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Esters of Pyromellitic Acid. Part II. Esters of Chiral Alcohols: Para Pyromellitate Diesters as a Novel Class of Resolving Agents and Use of Pyromellitates as Duplicands for Chiral Purification

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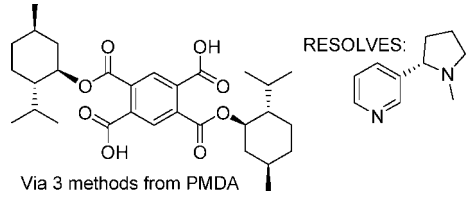

Methods are presented for the preparation of pyromellitate esters of chiral terpene alcohols, including *d*- (**3**) or *l*-menthol (4), *d*-isomenthol (**7**), *l*-borneol (**8**), or *d*- (**5**) or *l*-isopinocampheol (**6**). Alcoholysis of PMDA in CH_2Cl_2/Et_3N led to the formation of monoesters (e.g., **18**) or diesters (**11**, **12**), as needed, relying on the differential reactivity of the two anhydride groups. The easily isolated para diester (**11**) crystallized before the meta diester (**12**) from HOAc. Nicotine (**1**, **14**) was efficiently resolved as 1:1 salts with the menthyl (**11a**, **11b**) or bornyl (**11f**) para diesters, prototypes of what promises to be a large class of novel resolving agents. Recrystallization of para-di-*d*-menthyl pyromellitate (**11a**) greatly improved the chiral purity of the contained *d*-menthol (**3**), an example of purification by "duplication". An alternative synthesis of specific diesters took advantage of the easily separated benzyl diesters and their derived acid chlorides (**19**, **21**), with the benzyl esters serving as temporary blocking groups removable by catalytic hydrogenolysis. Pyromellitate tetraesters (**26**) were prepared by base-catalyzed transesterification of the tetraethyl ester (**25**). Tri-*l*-menthyl pyromellitate (**27b**) was obtained by catalytic hydrogenolysis of benzyl tri-*l*-menthyl pyromellitate (**31b**), itself prepared from the alcoholysis of benzyl pyromellitate triacid chloride (**30**) with *l*-menthol (**4**).

Introduction

Our interest in pyromellitate esters arose in the course of a synthetic program[1] to prepare[2] analogs of (*S*)-(−)-nicotine (**1**). These were generally prepared in racemic form and then resolved. Nicotine (**1**) had been traditionally resolved by crystallization of its salts of tartaric acid (**2,** R = H) or of its dibenzoyl (**2**, R = C_6H_5CO) or di-*p*-toluoyl (**2,** R = 4-$CH_3C_6H_4CO$) derivatives.[3] The low molecular weight and bifunctionality of nicotine ensure a high solubility for most of its salts, often making efficient recovery by crystallization difficult.

It was thought that a resolving agent of higher molecular weight might lower the solubility of the derived salts to a level such that the efficiency of a resolution would be significantly improved. Potential salts were envisioned as being derived from the class of phthalate monoesters available from the reaction of a range of inexpensively available terpene alcohols [*d*- (**3**) or *l*-menthol (**4**), *d*- (**5**) or *l*-isopinocampheol (**6**), *d*-isomenthol (**7**), *l*-borneol (**8**)] or cholesterol (**9**) with various commercially available phthalic anhydrides. Phthalic anhydride itself was found to give derivatives too soluble and too reluctant to crystallize with nicotine to be useful. This suggested that the numerous commercially available halogenated or nitrated phthalic anhydrides should be bypassed in favor of the commercially available symmetrical "double" phthalic anhydride, pyromellitic dianhydride (PMDA) (**10**) (Scheme 1).

Unlike any simple phthalate, any of the three possible specific pyromellitate diester isomers should possess C_2 symmetry, a feature desirable in any resolving agent for entropic reasons,

(1) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *J. Org. Chem.* **1981**, *46*, 3040–3048.
(2) Hu, M. W.; Bondinell, W. E.; Hoffmann, D. *J. Labelled Comp.* **1974**, *10*, 79–88.
(3) (a) Bowman, E. R.; McKennis, H., Jr.; Martin, B. *Synth. Commun.* **1982**, *12*, 871–879. (b) Aceto, M. D.; Martin, B. R.; Uwaydah, I. M.; May, E. L.; Harris, L. S.; Izazola-Conde, C.; Dewey, W. L.; Bradshaw, T. J.; Vincek, W. C. *J. Med. Chem.* **1979**, *22*, 174–177.

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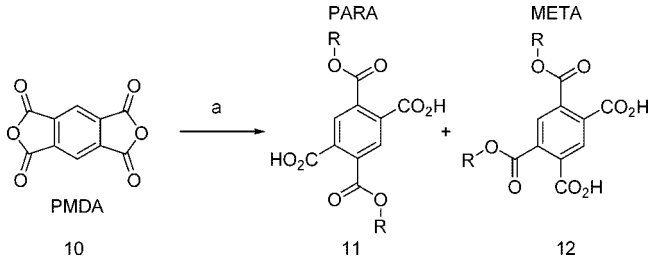
SCHEME 1. Synthesis of Chiral Para (11) and Meta Pyromellitate Diesters (12) from PMDA (10)[a]



[a] Numbering for **11** and **12**: **a**, ROH = *d*-menthol (**3**); **b**, ROH = *l*-menthol (**4**); **c**, ROH = *d*-isopinocampheol (**5**); **d**, ROH = *l*-isopinocampheol (**6**); **e**, ROH = *d*-isomenthol (**7**); **f**, ROH = *l*-borneol (**8**). Reagents and conditions: (a) 2ROH, $2Et_3N$, CH_2Cl_2, rt to reflux, or (a) ROH = *d*- or *l*-menthol (**3** or **4**) molten ROH, 140−190°C.

and furthermore would be of the desired molecular weight (typically at or above 526 for the derivatives from the chiral alcohols shown above). Finally, the derivatization of pyromellitic acid with the wide range of these and other available chiral primary or secondary alcohols would lead to an entire *class* of novel resolving agents. A number of these would be readily available as both antipodes.

To simplify the following discussion and the visualization of the compounds described, the trivial nomenclature employed in the preceding paper[4] will be continued. 1,2-Diester 4,5-dicarboxylic acids, 1,5-diester 2,4-dicarboxylic acids (**12**), and 1,4-diester 2,5-dicarboxylic acids (**11**) shall be referred to as "ortho", "meta", and "para" pyromellitate diesters, respectively because such are the respective relative relationships of the paired equivalent carbonyls in each.

