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A New Method to prepare an e,e,e Trisadduct of C_{60} Using a Protection-Deprotection Sequence

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Abstract. A racemic mixture of the *e,e,e* Bingel-trisadduct, tris[di(ethoxycarbonyl)methano][60]fullerene **3** was synthesized by malonate additions (Bingel reaction) following by retro Diels-Alder reactions using a C_{60} tris-*e,e,e* adduct of anthracene **1** as precursor. Using this approach, the anthracenes act as protective groups and help orient the new additions so that poly-adducts with particular geometries are obtained. From the e,e,e anthracene-trisadduct **1** we also obtained the mono[di(ethoxycarbonyl)methano][60]fullerene **6** and bis [di(ethoxycarbonyl)methano][60]fullerene **7**. This approach exhibits a total yield of 4,2 % for the e,e,e tris malonate adduct, gives rise to less complex reaction mixtures and makes it easier to separate and characterize the compounds than other methods. The compounds obtained where characterized by UV/VIS, FT-IR, ^{1}H NMR, and MALDI-TOF.
Key words: Fullerene C_{60}, Anthracene adducts, e,e,e-trisadduct, Bingel adductos

Resumen. El trisaducto e,e,e Bingel, tris[di(etoxicarbonil)metano][60]fullereno **3** fue sintetizado como una mezcla racémica mediante reacciones de adición de malonatos (reacción Bingel) y retro Diels-Alder, usando el trisaducto e,e,e de antraceno y C_{60} **1** como precursor. Utilizando este método, los antracenos actúan como grupos protectores y ayudan a orientar las nuevas adiciones, de tal forma que nuevos poliaductos con una geometría particular, pueden ser obtenidos. Del trisaducto con antraceno e,e,e **1** también se aislaron el mono[di(etoxicarbonil)metano][60]fullereno **6** y el bis[di(etoxicarbonil)metano][60]fullereno **7**. Este método tiene un rendimiento total de 4.2% para el trisaducto Bingel e,e,e **3**, genera mezclas de reacción menos complejas y hace más fácil separar y caracterizar los compuestos que por otros métodos. Los compuestos obtenidos fueron caracterizados mediante UV/VIS, FT-IR, ^{1}H RMN, y MALDI-TOF.
Palabras claves: Fullereno C_{60}, Aductos de antraceno, trisaducto-e,e,e, Aductos Bingel

Introduction

The synthesis of C_{60} poly-adducts with specific regiochemistry is one of the most difficult aspects of exohedral fullerene functionalization, primarily due to the considerable number of isomers that can be generated by multiple additions [1]. The formation of several different isomers often occurs, thus introducing the need for subsequent isolation of the isomers from the product mixture. This challenge has motivated researchers to search for methods for the preparation of regioselective poly-adducts that are simple and provide high yields.

Diels-Alder reactions of C_{60} with anthracenes are of particular interest [2] because the anthracene moieties serve as protecting groups and help direct further additions, while at the same time they are easy to remove thermally. This behavior arises because of the reversible nature of the cycloadditions and the sensitivity to small changes in reaction temperatures, which are crucial for removal and for the final equilibrium. Additionally, the effect of substituents on the dienophile plays an important role since increased reactivity is observed when substituted by electron donating groups on sites 9 and 10 of the anthracene [3]. For these reasons the Diels-Alder pathway is particularly useful for obtaining polyadducts with regioselective patterns.

Another useful reaction in fullerene chemistry is malonate addition, also known as the Bingel reaction, which occurs quickly at ambient temperature and generates many multiple adduct isomers including bis- and tris-adducts [4]. Several regioselective synthetic routes have been reported for the preparation of Bingel polyadducts. One route of particular relevance to the present work, is Kraeutler´s synthetic strategy, which consists of the preparation of an equatorial tetra-adduct by orthogonal transposition [5]. This method starts with a *trans*-1-bis-anthracene adduct of C_{60} to direct the addition of the Bingel addends to the equatorial positions. The two anthracenes block the *trans*-1 positions and direct the Bingel additions to the molecule's equator. Using this method, hexa-adducts with a 95% yield can be obtained. Additionally, if these poly-adducts are heated up for 5 minutes at a temperature of 195°C in an oxygen-free atmosphere, a retro-Diels-Alder reaction readily occurs that generates free anthracene and the Bingel all equatorial tetra-adduct [5].

