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An Expedient Synthesis of Mellitic Triimides

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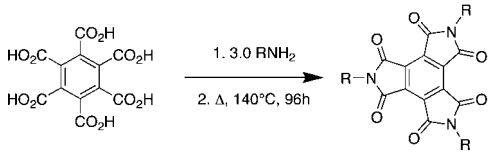
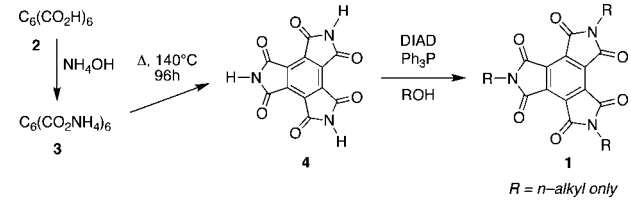


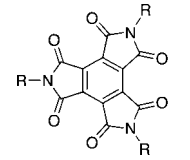
Heating of the solid ammonium salts obtained from treatment of mellitic acid with 3 equiv of a primary amine yields trisubstituted mellitic triimides via dehydration and imide ring closure. This surprisingly simple synthetic approach is amenable to incorporation of alkyl, aryl, and amino acid ester substituents, thereby opening broad access to a family of C_3-symmetric organic electron acceptors.

Triimides **1** containing the benzenehexacarbonyl core are attractive supramolecular building blocks by virtue of their relatively unusual planar 3-fold symmetic structure and powerful electron-accepting ability.[1] In these regards, they are closely related to, but distinct from, the ubiquitous diimide acceptors based on benzene, naphthalene, and perylene aromatic platforms that have found extensive application in myriad supramolecular designs.[2] They also represent a class of hexasubstituted benzene derivatives which have received little attention, at least in part for lack of an effective preparative route, while other heavily crowded benzene systems have found important roles in new functional materials.[3]

SCHEME 1. Outline Synthesis of Tri-*n*-alkylmellitic Triimides from Mellitic Acid via Mitsunobu Alkylation



We reported a viable, though limited, synthesis of tri-*n*-alkylmellitic triimides in 2001:[1] a small number of such derivatives were subsequently employed in the preparation of a class of donor–acceptor organized mesophases[4] and in an electrochemical study.[5] Aside from one other isolated, and unusual, example,[6] this synthetic approach represented the only published means to prepare mellitic triimide derivatives.[7] Here, we introduce a strikingly simple and far more general preparative approach, the versatility of which is revealed in the preparation of a range of susbtituted mellitic triimides **1**.



Our previously reported synthesis (Scheme 1) involved initial conversion of mellitic acid **2** to the crude unsubstituted triimide core **4** via thermal decomposition of the hexaammonium salt **3**.[1] Mitsunobu alkylation of crude **4** provided substituted derivatives (R = *n*-butyl, *n*-octyl, *n*-decyl, *n*-tetradecyl), but overall yields with respect to starting material were low, and lengthy chromatography was typically required to isolate the desired triimides from a variety of unwanted byproducts. The

(1) McMenimen, K. A.; Hamilton, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 6453–6454.