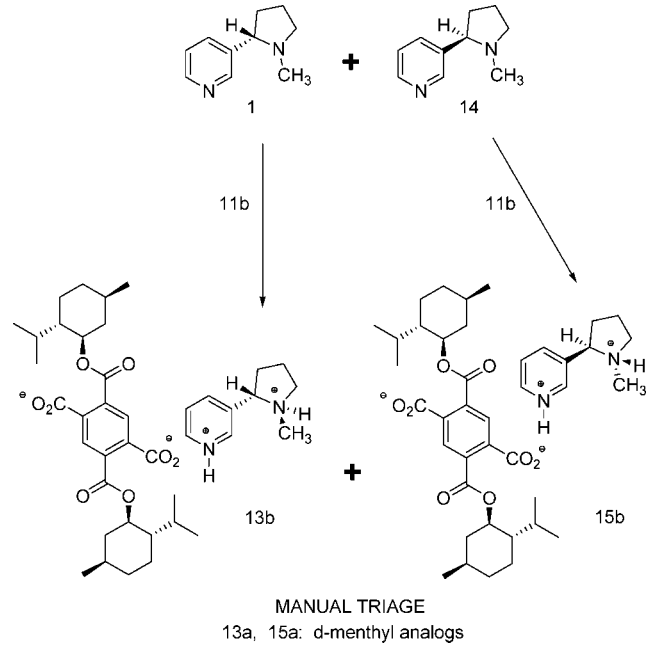
Results and Discussion

Pyromellitate Para Diesters of Menthol as Resolving Agents for Chiral Amines such as Nicotine (1). The initial experiment entailed heating PMDA (**10**) with an excess of molten *l*-menthol (**4**) (>2 equiv). The reaction mixture dissolved nicely in boiling glacial acetic acid, from which, upon slight cooling and modest aqueous dilution, a white granular powder soon separated in quantity. This proved to be the pure para diester (**11b**). Further aqueous dilution of the filtrates led to the crystallization of the meta diester (**12b**), subsequently purified by fractional crystallization (Scheme 1).

This first "wildcat" experiment (Scheme 1, ROH = *l*-menthol, **4**) "struck oil", when **11b** was found not only to give (in methanol, the first-chosen solvent) a 1:1 adduct (**13b**) with (*S*)-(−)-nicotine (**1**) as enormous transparent crystals of steep solubility coefficient but also to be capable of producing this salt from racemic nicotine.[5]

The resolution (Scheme 2) was clouded by the fact that (*R*)-(+)-nicotine (**14**) soon also gave a crystalline 1:1 adduct (**15b**) with **11b** and that once seeds of **15b** had formed, it was not possible to prevent cocrystallization of both diastereomers (when initially present in equimolar quantities). However, **15b** had crystallized from methanol with solvation that was easily lost, whereas the less extensive solvation of **13b** was tightly bound. Upon drying in air, **15b** quickly desolvated and become opaque white, while **13b** remained transparent (subsequently going opaque only upon prolonged storage). Resolution involved

SCHEME 2. Resolution of (*S*)-(−)-Nicotine (1) and (*R*)-(+)-Nicotine (14) as the 1:1 Salts of Para-di-*l*-menthyl Pyromellitate (11b): Manual Triage of "Transparent Salt" (13b) with (*S*)-(−)-Nicotine and "Opaque Salt" (15b) with (*R*)-(+)-Nicotine



merely physically separating the opaque white crystals from those that were transparent; a magnifying glass was not required. The separated diastereomers could be further purified by recrystallization; however it was found that **13b** converged to absolute purity considerably faster than **15b**. A test resolution, starting with deliberately prepared 90% (*S*)-(−)-nicotine (**1**) [and 10% (*R*)-(+)-nicotine (**14**)] gave only crystals of **13b**. By isolating the nicotine quantitatively from the mother liquors of each recrystallization and accounting for the total content of (*R*)-(+)-nicotine (**14**), it was possible to calculate that the crystals had to be 99.8% pure (*S*)-(−)-antipode after only two crystallizations! This purity was confirmed by isolating the nicotine (**1**) from the crystals and measuring the optical activity.

The high efficiency of "transparent salt" **13b** (or **15a**) makes it especially suitable for completing a resolution of nicotine (**1** or **14**), once an initial crude splitting has been made with another resolving agent. The difficultly scalable manual triage of **13b** and **15b** can be thus avoided.

It should be noted that the para pyromellitate diesters (**11**) are stable and can be recovered efficiently from the salts upon completion of the resolution. In the case of the above isolation of nicotine from the crystals, nearly quantitative recovery of intact resolving agent was achieved 12 *years* after the salt had been prepared.

The meta diester (**12b**) refused to crystallize with (*S*)-(−)-nicotine (**1**) and was not investigated further. Other areas that were left uninvestigated included possible suitability of pyromellitate meta or ortho diesters for resolution of substrates other than nicotine (**1**) and the possible use of thermal isomerization to convert the apparently less useful meta diesters (**12**) to their para isomers (**11**), by taking advantage of reversible anhydride formation in the pyromellitate system.[4]

d-Menthol (**3**) reacted in analogous fashion. Its para diester (**11a**) crystallized preferentially with (*R*)-(+)-nicotine (**14**). In practice, the system was somewhat less well behaved. The

(4) Paine, J. B. *J. Org. Chem.* **2008**, *73*, 4929–4938.
(5) Tsujino, Y.; Shibata, S.; Katsuyama, A.; Kisaki, T.; Kaneko, H. *Heterocycles* **1982**, *19*, 2151–2154.

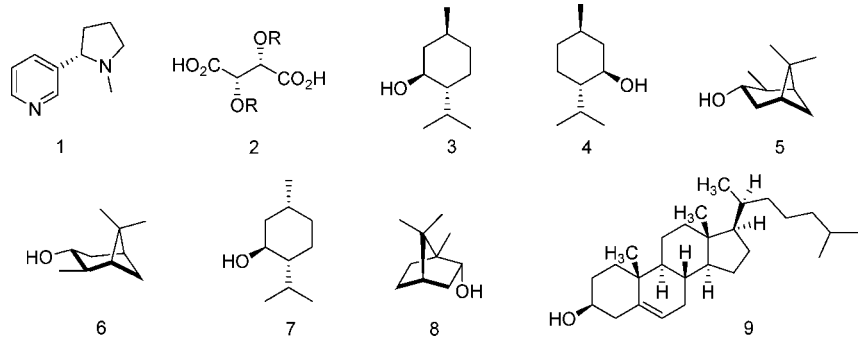


FIGURE 1. Structures of (*S*)-(−)-nicotine (**1**), tartrate resolving agents (**2**), and terpene alcohols (**3**−**9**) used in chiral pyromellitate ester synthesis.

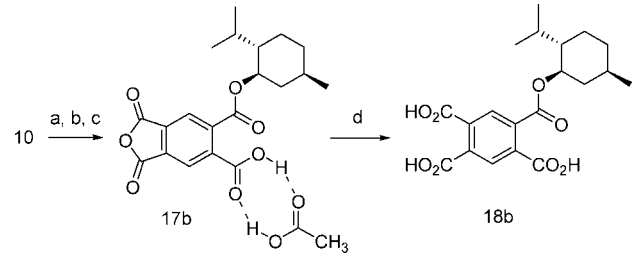
synthetic *d*-menthol (**3**) employed in the preparation contained about 2% of its antipode. By contrast the *l*-menthol (**4**) used previously was the natural (Brazilian, from *Mentha arvensis*) material and thus known to be optically pure.[6] The resulting **11a**, NMR-pure with respect to any meta isomer, had been used directly. As will be seen below, it takes several additional recrystallizations to render **11a** chirally pure.

Synthesis of Pyromellitate Diesters of Other Terpene Alcohols. The other terpene alcohols of Figure 1 (**5**−**9**) were also reacted with PMDA (**10**). Since these substrates were potentially unstable at high temperature (the isopinocampheols, **5** and **6**) or excessively high melting (*l*-borneol, **8**), the milder conditions (stoichiometric alcohols and triethylamine in CH_2Cl_2) described previously[4] were used to run the reaction. In practice, it became usual to add the amine gradually to a well-stirred suspension of PMDA in a solution of the chosen alcohol in dichloromethane. Because the second anhydride ring to react was found to be much less reactive than the first,[4,7] completion of diesterification could not be assumed to have occurred immediately after the system had become homogeneous or spontaneous boiling had ceased but required further time. Workup entailed acidification with aqueous HCl to remove Et_3N and then crystallization from acetic acid. In every instance, the para diester (**11c**−**f**) crystallized first and was easily isolated; the meta diesters (**12c**−**f**) varied somewhat in their ease of isolation. The two isomers were generally each isolated in yields ranging from 20% to 40%. The experimental details for much of this is presented in Supporting Information. The above mild conditions were also applied successfully to *d*- (**3**) and *l*-menthol (**4**).