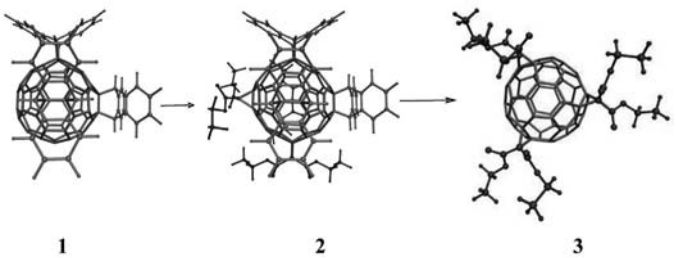
Studies have shown that the regioselectivity of cyclopropanation reactions on C_{60} is enhanced by the presence of 9,10-dimethylanthracene (9,10-DMA). The reversibly formed Diels-Alder adducts direct the cyclopropanations to the equatorial sites [6]. Other regioselective cyclopropanations of C_{60} can also be obtained by replacing 9,10-DMA with other substituted anthracenes such as 2,6-dimethoxy anthracene, which also acts as a directing group [7].

Further functionalization of Bingel polyadducts with a particular geometry allows for the synthesis of regiospecific

pyrrolidine derivatives. The Bingel adducts are usually characterized by a higher thermal stability than their Diels-Alder counterparts and they also act as protective and directing groups for subsequent additions [8]. A comprehensive and interesting review described the versatility of Diels-Alder reactions on C_{60} [9]. One of the most useful methods for the regioselective multiple additions of malonate groups to fullerenes is tether-directed remote functionalization, which was initially introduced by Diederich and his coworkers [10]. Both bis and tris-adducts have been regioselectively prepared using this approach.

The purpose of our work was the synthesis of the e,e,e tris-adduct tris[di(ethoxycarbonyl)methano][60]fullerene (**3,** Scheme 1). The overall scheme described here followed a series of protection-deprotection reactions on C_{60}. The first reaction consisted of a Diels-Alder cycloaddition between C_{60} and anthracene, to yield the e,e,e tris-adduct **1** [2b-c]. The tris-adduct was isolated by column chromatography. The following step consisted of a Bingel reaction in which tris-adduct **1** was cyclopropanated to obtain the hexa-adduct **2**. Finally, a retro-Diels-Alder reaction (at 180 °C) was performed to remove the anthracenes from the hexa-adduct to yield the final product, the tris-adduct **3** (Scheme 1), as a racemic mixture. Although this is not the first reported synthesis of this compound, it is the first time that the synthesis has been reported using this approach. The approach reported here generates a lower number of isomers upon synthesis of the tris-adduct **3**. This could be of great value for applications that require the use of derivatives of the e,e,e tris-adduct **3**. For example, other groups have reported the possible use of polar carboxylic acid C_{60} derivatives as neuroprotective agents and as therapeutic agents for acute or chronic neurodegenerative diseases [11], but no convenient and efficient synthetic strategies to prepare these compounds have been reported. The hexacarboxylic acid analogue of compound **3** has been shown to be particularly effective as a radical scavenger and neuroprotective agent [11].

Other approaches for synthesizing the e,e,e tris-adduct by a one step tether-directed Bingel addition have been reported [12]. Nevertheless, the tris-ester derivative with cyclotriveratrylene (CTV) does not easily hydrolyze to the triacid to release the CTV in this particular case. Until the present work, there have been no reports of convenient aproaches for regioselective synthesis of the tris-adduct e,e,e.



Scheme 1. shows the strategy to get the e,e,e Bingel-trisadduct, $C_{63}(COOEt)_6$ **3** from the e,e,e Anthracen- trisadduct **1**.