(2) These classes of aromatic diimides have proven, and continue to prove, to be versatile and valuable building blocks for new applications in molecular recognition and as components of functional materials. For selected examples from the past two years, see: (a) Bradford, V. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2008**, *130*, 1517–1524. (b) Sakai, N.; Sisson, A. L.; Bhosale, S.; Furstenberg, A.; Banerji, N.; Vauthey, E.; Matile, S. *Org. Biomol. Chem.* **2007**, *5*, 2560–2563. (c) Pascu, S. I.; Naumann, C.; Kaiser, G.; Bond, A. D.; Sanders, J. K. M.; Jarrosson, T. *J. Chem. Soc., Dalton Trans.* **2007**, 3874–3884. (d) Clark, A. E.; Qin, C.; Li, A. D. Q. *J. Am. Chem. Soc.* **2007**, *129*, 7586–7595. (e) Chu, Y.; Sorey, S.; Hoffman, D. W.; Iverson, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 1304–1311. (f) Che, Y.; Datar, A.; Balakrishnan, K.; Zang, L. *J. Am. Chem. Soc.* **2007**, *129*, 7234–7235. (g) Wang, W.; Wang, L.; Palmer, B. J.; Exarhos, G. J.; Li, A. D. Q. *J. Am. Chem. Soc.* **2006**, *128*, 11150–11159. (h) Reczek, J. J.; Villazor, K. R.; Lynch, V.; Swager, T. M.; Iverson, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 7995–8002. (i) Pengo, P.; Pantos, G. D.; Otto, S.; Sanders, J. K. M. *J. Org. Chem.* **2006**, *71*, 7063–7066. (j) Kato, S.; Matsumoto, T.; Ideta, K.; Shimasaki, T.; Goto, K.; Shinmyozu, T. *J. Org. Chem.* **2006**, *71*, 4723–4733. (k) Johnstone, K. D.; Bampos, N.; Sanders, J. K. M.; Gunter, M. J. *New J. Chem.* **2006**, *30*, 861–867. (l) Bhosale, S.; Sisson, A. L.; Talukdar, P.; Furstenberg, A.; Banerji, N.; Vauthey, E.; Bollot, G.; Mareda, J.; Roger, C.; Wurthner, F.; Sakai, N.; Matile, S. *Science* **2006**, *313*, 84–86. (m) Balakrishnan, K.; Datar, A.; Naddo, T.; Huang, J.; Oitker, R.; Yen, M.; Zhao, J.; Zang, L. *J. Am. Chem. Soc.* **2006**, *128*, 7390–7398.

(3) (a) Rochefort, A.; Bayard, E.; Hadj-Messaoud, S. *Adv. Mater.* **2007**, *19*, 1992–1995. (b) Traber, B.; Wolff, J. J.; Rominger, F.; Oeser, T.; Gleiter, R.; Goebel, M.; Wortmann, R. *Chem. Eur. J.* **2004**, *10*, 1227–1238. (c) Tulevski, G. S.; Bushey, M. L.; Kosky, J. L.; Ruter, S. J. T.; Nuckolls, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1836–1839. (d) Bushey, M. L.; Nguyen, T.-Q.; Zhang, W.; Horoszewski, D.; Nuckolls, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5446–5453. (e) Gearba, R. I.; Lehmann, M.; Levin, J.; Ivanov, D. A.; Koch, M. H. J.; Barberá, J.; Debije, M. G.; Piris, J.; Geerts, Y. H. *Adv. Mater.* **2003**, *15*, 1614–1618. (f) Bushey, M. L.; Nguyen, T.-Q.; Nuckolls, C. *J. Am. Chem. Soc.* **2003**, *125*, 8264–8269. (g) Ma, S.; Ni, B. *J. Org. Chem.* **2002**, *67*, 8280–8283.

(4) Park, L. Y.; Hamilton, D. G.; McGehee, E. A.; McMenimen, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 10586–10590.

(5) Carroll, J. B.; Gray, M.; McMenimen, K. A.; Hamilton, D. G.; Rotello, V. M. *Org. Lett.* **2003**, *5*, 3177–3180.

(6) Augustin, M.; Jeschke, P. *Z. Chem.* **1987**, *27*, 257–258.

(7) Mellitic triimides have been reported as components of network polymers. Clemenson, P. I.; Pandiman, D.; Pearson, J. T.; Lavery, A. J. *Polym. Eng. Sci.* **1997**, *37*, 966–977.

(8) Some of this chemistry was explored in parallel with that reported in ref 1.

(9) (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *28*, 539–556. (b) Agenet, N.; Gandon, V.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2007**, *129*, 8860–8871.

(10) For example, treatment of tetramethyl pyromellitate with 2 equiv of *n*-butylamine in DMF at 140 °C for 16 h gave a 35% yield of *N,N′*-di-*n*-butylpyromellitimide.

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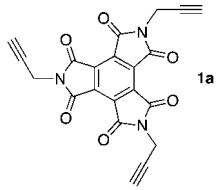
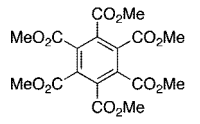
limit of usefulness of this approach, in our hands at least, was reached with the preparation of acetylenic triimide derivative **1a** (see the Supporting Information). The difficulties encountered here only served to further highlight the desirability of a more reliable and general synthetic approach.