The use of *1 equiv* of *l*-menthol (**4**) and triethylamine with PMDA suspended in CH_2Cl_2 also led to the formation of a homogeneous solution under these conditions and afforded good yields of the pyromellitate monoester (**18b**) after workup (Scheme 3). An important feature of the intermediate pyromellitate monoester anhydrides such as **17b** is their propensity to crystallize as 1:1 adducts with acetic acid. It is therefore advantageous to include acetic anhydride and acetic acid in the workup procedure.

Brief attempts to generate pyromellitate diesters of higher molecular weight from sesquiterpene *tertiary* chiral alcohols such as cedrol or patchouli alcohol were not successful. No attempt was made to prepare pyromellitate diamide dicarboxylic acid analogs of the above diesters, using chiral *disubstituted* amines, although this should be a promising area for future study. It should be further noted that the differential activity[4,7] of the two anhydride rings of PMDA (**10**) would allow two *different* chiral alcohols (or amines or one of each) to be appended in sequential fashion. However, such derivatives would lack the C_2 symmetry that is generally considered advantageous (since all favorable states and interactions a 2-fold symmetric resolving agent might have with its substrate are doubled in probability).

SCHEME 3. Synthesis of Mono-*l*-menthyl Pyromellitate (18b) from PMDA (10)[a]



[a] Reagents and conditions: (a) ROH = *l*-menthol, Et_3N, CH_2Cl_2, rt to reflux; (b) HCl, H_2O; (c) HOAc, Ac_2O; (d) H_2O, HOAc, brief reflux.

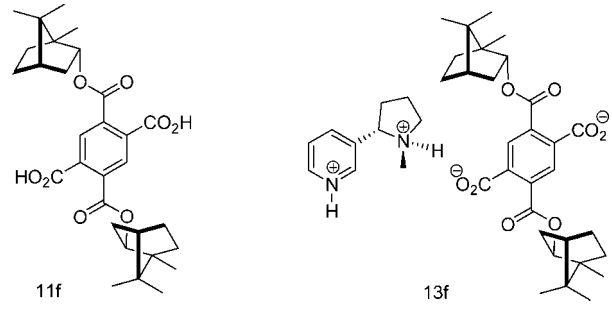


FIGURE 2. Para-di-*l*-bornyl pyromellitate (**11f**) and its salt (**13f**) with (*S*)-(−)-nicotine.

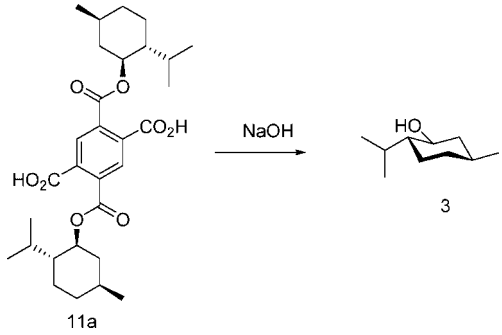
Other Para Pyromellitate Diesters in Nicotine Resolution. Although all of the para diesters (**11**) examined gave crystalline derivatives with (*S*)-(−)-nicotine (**1**), only the *l*-bornyl derivative (**11f**, Figure 2) also proved capable of resolving (*S*)-(−)-nicotine (**1**) from the racemic form.[5] The others deposited different phases from (*R,S*)-nicotine (**1** + **14**) than from (*S*)-(−)- nicotine (**1**) alone.

In the *l*-bornyl case, a single solid phase of low solubility formed (**13f**), which was greatly enriched in the (*S*)-(−)-antipode of nicotine, but this did not converge to absolute purity upon recrystallization nearly as well as **13b**. However, **11f** could be

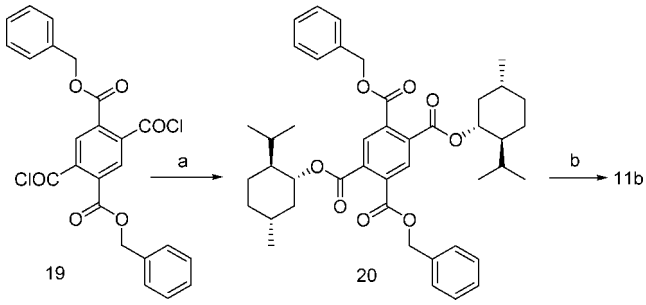
(6) (a) Ravid, U. *Perfum. Flavor.* **1998**, *23*, 25–28, 30. (b) Werkhoff, P.; Hopp, R. *Progress in Essential Oil Research*; Brunke, E. J., Ed.; Walter de Gruyter: New York, NY, 1986; pp 529−549. (c) Coleman, W. M., III; Perfetti, T. A.; Suber, R. L., Jr *J. Chromatogr. Sci.* **1998**, *36*, 318–321.

(7) Kreuz, J. A.; Angelo, R. J.; Barth, W. E. *J. Polym. Sci., Part A-1* **1967**, *5*, 2961–2963.

SCHEME 4. Chiral Purification of *d*-Menthol as the Para Pyromellitate Diester



SCHEME 5. Benzyl Ester Assisted Synthesis of Para-di-*l*-menthyl Pyromellitate (11b)[a]



[a] Reagents and conditions: (a) 2ROH = *l*-menthol, $2Et_3N$, CH_2Cl_2, rt; (b) H_2, Pd−C, THF, 1 atm, rt.

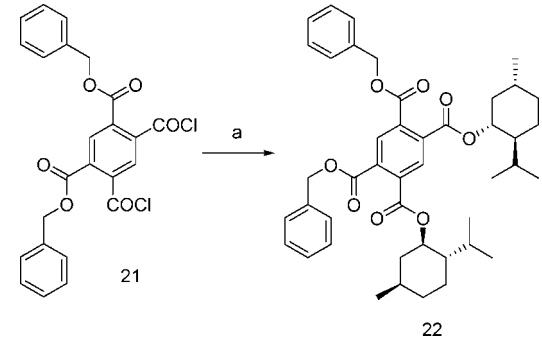
employed as the resolving agent to provide the initial crude splitting of the antipodes **1** and **14**, allowing **11a,b** to complete the resolution of **1** and **14** without need for manual triage. Under these conditions, the maximally efficient "transparent salt" (**13b** or **15a**) was the only phase formed.

Unfortunately, when extended to some of the analogs of nicotine, these resolving agents failed in our hands, either giving seed crystals only with difficulty or else unresolvable solids.