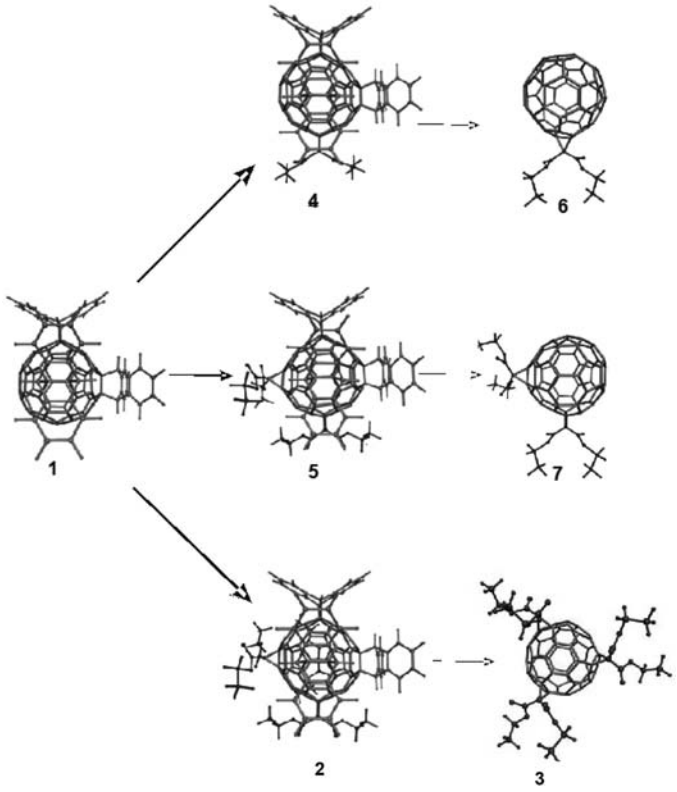
Results and Discussion

Characterization of the obtained compounds

Four distinct bands were clearly observed during the column chromatography of the obtained mixture from the Bingel reaction with **1**. Each band was separated and analyzed by TLC. Bands one, two, and four were characterized by UV/VIS, FT-IR, ^{1}H NMR and MALDI-TOF. Characterization of the third band could not be performed due to the low quantity obtained (Rf 0.24, orange). Scheme 2 shows the possible compounds present before and after the Bingel and retro Diels-Alder reactions.

The first band to elute shows a distinct orange color in solution and also in the solid phase upon solvent removal. This band corresponds to the tetra-adduct **4** (Scheme 2) in which three anthracene groups and one Bingel group are attached to the C_{60}.

The ^{1}H NMR spectrum shows multiple signals at δ = 7.34, 7.28, and 7.21 ppm, that integrate for 24 H, which correspond to the aromatic protons. This also indicates the presence of the three anthracene addends, which is corroborated by the six signals obtained at δ = 4.99, 4.88, 4.87, 4.46, 4.41, and 4.38 ppm, each of which integrated for one proton, since these signals correspond to the bridgehead protons of the anthracene groups. The two sets of quartets at δ = 4.436 and 4.345 ppm



Scheme 2. Compounds formed after performing the Bingel **2, 4, 5** and retro Diels-Alder reactions **3, 6, 7** on the e,e,e -anthracene trisadduct **1**.

correspond to the $–CH_2$ of the ester in the cyclopropane group added to the C_{60}, while the two sets of triplets at δ = 1.383 and 1.359 ppm correspond to the $–CH_3$ groups.

Additional evidence of the presence of the tetra-adduct comes from the mass spectrometry analysis which shows a single peak at m/z = 878.06, corresponding to a Bingel mono-adduct (Figure 1). The molecular ion peak does not appear in the spectrum due to the instability of the anthracene adducts.

The second band to elute was orange, both as a solid and in solution. This band corresponds to the penta-adduct **5** (Scheme 2), in which there are three anthracenes and two malonate addends on the C_{60}.

The ^{1}H NMR spectrum shows three groups of multiple signals at δ = 7.37, 7.21, and 7.17 ppm, that correspond to 24 aromatic protons. This indicates the presence of the three anthracenes, which is corroborated by the six signals that appear at δ = 5.04, 4.96, 4.76, 4.63, 4.53, and 4.36 ppm, that correspond to one proton each, assigned to the anthracene bridgehead protons. The quartet at δ = 4.274 ppm corresponds to the $–CH_2$ of the ester of the Bingel group added to the C_{60}, while the triplet at δ = 1.336 ppm corresponds to the $–CH_3$ group.

Mass spectroscopy analysis shows a single peak at m/z = 1036.12, corresponding to a Bingel bis-adduct (Figure 1). The molecular ion peak is not present due to the instability of the anthracene adducts.

Band four exhibits a light yellow color both as a solid and in solution. This band corresponds to the equatorial hexa-adduct **2**, in which there are three anthracenes and three cyclopropane groups added to C_{60}.