A straightforward alternative synthesis[8] needed to begin with a hexacarbonyl benzene, and the inexpensive hexamethyl ester **5**, the benchmark product of metal-catalyzed acetylene cyclotrimerizations,[9] was attractive. However, while reaction of 1,2,4,5-tetramethyl pyromellitate with primary amines affords acceptable yields of the corresponding diimides,[10] parallel reactions of hexaester **5** gave only limited evidence of triimide formation, with one ultimately instructive exception (vide infra). Reactions of primary amines with hexachlorocarbonyl benzene also presented very limited evidence of triimide formation.[11] Naturally, trianhydride **6**[12] was an extremely attractive triimide precursor as the vast majority of aromatic diimides are prepared from their corresponding dianhydrides.[2] However, our efforts to establish a reliable preparation of pure **6** from mellitic acid **2** were unsuccessful, and while some triimides were formed in low yield from reactions involving mixtures imputed to contain **6** we could not rely on this approach as a general method.[13]



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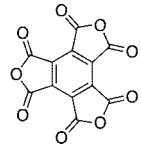

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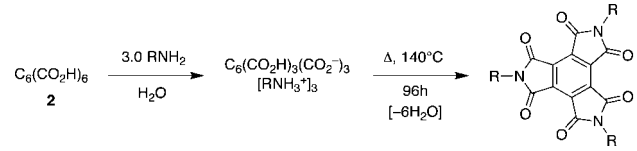
These considerations prompted further review of our original synthetic approach—the Mitsunobu chemistry outlined in Scheme 1—and a lone success from the reaction of an aniline with hexaester **5**. This solitary successful reaction involved *p*-toluidine, the triimide derivative of which precipitates from a high temperature reaction in DMSO in low yield.[14] Unambiguous structural assignment could be made by comparison with the literature as this particular derivative represents, to the best of our knowledge, the only other reported mellitic triimide (prepared by a nongeneral, multistep route).[6] However, the failure of related reactions with a variety of aniline derivatives to deliver triimide products suggested that the unique success with *p*-toluidine may be the result of the product trimide precipitating from solution, thereby avoiding further (destructive)

SCHEME 2. Substituted Mellitic Triimide Synthesis via Solid-State Dehydration of Triammonium Salts of Mellitic Acid



reaction with potent amine nucleophiles.[15] Solution chemistry involving amines therefore appeared generally problematic, especially when coupled with the relatively high temperatures typically required for imide ring closure. Solid-state chemistry was predicted to mitigate this problem and had, of course, already proven successful in the conversion of hexammonium salt **3** to crude unsubstituted mellitic triimide **4**.[1] Accordingly, attention was turned to arguably the simplest approach of all: formation of a triammonium salt of mellitic acid, followed by solid-state thermal dehydration to the triimide (Scheme 2).

For comparative purposes, syntheses of *n*-alkylmellitic triimides prepared by our earlier route (**1b**−**d**) were first attempted. Treatment of an aqueous solution of mellitic acid (1.5mmol scale) with 3 molar equiv of the appropriate amine followed by evaporation, heating, and chromatographic isolation gave the desired triimides in acceptable yields (see the Example Preparative Procedure, Supporting Information, and Table 1). Separation of the desired products from the potentially complex array of materials formed in these nonselective processes was substantially eased by the fact that the mellitic triimides were the least polar components of the product mixture. These preparations were also used to explore optimal molar ratios, reaction temperatures, and reaction times: increasing the ratio of amine to mellitic acid from 3:1 to as high as 6:1 lowered the isolated yield of triimide while increasing the amount of intractable polar product.[16] Both shorter reaction times (24 h at 140 °C) and lower temperatures (100 °C for 96 h) led to substantially reduced yields, as did extended times (10 days at 140 °C) or higher temperatures (180 °C for 96 h). While incremental improvements in specific cases were likely available, the standard conditions detailed in Scheme 2 were therefore employed in all subsequent triimide syntheses. Finally, a preparation of triimide **1b** was conducted at five times the standard scale, with no apparent reduction in overall efficiency, affording >1 g of the triimide product.[17]

Extension to alkyl substituents that could not be successfully introduced using the earlier route was readily accomplished

(11) Ranganathan, S.; Muraleedharan, K. M.; Chandrashekhar Rao, C. H.; Vairamani, M.; Karle, I. L.; Gilardi, R. D. *Chem. Commun.* **2001**, 2544–2545, Traces of triimide formation could be found from reactions of this material with 3 equiv of primary amines; however, the major isolable products were hexaamides.