Pyromellitate Para Diesters as Duplicands for Purification of the Contained Chiral Alcohols. Interest in these resolving agents was rekindled when a need for highly purified menthol diastereomers arose. It was soon found that *d*-menthol (**3**), typically offered commercially in 96−98% chiral purity, could be quickly upgraded to 99.95% chiral purity by only two additional recrystallizations of the para pyromellitate diester **11a** from methanol. The contained *d*-menthol (**3**) could be easily recovered nearly quantitatively by saponification in dilute aqueous alkali, followed by a modified "steam" distillation (Scheme 4). This is an example of a purification by "duplication".[8]

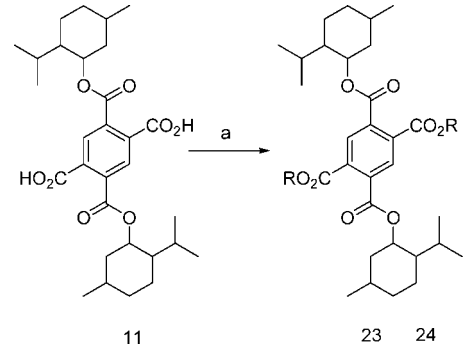
Benzyl Ester Route to Chiral Para Pyromellitate Diesters. The yields of the generally preferred para diesters **11** that have been isolated from direct reactions with PMDA (**10**) have only generally ranged from 20% to 40% (when crystallization was used). Therefore, the direct reaction of terpene alcohols with PMDA (**10**) can hardly be considered sufficiently efficient for use in duplicative purification of such alcohols. To improve the yields of **11** from terpene alcohols, the use of benzyl esters was investigated (Scheme 5). The sacrifice to the unwanted meta diesters was therefore intended to be made by benzyl alcohol

SCHEME 6. Synthesis of Meta Dibenzyl Di-*l*-menthyl Pyromellitate (22)[a]



[a] Reagents and conditions. (a) 2ROH = *l*-menthol, $2Et_3N$, CH_2Cl_2, rt.

SCHEME 7. Esterification of Para Dimenthyl Pyromellitates (11a, 11b) with Orthoformate Esters[a]



[a] Numbering for **11**, **23** (R = methyl), and **24** (R = ethyl): **a**, *d*-menthyl series; **b**, *l*-menthyl series. Reagents and conditions: (a) $HC(OR)_3$, reflux.

and PMDA (**10**) and not the potentially valuable or precious chiral alcohols.

Para dibenzyl pyromellitate diacid chloride (**19**)[4] reacted smoothly but slowly with *l*-menthol (**4**) in CH_2Cl_2/Et_3N at room temperature, and the resulting para dibenzyl di-*l*-menthyl pyromellitate (**20b**) was isolated in pure form by crystallization. The hydrogenolysis of **20b** over Pd−C in THF led quantitatively to **11b**, demonstrating the amenability of the chemistry and the viability of the approach (Scheme 5). This approach avoids the tedium of recycling unwanted byproducts, either by saponification or thermal isomerization. The meta dibenzyl di-*l*-menthyl pyromellitate (**22**) could be prepared similarly from **21** (Scheme 6).

Other Pyromellitate Mixed Tetraesters as Duplicands for Menthol. Prepared from **11a** or **11b** and trimethyl or triethyl orthoformate[4,9] (Scheme 7) were specific para dimethyl (**23**) or diethyl dimenthyl pyromellitates (**24**). Of these, **24a,b** proved less efficient at resolving the contained menthol than the para diester precursors (**11a,b**). This may be a consequence of the effects of hydrogen-bonding upon the crystal structure, an option only available to **11a,b** and not its derived tetraesters.

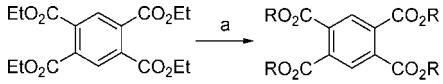
Pyromellitate Tetraesters as Potential Quadruplicands (or Bis-duplicands) for the Purification of the Contained Chiral Alcohols. Tetraethyl pyromellitate (**25**)[4] was found to transesterify smoothly with terpene alcohols in boiling xylene, to which small portions of NaH catalyst were periodically added (Scheme 8).

The resulting terpene tetraesters (**26**), typically of MW around 800, had steep solubility coefficients in solvents such as

(8) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055–1059.

(9) Cohen, H.; Meier, J. D. *Chem. Ind.(London)* **1965**, 349–350.

SCHEME 8. Synthesis of Chiral Pyromellitate Tetraesters (26) by Transesterification[a]



25 26

[a] Numbering for **26**: **a**, ROH = *d*-menthol; **b**, ROH = *l*-menthol; **c**, ROH = *d*-isopinocampheol; **d**, ROH = *l*-isopinocampheol; **e**, ROH = *d*-isomenthol; **f**, ROH = *l*-borneol. Reagents and conditions: (a) ROH, catalytic NaH, xylene, reflux.

n-butanol. Their resolution efficiency was low, no doubt due to extensive possibilities for solid solution. However, this was offset in part by their direct availability from precursors in high yield. These represent examples of "quadruplication" (or more strictly "bis-duplication" since the symmetry is not higher than D_2). [Not investigated was the possibility that certain members of this class might prove amenable to purification by zone refining.]

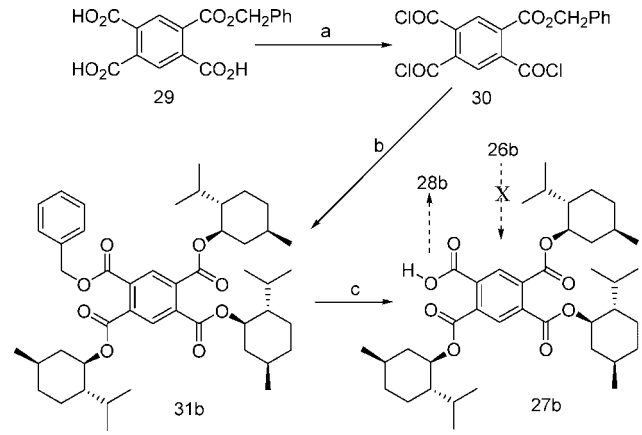
The above base-catalyzed transesterification is an alternative approach to this class of compounds, which lately have been of interest as sensitizers for chiral photochemistry.[10–16] The Inoue group prepared these materials by the alcoholysis of pyromellitoyl tetrachloride,[16,17] reporting yields of 73−74% after recrystallization from ethanol.

The above work led conceptually into the significantly improved procedures for the "duplicative" purification of terpene alcohols, using symmetrical aromatic diesters, which we shall report in the future.[18]

Tri-*l*-menthyl Pyromellitate: Use of Benzyl Esters To Avoid a Difficult Saponification. Tetra-*l*-menthyl pyromellitate (**26b**) was envisioned as a precursor to the triester (**27b**) and the ortho diester anhydride (**28b**) upon saponification and pyrolysis, respectively (Scheme 9). However, **26b** was found to be too insoluble in solvents which would also dissolve NaOH (poly(ethylene glycol) ethers were not investigated), vulnerable to partial transesterification in alcohols in the presence of base, and generally slow to react, no doubt due to steric congestion near the carbonyl groups. Instead, a benzyl ester approach was employed to prepare the triester (**27b**).

Thus, monobenzyl pyromellitate (**29**)[4] was converted to benzyl pyromellitate triacid chloride (**30**) using oxalyl chloride in dichloromethane with catalytic amounts of *N*,*N*-dimethyl formamide. In crude form, **30** was reacted with excess *l*-menthol (**4**) and triethylamine in dichloromethane. The resulting benzyl tri-*l*-menthyl pyromellitate (**31b**) was readily purified by chromatography and subsequent crystallization. Upon catalytic hydrogenolysis over Pd−C in tetrahydrofuran, **31b** afforded **27b** smoothly and quantitatively. The ^{1}H NMR spectrum of **31b** was noteworthy: the asymmetry of the molecule rendered the benzyl methylene protons nonequivalent and produced a magnificent AB quartet as a result; **20** and **22** behaved similarly.

