was formed by the loss of two molecules of acetic acid.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(25) For the sake of comparison, the calculated p_z atomic orbitals coefficients of HOMO at C2′ of **6** are 0.23782/0.17280.