(12) Most of the literature concerning the preparation and properties of mellitic trianhydride is quite dated. (a) Meyer, H.; Raudnitz, H. *Chem. Ber.* **1930**, *63*, 2010–2018. (b) Orlov, N. A.; Mustafin, I. S. *Khim. Tverd. Topl. (Moscow, Russ. Fed.)* **1936**, *7*, 877–890. (c) Mustafin, I. S. *Russ. J. Gen. Chem.* **1947**, *17*, 560–564. (d) Rosenberg, H. M.; Eimutis, E.; Hale, D. *J. Phys. Chem.* **1966**, *70*, 4096–4097. (e) Casellato, F.; Casu, B.; Vecchi, C.; Girelli, A. *Chim. Ind. (Milan, Italy)* **1974**, *56*, 603–609. (f) Casellato, F.; Vecchi, C.; Girelli, A. *Chem. Ind. (London, U. K.)* **1974**, 918–919. The more recent exceptions principally relate to structure. (g) Ermer, O.; Neudorfl, J. *Helv. Chim. Acta* **2000**, *83*, 300–309. (h) Erkoc, S. *THEOCHEM* **2001**, *542*, 95–99.

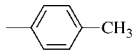
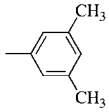
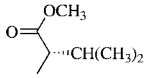
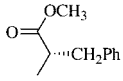
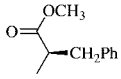
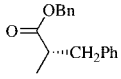
(13) Reference 12a reports the preparation of mellitic trianhydride from mellitic acid by treatment with acetyl chloride. Our attempts to reproduce this chemistry led to inconclusive results: the poor solubility of the product, or products, eliminated the possibility of solution NMR, while both IR and solid-state NMR spectra were inconclusive. When susbstituted for mellitic acid in the preparations described here, mellitic triimides were formed in low and variable yield. However, the acid−amide materials potentially formed en route to trimides via anhydride ring opening in this case would also be formed in the initial dehydrations of the triammonium salts described in this work. Thus, initial preparation of mellitic trianhydride may now be regarded as an uneccessary embellishment of the current synthesis.

(14) Reaction of the hexamethyl ester of mellitic acid with 3 equiv of *p*-toluidine in DMSO at 170 °C for 16 h gave a 10% yield of triimide **1h**. This material was spectroscopically indistinguishable from samples prepared by the current route and also proved a match to the material described in ref 6.

(15) Solution NMR experiments have revealed that *n*-alkyl triimides are slowly attacked by primary amines. Furthermore, ref 11 describes the preparation of a mellitic hexaamide resulting from in situ solution ring opening of an intermediate imide.

(16) For example, a preparation of triethylmellitic triimide (**1e**) that employed a 6:1 ratio of amine to mellitic acid reduced the isolated yield of product to 22%.

TABLE 1. Structure, Core ^{13}C NMR Shifts, and Yields for Mellitic Triimides 1b−m Prepared According to Scheme 2

Entry	R	δ ^{13}C core[a]	Yield[b]
1b	$-(CH_2)_3CH_3$	162.7, 133.5	44 (<10)[c]
1c	$-(CH_2)_7CH_3$	162.7, 133.6	42 (<10)[c]
1d	$-(CH_2)_{13}CH_3$	162.7, 133.5	25 (<10)[c]
1e	$-CH_2CH_3$	162.5, 133.6	34
1f	$-CH(CH_3)_2$	162.7, 133.5	50
1g	$-CH_2Ph$	162.2, 133.7	55
1h		161.6, 134.0	28 (18)[d]
1i		161.6, 134.0	22
1j		162.0, 133.8	41
1k		161.5, 133.3	33
1l		161.5, 133.3	30
1m		161.5, 133.2	28

[a] Carbonyl and aromatic resonances respectively. [b] Isolated yield, average of three runs. [c] Parenthetical yields are upper limit estimates (from mellitic acid) for a previous route (refs 1, 4). [d] Parenthetical yield refers to an alternative multi-step route (ref 6).