The ^{1}H NMR spectrum (Figure 2) shows three groups of multiple signals at δ = 7.34, 7.30, and 7.20 ppm corresponding to 24 aromatic protons. This is indicative of the presence of the three anthracene addends, which is corroborated by the two signals that appear at δ = 4.83, and 4.40 ppm that correspond to six protons assigned to the bridgehead protons. These signals also indicate that the Bingel groups were added on the "e" positions, based on to the observed symmetry. The quartet at δ = 4.273 ppm corresponds to the $–CH_2$ of the ester group, while the two triplets at δ = 1.358 and 1.301 ppm correspond to the $–CH_3$.

Mass spectroscopy for this compound shows a peak at m/z = 1194.17, that indicates the presence of a malonate tris-adduct. There is no molecular ion peak in the spectrum due to the instability of the anthracene adducts. The m/z = 1147.97 peak is indicative of the loss of the $–O-CH_2CH_3$ group which is present on the malonate adducts. The light yellow color of the compound, and further UV/VIS, ^{1}H NMR, and MALDI spectra analysis lead to the conclusion that the obtained compound is the equatorial hexa-adduct **2**. Figure 3 shows the UV-VIS spectra of the synthesized compounds.

The FT-IR spectra of compounds **2, 4** and **5** show asymmetric and symmetric vibrations of the CH_3 between 2923 and 2924 cm^{-1} and 2852-2854 cm^{-1}, C = O stretching between 1735 and 1743 cm^{-1}, and asymmetric and symmetric stretching of C-O-C between 1227 and 1248 cm^{-1} and between 1090 and 1115 cm^{-1}, respectively. The IR bands indicate the presence of the ester of the Bingel group added to the C_{60} in all cases [13].

The retro Diels-Alder reaction of compounds **2**, **4** and **5**, led to a noticeable change of color: compound **4** changed from orange to brown and its solubility in CS_2 and CH_2Cl_2 was diminished; compound **2** changed from a light yellow to a red color and compound **5** changed from orange to a red-orange color. These color changes occur because of the differences in the conjugated systems on the C_{60}.

The malonate tris-*e,e,e* adduct 3 was obtained, as a racemic mixture, via the retro Diels-Alder reaction of compound **2**, the Bingel mono-adduct **6** (Scheme 2) was obtained via the retro Diels-Alder reaction of compound **4**, and the Bingel bis-e adduct **7** was obtained via the same reaction of compound **5**. The disappearance of the signals corresponding to the aromatic and bridgehead protons confirmed that the retro Diels-Alder reaction was complete. Compounds **3**, **6**, **7**, were characterized by UV/VIS and ^{1}H NMR spectroscopy according to the existing literature [1, 4].

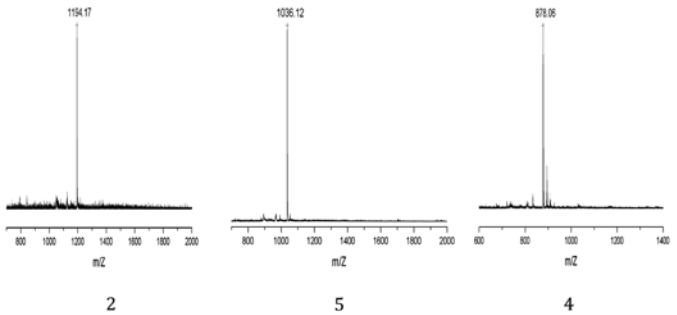


Fig. 1. MALDI-MS spectra of the compound **2, 4** and **5**.

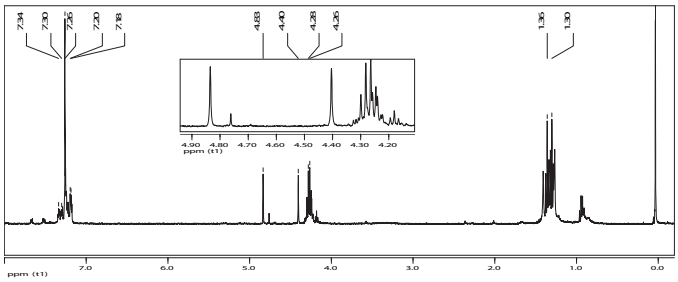


Fig. 2. ^{1}H NMR ($CDCl_3$-400 MHz) spectrum for **2**.