SCHEME 9. Synthesis of Tri-*l*-menthyl Pyromellitate (27b), Precursor to the Ortho Diester Substitution Pattern[a]



[a] Reagents and conditions: (a) $(-COCl)_2$, catalytic $HCONMe_2$, CH_2Cl_2, rt to reflux; (b) 3*l*-menthol, $3Et_3N$, CH_2Cl_2, rt; (c) H_2, Pd−C, THF, 1 atm, rt.

TABLE 1. Manual Resolution of (*R*,*S*)-Nicotine (1 + 14) with Para-di-*l*-menthyl Pyromellitate (11b) on a 0.05 mol Scale

	13b, "transparent salt"	**15b**, "opaque salt"
round 1, yield (g)	3.92	1.11
round 2, yield (g)	11.27	14.60
total yield (g)	15.19	15.71
recrystallized yield (dried in air) (g)	10.66	10.89
recovery (%)	70.1	69.3
overall yield (%)	61.5	62.9
$[\alpha]^{20}_{589}$ (neat) of contained nicotine	−166.15	+161.8
purity of contained (%) nicotine	98.7 (*S*)-(−)	97.4 (*R*)-(+)-

Experimental Section

General Experimental Methods. General methods are presented in detail in Supporting Information. Chiral purities of products are expressed as absolute purities or (occasionally) as (apparent) optical purities, rather than as the highly artificial concept of an "enantiomeric excess".[19] The concept of "ee" based on the determination of optical rotations is not strictly applicable to systems involving duplication (or the higher orders of "multiplication"), since *diastereomers* of the principal homochiral derivative may be present as impurities, as well as the antipode. (However, the optical purity of a *duplicated* derivative does correlate to the underlying monomer composition.)

As a routine safety measure, all manipulations and reactions were performed (in the usual glassware) within the confines of large-size polypropylene trays to contain potential spillage. Hot erlenmeyer flasks removed from hot-plates for pouring of contents were handled with gloves and supported by clamps at the neck, and from below by enameled steel bowls or stainless steel trays to contain potential breakage or spillage of the hot contents.

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(19) The author adheres strongly to the view that "ee" is best used to describe the outcome of chemical *reactions*, particularly those reactions wherein the overall chiral composition is affected by the reaction mechanism and the outcome is being compared to that from a random process. For the description of actual samples or preparations, from which, in principle, ***all*** of a particular antipode is available to be isolated or used, the concept of "absolute purities" or "chiral purities" is far more useful.

TABLE 2. Efficiency of Resolution of Nicotine (1) with 11b, Starting with (90% *S*/10% *R*)-Nicotine, 0.1 mol Scale

	round 1	round 2
starting materials	0.1 mol: 16.24 g (90% *S*) nicotine; 1.624 g of original (*R*)-nicotine (**14**) content	50.56 g of **13b** (93.4% of the round 1 yield)
yield of "transparent salt", **13b**	54.11 g (78% absolute or 86.7% relative to the (*S*)-nicotine (**1**) content of the system)	45.57 (90.1% recovery)
nicotine isolated from mother liquors (g)	3.85	1.14 (theory = 1.15 g)
$[\alpha]_{589}^{20}$ (neat) of nicotine from mother liquors	−33	−153.8; $[\alpha]_{546}^{20}$ −185.0 (neat)
content of **14** (%)	40.26 (1.55 g)	4.8 (0.0547 g)
content of **14** remaining in **13b** (g)	0.074 (of which 0.069 g was carried into round 2)	0.0144

TABLE 3. Resolution of Nicotine and Purification of (*R*)-(+)-Nicotine (14) using Para-di-*l*-bornyl Pyromellitate (11f) for Initial Partition and Para-di-*d*-menthyl Pyromellitate (11a) for Further Purification

initial splitting	round 1A	round 1B	(*R*)-nicotine (**14**) purification	from mother liquors of rounds 1A and 1B
(*R*,*S*)-nicotine taken (g)	3.25 (20.03 mmol)	8.13 (50.11 mmol)	$(\alpha)_{589}^{20}$ (neat)	+96.4 (neat)
11f taken (g)	10.55 (20.03 mmol)	26.36 (50.06 mmol)	% of **14**	78.25
methanol used (g)	24.58	40.51	weight of nicotines taken (g)	5.51 (33.96 mmol)
yield of **13f** (g)	7.00 + 0.92 second crop	14.42 + 5.34 second crop	**11a** taken (g)	18.02 (33.96 mmol)
recrystallization of **13f**		19.71 g of **13f** with 83.62 g methanol; yield 14.62 g (74.1% recovery of solids)	methanol used (g)	39.17 g
$[\alpha]_{589}^{20}$ (neat) of nicotine in **13f**	−98.4 (neat), or 78.8% (*S*)-(−)-nicotine (**1**) (from first crop of round 1A)	−153.4 (neat), 95.0% (*S*)-(−)-nicotine (**1**) (in the combined recrystallized **13f**)	yield of **15a** (g)	14.95 (63.5% absolute yield or 81% based on system content of **14**)
			purity of contained **14** (%)	98.26

2,5-Bis-[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxycarbonyl]terephthalic Acid (Para-di-*l*-menthyl Pyromellitate) (11b). Method A. 1,2,4,5-Benzenetetracarboxylic dianhydride (PMDA) (**10**) (227.67 g, 1.0438 mol) was added in portions to fused (1*R*,2*S*,5*R*)-(−)-menthol (**4**) (471.6 g, 3.018 mol) at 140 °C (Erlenmeyer flask, hotplate-stirrer) with stirring until the mixture congealed. The internal temperature was raised to 180 °C to refluidize the mixture, which was stirred with a spatula, as needed. The hot mixture was then poured cautiously into boiling glacial acetic acid (1000 mL). Acetic acid (500 mL) was used to rinse the melt from the flask. When the solution had cooled to 115 °C, H_2O (200 mL) was added, with magnetic stirring, followed by seed crystals of **11b**. Stirring was continued until the temperature of the slurry fell to 90 °C, whereupon the solids were filtered off (coarse frit). The solids were rinsed with minimal glacial acetic acid, followed by 75% and 50% aqueous acetic acid, until the rinsings were colorless, and then H_2O (300 mL). The product was dried in air. Yield: 157.71 g (0.297 mol, 28.5%). Later crops of 13.55 and 152.70 g, the latter after further aqueous dilution, were obtained of mixed isomers. Mp 240.0−246.5 °C (dec, menthol odor was noted; the mp is not very reproducible.); mp (twice crystallized from methanol) 245.0−248.5 °C dec; optical rotation $[\alpha]_{589}^{20}$ −123.75, $[\alpha]_{578}^{20}$ −130.65, $[\alpha]_{546}^{20}$ −150.99 (*c* 10.415, tetrahydrofuran); ^{1}H NMR (CD_3OD) δ 0.83 (6 H, d, J = 6.92 Hz), 0.92 (6 H, d, J = 6.98 Hz), 0.96 (6 H, d, J = 6.57 Hz), [2H, m obscured by methyl doublet], 1.14 (4 H, m), 1.51 (4 H, br t), 1.74 (4 H, br d), 1.97 (2 H, m), 2.17 (2 H, br d), [3.31 (2 H, quintet) solvent, CD_2HOD], peak around 4.95 (2H, m) obscured by solvent, water protons, 7.96 (2 H, s) (2 COOH exchanged with solvent); ^{13}C NMR (CD_3OD at 49.0) δ 168.7, 167.2, 136.3, 135.8, 130.1, 77.7, 48.4*, 41.4, 35.4, 32.8, 27.4, 24.5, 22.5, 21.1, 16.7 (all peaks 2 C) (*solvent interference). Anal. Calcd for $C_{30}H_{42}O_8$: C, 67.90; H, 7.98. Found (first crop): C, 68.24; H, 8.01. Found (after recrystallization from methanol): C, 67.89; H, 8.22. **Method B.** From the catalytic hydrogenolysis of the dibenzyl ester (**20b**) in essentially quantitative yield. See below.