(**1e**−**g**) in yields sometimes exceeding 50% (Table 1). Aromatic substituents were also readily introduced (**1h**,**i**) by employing aniline derivatives, albeit in lower average yields.[18] Finally, and most significantly in terms of added functionality, amino acid methyl esters also proved amenable to this reaction (**1j**−**l**). The benzyl ester of L-phenylanaline could also be introduced in comparable yield (**1m**) affording a derivative with readily removed carboxyl protecting groups. For all of the examples quoted in Table 1 infrared spectra revealed the characteristic two absorption signature of the imide ring (1775 ± 5, 1730 ± 10 cm^{-1}),[19] while ^{13}C NMR spectra displayed the symmetry and consistency expected for the mellitic triimide core.

The proton NMR spectra of amino acid methyl ester substituted triimides **1j**−**l** did not provide evidence of racemization during synthesis. Nevertheless, it was possible that each *N*-substituent group was sufficiently remote from the others to render distinctions between possible diastereoisomers too small to be apparent by this means. Therefore an additional preparation was conducted employing a racemic mixture of D- and L-phenylalanine methyl esters. An expanded view of the methine proton region of the products of this reaction is shown in Figure 1, alongside the corresponding region for triimide **1k** derived from L-phenylalanine. The mix of diastereoisomers expected

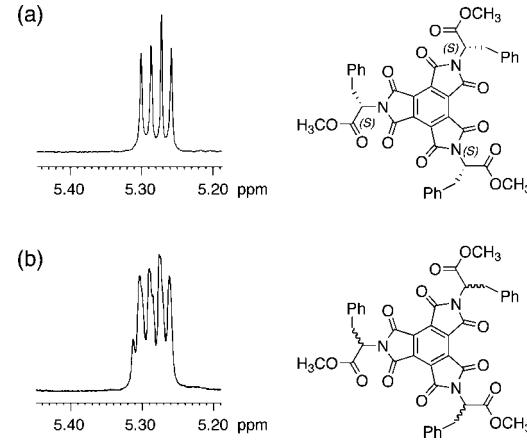


FIGURE 1. Expanded view of the methine proton (N-C*H*) regions of the 400 MHz ^{1}H NMR spectra of (a) triimide **1k** derived from L-phenylalanine methyl ester and (b) the diastereomeric mixture of triimides expected from employment of *racemic* phenylalanine methyl ester.

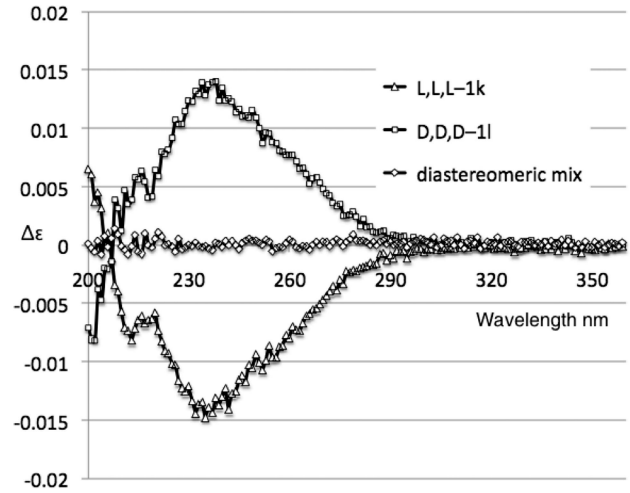


FIGURE 2. Aromatic absorption region of the circular dichroism spectra of L,L,L-triimide **1k**, D,D,D-triimide **1l**, and the mixture of diastereomeric triimides obtained from *racemic* phenylalanine methyl ester (Δε units are M^{-1} cm^{-1}).

from employment of the racemate (L,L,L; L,L,D; L,D,D; D,D,D) clearly presents a more complex multiplet and suggests that the methine proton resonance detailed in Figure 1a therefore represents a single environment. Additionally, the specific rotations of L,L,L-triimide **1k** and D,D,D-triimide **1l** were found to be of equal magnitude and opposite sign (**1k** $[\alpha]^{20}_D = -215 \pm 10$; **1k** $[\alpha]^{20}_D = +215 \pm 10$) while that of the prepared mix of diastereoisomers was found, within experimental error, to be zero. Finally, circular dichroism spectra (0.25 mM, MeOH) of L,L,L-triimide **1k**, D,D,D-triimide **1l**, and the prepared mix of diastereoisomers entirely support the argument for stereochemical integrity (Figure 2). The aromatic absorbances for L,L,L-triimide **1k** and D,D,D-triimide **1l** present the mirror image relationship expected of enantiomers, while the mix of products obtained from use of racemic phenylalanine in the preparation reveals the lack of absorption predicted for the resultant (optically neutral) diastereomeric mix.