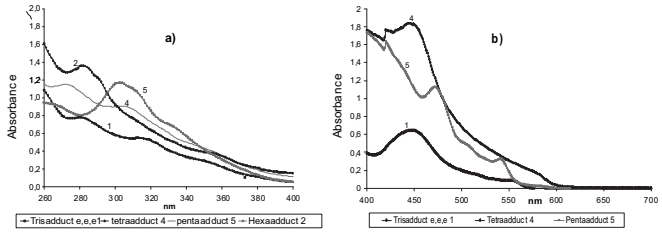


Fig. 3. – a) UV Spectra and b) VIS spectra (CH_2Cl_2) of the synthesized compounds **1**, **2**, **4** and **5**.

Conclusions

For the first time we were able to separate and characterize compounds **2**, **4** and **5**, which were obtained by performing a Bingel reaction with the anthracene tris-*e,e,e* adduct **1** of C_{60}. These compounds are unstable in solution. The synthesized compounds were used as precursors to obtain Bingel adducts in a selective manner. The obtained adducts were the bis-e Bingel-adduct **7** and the tris-*e,e,e* Bingel-adduct **3**. The protection-deprotection method used proved to be adequate for obtaining the tris-e,e,e Bingel-adduct **3** with an overall yield of 4,2%. The main advantage is a much less complex reaction mixture that was easy to separate and characterize.

Experimental Results

Preparation of eee-Anthracen-tris-adduct 1 by anthracene cycloaddition to C_{60}.

The synthesis of the e,e,e tris-adduct **1** of C_{60} with anthracene was performed according to reported procedures [2b-c]. Using a 100 mL flask, 1.0 gram of C_{60} (0.00139 mol) and 10 grams of anthracene (0.0561 mol) were dissolved in 50 mL of carbon disulfide. This solution was stored in the dark at ambient temperature for a period of 60 days. The separation of the adducts was performed by column chromatography using 320 g of silica gel in a column with a length of 30 cm and a diameter of 6 cm, using a mixture of carbon disulfide and petroleum ether (3:2) as eluant. The last band to elute, having a distinct orange color, corresponds to the adduct of interest: the tris-*e,e,e* adduct (75,3 mg, 4,3 %) . UV/VIS, FT-IR, and ^{1}H NMR were performed to characterize the material. The spectrum was in agreement with previous reports [2b-c]: in the UV/VIS there was a clear absorption maximum at 447 nm, characteristic of the tris-e,e,e adduct of C_{60} with anthracene. The ^{1}H NMR spectrum showed two clear signals at δ = 4.31 and 4.92 ppm, that correspond to the six anthracene bridgehead protons. The symmetry of the spectrum reflects the C_3 symmetry of the molecule.

Synthesis of Bingel derivatives from the *e,e,e*-anthracene trisadduct 1 [13].

Diethyl bromoalonate (24 mL, 1.41 × 10^{-4} mol) and 1,5 - diazabiciclo [5.4.0] undecene - 5 (DBU, 22mL 1.41 × 10^{-4} mol) were added to a dissolved mixture of 22.3mg (1.77 × 10^{-5} mol) of the tris-adduct **1** in 10 ml of dichloromethane. The mixture was stirred for 20 minutes and then stored for 5 hours. After storage, the solvent was removed using a rotary evaporator at 30 °C and reduced pressure. The separation of the mixture was performed by column chromatography (using 50 g of silica gel H in a column with a length of 34 cm and a diameter of 3 cm) using a mixture of carbon disulfide and petroleum ether (3:2) as solvent. During the separation, 4 distinctly colored bands were observed, each corresponding to the newly formed adducts.

UV/VIS, IR, ^{1}H NMR, and MALDI-TOF spectroscopy were performed on the 1st, 2nd, and 4th bands. Characterization of the 3rd band could not be performed due to the low quantity obtained (Rf 0.24, orange). Upon characterization we could establish that the first band corresponded to the tetra-adduct **4** (5.3 mg, 20.5%), the second band to the penta-adduct **5** (8.7 mg, 30,2%), and the fourth band corresponded to the desired hexa-adduct **2** (5,0 mg, 15,8 %), (Scheme 2)

Retro Diels-Alder reactions performed on the obtained compounds

Compounds **2**, **4** and **5** were heated at 180 °C for 15 minutes in a nitrogen atmosphere. Compounds **4** and **5** changed from an orange color to a brown-red color. Compound **2** changed from a light yellow color to a light red-orange. It was also observed that the solubility of these compounds in both dichloromethane and carbon disulfide was reduced after the thermalizations.