4,6-Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxycarbonyl]isophthalic Acid (Meta-di-*l*-menthyl Pyromellitate) (12b). Isolated by fractional crystallization from the above experiment, Method A. Mp 217.0−218.0 °C; optical rotation $[\alpha]_{589}^{20}$ −97.19, $[\alpha]_{578}^{20}$ −102.52, $[\alpha]_{546}^{20}$ −118.14, (*c* 10.545, tetrahydrofuran); ^{1}H NMR (CD_3OD) δ 0.84 (6 H, d, J = 6.93 Hz), 0.93 (6 H, d, J = 7.07 Hz), 0.97 (6 H, d, J = 6.65 Hz), [2 H, m: obscured by methyl doublet], 1.15 (4 H, br quintet), 1.52 (4 H, br t), 1.75 (4 H, br d), 1.96 (2 H, m), 2.19 (2 H, br d), 3.31 (2 H, quintet), peak near 4.95 (2H, m) obscured by solvent protons, 7.79 (H, s), 8.14 (H, s) (2 COOH exchanged with solvent); ^{13}C NMR (CD_3OD at 49.0) δ 168.7, 167.6, 136.5, 135.6, 130.9 (1C), 129.3 (1C), 77.7, 48.4, 41.4, 35.4, 32.7, 27.5, 24.6, 22.5, 21.2, 16.7 (2C each unless otherwise noted). Anal. Calcd for $C_{30}H_{42}O_8$: C, 67.90; H, 7.98. Calcd for $2C_{30}H_{42}O_8.H_2O$: C, 66.77; H, 8.03. Found: C, 66.57; H, 8.14.

2,5-Bis[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxycarbonyl]terephthalic Acid (Para-di-*d*-menthyl Pyromellitate) (11a). Method A. From PMDA (**10**) (222.11 g, 1.018 mol) and (1*S*,2*R*,5*S*)-(+)-menthol (**3**) (475.5 g, 3.043 mol), as above. Only 1330 mL in all of acetic acid was used to dissolve the melt. The 200 mL of water added at 115 °C lowered the temperature of the mixture to 97 °C and the product was filtered off at 75 °C. The solids were rinsed with acetic acid (30 mL), then 50% (v/v) aqueous HOAc (200 mL), and finally H_2O (200 mL). Yield: 175.01 g (0.330 mol, 32.4%). The filtrates on standing deposited further solids (285.0 g, 0.537 mol, 52.7%), consisting largely of the meta isomer **12a**. Mp (twice recrystallized from methanol): 245.0−249.5 °C (dec); optical rotation (respectively: original first crop, once recrystallized from methanol, and twice recrystallized from methanol): $[\alpha]_{589}^{20}$ +120.86, +122.82, +123.88; $[\alpha]_{578}^{20}$ +127.60, +129.66, +130.78; $[\alpha]_{546}^{20}$ +147.48, +148.82, +151.16. (*c* 10, tetrahydrofuran); ^{1}H NMR (CD_3OD) δ 0.83 (6 H, d, J = 6.89 Hz), 0.92 (6 H, d, J = 7.08 Hz), 0.97 (6 H, d, J = 6.55 Hz), [2 H, m: obscured by methyl doublet], 1.16 (4 H, m), 1.51 (4 H, br t), 1.74 (4 H, br d), 1.97 (2 H, m), 2.17 (2 H, m), [3.32 (2 H, m, CD_2HOD in solvent)], peak near 4.95 (2H, m) obscured by water/solvent protons, 7.97 (2 H, s) (2 COOH exchanged with solvent); ^{13}C NMR (CD_3OD at 49.4) δ 168.7, 167.6, 136.3, 135.8, 130.1, 77.7, 48.4, 41.4, 35.3, 32.7, 27.4, 24.5, 22.4, 21.1, 16.7 (2C each peak); Anal. Calcd for $C_{30}H_{42}O_8$: C, 67.90; H, 7.98. Found (recrystallized from ethanol): C, 67.80;

H, 8.11. **Method B.** PMDA (**10**) (22.47 g, 0.103 mol) and (*1S,2R,5S*)-(+)-menthol (**3**) (33.22 g, 0.2126 mol) were suspended in CH_2Cl_2 (250 mL) under moisture-exclusion conditions (magnetic stirrer), and treated, over about a minute, with triethylamine (43.5 mL, 0.312 mol). The normally insoluble anhydride dissolved quickly, and the solution boiled briefly. After standing overnight, the solution was filtered, and shaken with HCl (50 mL conc.) - H_2O (200 mL). The organic phase was isolated, dried over Na_2SO_4, and filtered. Acetic acid (200 mL) was added to the filtrates, which were concentrated to a slurry in vacuo (rotary evaporator). The slurry was heated and the volume adjusted to 275 mL with acetic acid. H_2O (32 mL) was added to the resulting hot solution. Solids appeared on cooling to 102 °C. These were filtered off at 95 °C, and washed with 50% aqueous acetic acid and then H_2O. Yield: 26.94 g (0.0508 mol, 49.3%). The filtrates deposited the meta isomer **12a** (13.26 g, 0.0250 mol, 24.3%).

2,5-Bis{*endo*-(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxycarbonyl}terephthalic Acid (Para-di-*l*-bornyl Pyromellitate) (11f). *endo*-(1*S*)-(−)-Borneol (**8**) (240.68 g, 1.56 mol, Aldrich 98% grade) was dissolved in CH_2Cl_2 (1000 mL) and filtered to remove minor sediment. PMDA (**10**) (170.2 g, 0.78 mol) was added to the filtrates followed by redistilled Et_3N (250 mL, 1.79 mol), added cautiously to the stirred suspension in a 4 L erlenmeyer flask over about 1 min. The PMDA dissolved promptly and the mixture boiled vigorously. After standing overnight at room temperature, the mixture was shaken with concentrated HCl (182 mL)−H_2O (500 mL). The organic phase was isolated promptly before product could crystallize. Acetic acid (777 mL) was added to the filtrate. After concentration on a rotary evaporator, the resulting slurry was filtered. The solids were washed with HOAc, 50% HOAc, and H_2O. The yield, after drying in air, was 114.86 g (0.218 mol, 28.0%). A sample was recrystallized for analysis from MeOH. Mp 279−286 °C (dec), but mostly at 284−286 °C (dec); optical rotation $[\alpha]^{20}_{589}$ −62.01, $[\alpha]^{20}_{578}$ −65.28, $[\alpha]^{20}_{546}$ −74.89 (*c* 10.29, tetrahydrofuran); ^{1}H NMR (CD_3OD) δ 0.93 (12 H, s), 0.99 (6 H, s), 1.26−1.41 (6 H, m), 1.70−1.80 (4 H, m), 1.93−2.01 (2 H, m), 2.44 (2 H, m), 5.09−5.14 (2 H, m), 8.02 (2 H, s) (2 COOH exchanged with solvent); ^{13}C NMR (CD_3OD at 49.0) δ 168.8, 168.6, 136.3, 136.0, 130.4, 83.9, 50.1, 49.2, 46.3, 37.0, 28.8, 28.2, 20.1, 19.3, 13.9 (2C each peak). Anal. Calcd for $C_{30}H_{38}O_8$: C, 68.42, H, 7.27. Found: C, 68.59; H, 7.30.