The nature of the reaction conditions employed for the triimide syntheses described here made it likely that we would encounter functional group incompatibilities and/or isolation issues in attempting to broaden the approach. Such proved to

(17) Reactants and solvents were used at exactly five times the amounts and volumes reported in the Example Preparative Procedure (Supporting Information). A 1 L flask was employed to ensure the intermediate ammonium salt was spread into a relatively thin crust on evaporation. Yield: 1.26g, 37%.

(18) The lower average yields in these cases may reflect the lower nucleophilicity of anilines, when compared with amines, in the imide ring-closing reaction, though steric factors are also likely involved.

(19) All IR spectra were recorded as Nujol mulls.

be the case when attempting to introduce substituents bearing carbon−carbon multiple bonds or protected amines or aldehydes.[20] In these cases, it is likely that a confluence of elevated temperature and the relatively high acidity of the intermediate triammonium/triacid salts conspires to prohibit the desired reaction. These results further suggest that preparation of protected triimides (such as **1m**) offers the most straightforward entry to more elaborate derivatives, serving as a trifunctional core upon which to build using established chemistry.

The solid-state route[21] introduced here offers an extremely straightforward entry to hitherto inaccessible alkyl and aryl mellitic triimides for materials chemistry applications, e.g., donor–acceptor organized mesophases,[4,23] and other functional π-stacked architectures.[23] The ready entry to amino acid ester derivatives further provided by this approach will likewise allow the development of novel supramolecular systems and materials inspired by the wealth of diimide analogues.[2]

(20) The amines or anilines employed in these attempted syntheses were 6-amino-1-hexene, 4-vinylaniline (Bertini, V.; Silvana, A.; Pocci, M.; Lucchesini, N.; Picci, N.; Iemma, F. *Tetrahedron* **2004**, *60*, 11407–11414.), propargylamine (to prepare the known triimide **1a**), 4-ethynylaniline, 4-aminobutryaldehyde dimethyl acetal, 3-aminobenzaldehyde dimethyl acetal (Dear, A. E.; Liu, H. B.; Mayes, P. A.; Perlmutter, P. *Org. Biomol. Chem.* **2006**, *4*, 3778–3784.), and *N*-Boc-ethylenediamine.

(21) A related solid-state synthetic approach to pyromellitic diimide derivatives has recently been reported: Neels, A.; González Mantero, D.; Stoeckli-Evans, H. *Cryst. Growth Des.* **2008**, *8*, 1147–1153.

(22) Reczek, J. J.; Villazor, K. R.; Lynch, V.; Swager, T. M.; Iverson, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 7995–8002.

(23) Bhosale, S.; Sisson, A. L.; Sakai, N.; Matile, S. *Org. Biomol. Chem.* **2006**, *4*, 3031–3039.

Experimental Section

Example Preparative Procedure. Tri-*n*-butylmellitic triimide (**1b**): To a solution of mellitic acid (0.50 g, 1.5 mmol) in water (10 mL) in a large (250 mL) round-bottomed flask was added *n*-butylamine (322 mg, 437 μL, 4.4 mmol). After the mixture was stirred for 10 min, the water was evaporated and the reaction flask transferred to a standard glassware drying oven and maintained at 140 °C for 4 days. After the mixture was cooled to room temperature, chloroform (10 mL) was added and the resulting mixture sonicated for 2 min. Silica gel (10 g) was added, the solvent evaporated, and the silica loaded onto a preprepared column. Elution (1:2 EtOAc/hexanes, product $R_f = 0.48$) gave the desired triimide **1a** as an off-white solid (0.28 g, 42%): mp 140–142 °C (lit.[1] mp 141.5–143 °C). All other spectroscopic data were in accord with those previously reported.[1]

Acknowledgment. We thank the National Science Foundation (Award 0314514) and Mount Holyoke College for financial support of this work and Dr. Kalani J. Seu for assistance in recording the circular dichroism spectra.

Supporting Information Available: General experimental details, preparative and isolation procedures, and NMR spectra for mellitic triimides **1a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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