A control experiment on a TLC, using the solvent mixture of dichloromethane and petroleum ether (3:2) showed the presence of anthracene on the detector, confirming that the Diels-Alder reaction had occurred. We also found that, when heated at 180 °C, compounds **2**, **4**, and **5** produce the tris-adduct **3** (3 mg, 90%), the mono-adduct **6** (3,4 mg, 92%) and the bis-adduct **7 (**5,8 mg, 92%), respectively (Sheme 2). The overall conversión is probable close to quantitative, but there are losses due to simple manipulations. UV/VIS, FT-IR, ^{1}H NMR, and MALDI-TOF spectra were compared to those previously reported [1,4] to confirm these results.

Spectroscopic characterization Details

Hexaadduct 2; light yellow solid (5.0 mg), Rf (SiO_2, CH_2Cl_2/ Petroleum Ether: 3/2) = 0.13, UV/VIS (CH_2Cl_2) λ_{max} 262, 302, 309 sh, 331 sh, 450. NMR ^{1}H (400 MHz) $CDCl_3$: δ = 1.36, 1.30 (2t, *J* = 7.1 Hz, 18 H, CH_3), 4.26, 4.28 (dq, *J* = 7.17Hz, 12H, CH_2), 4.83, 4.40 (2s, 6H, bridge-head) 7.17-7.19, 7.28-7.31, 7.32-7.33 (m, 24 H). MALDI – TOF, m/z = 1194.17 (4.0), 1192.82 (4.0), 1147.97 (0.4), 840.62 (0.7), 841.62 (0.7), FT-IR; 2924 (s), 2853 (m), 1743 (s, C = O), 1654 (m), 1636 (m), 1561 (m), 1460 (s), 1370 (m), 1227 (s), 1163 (m), 1021 (m), 757 (s), 703 (s), 541 (s).

Tetraadduct 4; orange solid (5.3 mg), Rf (SiO_2, CH_2Cl_2/ Petroleum Ether: 3/2) = 0.64, UV/VIS (CH_2Cl_2) λ_{max} 281, 290 sh, 355 sh, 445, 582 sh. NMR ^{1}H (400 MHz) $CDCl_3$: δ = 1.43 (m, CH_3), 4.44 (m, CH_2), 4.38, 4.41, 4.46, 4.87, 4.88, 4.99 (6S, H bridge-head, 6H), 7.21, 7.28, 7.34 (3m, 24 H, aromatic). MALDI – TOF, m/z = 878.06 (1.2) ; FT-IR: 2923 (s), 2852 (s); 1735 (s, C = O), 1654 (m), 1636 (m), 1560 (m), 1459 (s), 1382 (m), 1248 (m), 1115 (m), 1021 (m), 745 (s), 695 (s), 547 (m).

Pentaadduct 5; orange solid (8.7 mg), Rf (SiO_2, CH_2Cl_2/ Petroleum Ether: 3/2) = 0.32, UV/VIS (CH_2Cl_2) λ_{max} 272, 305, 350,473, 542, 506, sh. NMR ^{1}H (400 MHz) $CDCl_3$: δ = 1.35 (m, CH_3), 4.28 (m, CH_2), 4.36, 4.53, 4.63, 4.76, 4.96,

5.04 (6S, 6H, bridge-head), 7.15-7.17, 7.21-7.22, 7.34-7.37 (m, 24 H). MALDI – TOF, m/z = 1036.12 (3.5).; FT-IR: 2924 (s), 2854 (s), 2364 (m), 1740 (s, C = O), 1653 (m), 1560 (m), 1541 (m), 1459 (s), 1370 (m), 1228 (s) , 1019 (m), 747 (s), 697 (s), 536 (m).

Chemical Providers

Southern Chemical Group: C_{60} fullerene 99.5%. Merck: Carbon disulfide (CS_2) and anthracene. For chromatography: petroleum ether, dichloromethane (CH_2Cl_2), and Silica Gel H and 20 × 20cm plates. Sigma-Aldrich: diethyl bromomalonate 92%, 1,8-diazabicycle[5.4.0]undecene (DBU) 98%, and Deuterated Chloroform ($CDCl_3$) 99.8% D. Macherey-Nagel: Silica Gel POLYGRAM SIL G/UV_{256} plates for purity control.

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