4,6-Bis{*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxycarbonyl}isophthalic Acid (Meta-di-*l*-bornyl Pyromellitate) (12f). The acetic acid filtrates from the preparation of **11f** were concentrated to a syrup on a rotary evaporator. Overnight, this went solid with balls of needles. The solids were isolated after a tedious filtration and washed with the usual progression of solvents (HOAc/H_2O: 1:0; 1:1; 0:1). Yield: 99.11 g (0.188 mol, 24.1%). Mp 231.0−238.0 °C (dec); optical rotation $[\alpha]^{20}_{589}$ −59.76, $[\alpha]^{20}_{578}$ −62.89, $[\alpha]^{20}_{546}$ −72.02 (*c* 10.1535, tetrahydrofuran); ^{1}H NMR (CD_3OD) δ 0.917 (6 H, s), 0.923 (6 H, s), 0.974 (6 H, s), 1.25−1.35 (6 H, m), 1.69-ca. 1.9 (4 H, m), 1.99 (2 H, m), ca. 2.4 (2H, m), 5.11 (2 H, m), 7.95 (H, s), 8.16 (H, s) (2 COOH exchanged with solvent); ^{13}C NMR (CD_3OD at 49.0) δ 168.7, 168.4, 136.4, 135.8, 130.8 (1C), 130.0 (1C), 83.8, 50.0, 49.3, 46.2, 37.0, 28.7, 28.2, 20.1, 19.3, 13.9 (2C each unless otherwise noted). Anal. Calcd for $C_{30}H_{38}O_8$: C, 68.42, H, 7.27. Found: C, 68.22, H, 7.40.

5-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxycarbonyl-]benzene-1,2,4-tricarboxylic Acid (Mono-*l*-menthyl Pyromellitate) (18b). A. 6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxycarbonyl]-1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxylic Acid, 1:1 Solvate with Acetic Acid (Mono-*l*-menthyl Pyromellitate Anhydride, 1:1 Acetic Acid Adduct) (17b). A suspension of PMDA (**10**) (68.53 g, 0.3142 mol) in a solution of *l*-menthol (**4**) (46.89 g, 0.3001 mol) in CH_2Cl_2 (500 mL) was treated with pyridine (26.5 mL), and when this appeared to have little effect, with triethylamine (44 mL). After several minutes of swirling, the mixture had become homogeneous. After 90 min, the solution was shaken with a solution of concentrated HCl (63 mL) in H_2O (300 mL). The organic phase was isolated promptly, diluted with acetic anhydride (50 mL), and then concentrated on the rotary evaporator. The resulting dark greenish brown syrup was diluted with glacial acetic acid (100 mL); the product crystallized at once. The resulting slurry was filtered. The solids were rinsed with glacial acetic acid (100 mL) and then *n*-hexane (85 mL). Yield: 99.41 g (0.229 mol, 76.3%). Mp 172.5−175.5 °C (dec), after slow heating to drive off HOAc. Two later crops came to 16.30 g (0.0375 mol, 12.5%) for a total of 115.71 g (0.266 mol, 88.76%). ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, d, J = 6.96 Hz), 0.92 (3H, d, J = 6.96 Hz), 0.96 (3H, d, J = 6.46 Hz), [1 H obscured by methyl doublet], 1.13 (2H, q, J = 11.7 Hz), 1.51 (2H, t, J = 11.7 Hz), 1.75 (2H, d, J = 11.79 Hz), 1.93 (H, m), 2.15 (3H, s, C**H**$_3$CO$_2$H), 2.20 (H, d, J = 12.56 Hz), 5.02 (H, t of d, J = 10.9 and 4.2 Hz), 8.24 (H, s), 8.45 (H, s), 12.01 (2H, s, CO_2H) (*1 H obscured by* 0.96 methyl doublet); ^{13}C NMR ($CDCl_3$ at 77.1) δ 178.4, 170.2, 164.9, 161.0, 160.9, 141.1, 137.6, 133.7, 132.7, 126.8, 125.9, 77.7, 47.0, 40.2, 34.1, 31.5, 26.2, 23.3, 22.0, 20.8, 20.7, 16.1. Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Calcd for $C_{20}H_{22}O_7.C_2H_4O_2$: C, 60.82; H, 6.03. Found: C, 60.77; H, 6.11.

B. Mono-*l*-menthyl Pyromellitate (18b). The preceding first crop of **17b** (0.218 mol) was slurried in glacial acetic acid (300 mL) and heated (water bath at 100 °C). Water (50 mL) was added and the anhydride dissolved over several minutes. The hot solution was filtered through a glass frit and rinsed through with HOAc (100 mL). Water was filtered through next, to a total volume of ca. 1.5 L. The product crystallized without oiling as snow white flakes. These were filtered off, washed with H_2O, and dried. Yield: 88.55 g (0.218 mol, 99.9% based on **17b**). Mp 198.5−203.5 °C (dec); optical rotation $[\alpha]^{20}_{589}$ −76.19, $[\alpha]^{20}_{578}$ −80.43, $[\alpha]^{20}_{546}$ −92.85 (*c* 10.025, as-is hydrate, tetrahydrofuran); ^{1}H NMR (CD_3OD) δ 0.83 (3H, d, J = 6.73 Hz), 0.90 (3H, d, J = 7.11 Hz), 0.95 (3H, d, J = 6.19 Hz), [1 H, m, obscured by methyl doublet], 1.09−1.24 (2H, m), 1.46−1.62 (2H, m), 1.69−1.78 (2H, m), 1.97 (H_2O), 1.99−2.07 (H, m), 2.17−2.24 (H, m), 4.92−5.00 (H, t of d), 8.01 (H, s), 8.20 (H, s) (3 COOH exchanged with solvent); ^{13}C NMR (acetone-d_6 at 29.8, 206.4) δ 167.4, 167.3, 167.0, 166.5, 136.4, 136.1, 135.3, 134.8, 130.5, 129.6, 76.7, 47.9, 41.1, 35.0, 32.2, 26.9, 24.1, 22.3, 21.0, 16.6. Anal. Calcd for $C_{20}H_{24}O_8$: C, 61.22; H, 6.16. Calcd for $4C_{20}H_{24}O_8.3H_2O$: C, 59.18; H, 6.33. Found: C, 59.37, 59.14; H, 6.39, 6.40. Found (after heating in vacuo at 60 °C overnight): C, 60.93; H, 6.20.

1-Benzyl 2,4,5-Tri[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] Benzene-1,2,4,5-tetracarboxylate (Benzyl-tri-*l*-menthyl Pyromellitate) (31b). Benzyl pyromellitate (**29**)[4] (18.13 g, 52.66 mmol) was suspended in CH_2Cl_2 (150 mL) and treated with oxalyl chloride (12.0 mL) and *N*,*N*-dimethylformamide (DMF, 2 drops). After standing overnight with only partial reaction, the mixture was warmed intermittently (water bath) and treated with further oxalyl chloride (4.6 mL) and DMF (4 drops) until the solids had dissolved completely. The solvent was removed in vacuo to give a tan syrup (25.55 g, of which 0.49 g was reserved for NMR investigation.[20,21]) The crude triacid chloride (**30**) (0.05165 mol nominal) was dissolved in CH_2Cl_2 (250 mL) and treated with *l*-menthol (**4**) (30.45 g, theory = ca. 24.69 g) and Et_3N (32.5 mL). The mixture was kept at room temperature for 7 days, protected from atmospheric moisture. The

(20) The crude acid chloride was investigated by NMR and found to consist of two principal components. The major product was benzyl pyromellitate triacid chloride (**26**): ^{1}H NMR ($CDCl_3$) δ 5.40 (2 H, s), 7.30−7.43 (5 H, m), 8.11 (H, s), 8.37 (H, s); ^{13}C NMR ($CDCl_3$ at 77.1) δ 165.75, 165.61, 165.47, 162.4, 140.3, 136.4, 136.2, 133.8, 132.5, 131.0, 128.63, 128.56*, 128.50 (2 C), 128.41 (2 C), 68.9.

(21) The minor product displayed NMR chemical shifts consistent with assignment as benzyl pyromellitate anhydride acid chloride. The ratio of **26** to this was circa 4:1. ^{1}H NMR ($CDCl_3$) δ 5.22 (2 H, s), 7.28−7.43 (5 H, m), 8.16 (H, s), 8.46 (H, s). Four minor pyromellitate protons of nearly equal intensity, and presumably due to two compounds, possibly mixed carboxylic acid/acid chloride species, occurred at δ 8.04, 8.15, 8.33, and 8.39; ^{13}C NMR ($CDCl_3$ at 77.1) δ 166.1, 162.7, 160.07, 159.99, 143.4, 135.4, 133.6, 133.0, 127.78, 127.72, 127.07, 127.01, 124.30, 124.23, 68.7. Other peaks were noted, enough for two compounds, at intensity circa one-half of this.

reaction mixture was shaken with H_2O (200 mL) and then with concentrated HCl (50 mL)−H_2O (150 mL). The organic phase was concentrated in vacuo to give a brown viscous oil (50.13 g). This was redissolved in CH_2Cl_2 and chromatographed on silica gel (Merck # 7734, Kieselgel 60, 70−230 mesh), the product eluting rapidly as single-spot material. Yield: 32.72 g (0.0431 mol, 83.5%). The compound was recrystallized from 100% ethanol, yield 24.38 g (0.0321 mol, 62.2%). Mp 111.5−114.0 °C; optical rotation $[\alpha]^{20}_{589}$ −83.19, $[\alpha]^{20}_{578}$ −87.48, $[\alpha]^{20}_{546}$ −100.00 (*c* 10.08924, toluene); ^{1}H NMR ($CDCl_3$) δ 0.807 (3H, d, J = 6.60 Hz), 0.830 (3H, d, J = 6.89 Hz), 0.853 (3H, d, J = 7.02 Hz), 0.903 (3H, d, J = 6.41 Hz), 0.916 (3H, d, J = 6.35 Hz), 0.925 (6H, d, J = 6.83 Hz), 0.947 (3H, d, J = 6.35 Hz), 0.955 (3H, d, J = 6.64 Hz), [3 H, m: obscured by methyl doublets], 1.05 − 1.18 (6H, m), 1.46 − 1.53 (6H, m), 1.68 − 1.73 (6H, m), 1.90 − 1.99 (3H, m), 2.10 − 2.26 (3H, m), 4.88 − 5.01 (3H, m), 5.34 and 5.41 (calc.) (2H, AB q, J = 12.3 Hz), 7.30 − 7.43 (5H, m), 8.012 (H, s), 8.020 (H, s); ^{13}C NMR ($CDCl_3$ at 77.1) δ 165.7, 165.1, 164.73, 164.67; 134.84, 134.76, 134.4, 133.9 (2C*?); 129.1 (2C*?); 128.2 (2C), 128.1, 127.9 (2C); 76.2, 76.0 (2C*); 67.6; 46.95 (2C*), 46.87; 40.36, 40.32, 40.25; 34.13 (2C*), 34.05; 31.36 (2C*), 31.30; 26.27, 26.20, 26.07; 23.38 (2C*), 23.30; 21.99 (2C*), 21.92; 20.78 (2C*), 20.69; 16.38, 16.30 (2C*) (*accidental degeneracy; 1 C per peak unless otherwise noted). Anal. Calcd for $C_{47}H_{66}O_8$: C, 74.37; H, 8.76. Found: C, 74.48; H, 8.79.

2,4,5-Tris[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxycarbonyl]benzoic Acid (Tri-*l*-menthyl Pyromellitate) (27b). Benzyl tri-*l*-menthyl pyromellitate (**31b**) (7.69 g, 10.1 mmol) and 10% Pd/C (0.51 g) were stirred in tetrahydrofuran (120 mL) under H_2 at 1 atm and ambient temperature until gas uptake (254 mL) ceased (95 min). The catalyst was filtered off and the filtrates evaporated to dryness in vacuo. Yield: quantitative. This was characterized only by NMR. ^{1}H NMR ($CDCl_3$) δ 0.824 (6 H, d, J = 6.86 Hz), 0.836 (3 H, d, J = 6.90 Hz), 0.900 (3 H, d, J = 6.97 Hz), 0.914 (6 H, d, J = 7.05 Hz), 0.945 (3 H, d, J = 6.64 Hz), 0.952 (3 H, d, J = 6.46 Hz), 0.959 (3 H, d, J = 6.38 Hz), [3 H, m: obscured by methyl doublets], 1.05−1.18 (6 H, m), 1.44−1.53 (6 H, m), 1.70−1.74 (6 H, m), 1.87−1.96 (3 H, m), 2.16−2.25 (3 H, m), 4.92−5.01 (3 H, m), 7.89 (H, s), 8.16 (H, s), 9.22 (H, br s); ^{13}C NMR ($CDCl_3$ at 76.9) δ 169.5, 165.8, 165.4, 164.8; 135.8, 135.5, 134.0, 132.1; 129.8, 128.7; 76.49, 76.32, 76.18; 46.91 (3 C*); 40.41, 40.27, 40.10; 34.15 (3 C*); 31.42 (3 C*); 26.18 (3 C*); 23.36 (3 C*); 21.99 (3 C*); 20.79 (2 C*), 20.71; 16.33 (2 C*), 16.20 (*accidental degeneracy).

1,4-Dibenzyl 2,5-Di[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] Benzene-1,2,4,5-tetracarboxylate (Para-dibenzyl-di-*l*-menthyl Pyromellitate) (20b). Para dibenzyl pyromellitate[4] (13.04 g, 0.03 mol), suspended in CH_2Cl_2 (100 mL), was treated with oxalyl chloride (8.0 mL, ca. 11.64 g, 0.0917 mol) and *N*,*N*-dimethylformamide (5 drops). Gas evolution (hood!) began as soon as the DMF was added. After standing overnight at room temperature, protected from atmospheric moisture, the reaction mixture was concentrated (rotary evaporator). The residual crude acid chloride **19**[4] (14.27 g, 14.15 *g* = theory) was dissolved in CH_2Cl_2 (108 mL) and treated with *l*-menthol (**4**) (14.73 g, 0.094 mol) and Et_3N (10.0 mL, 7.34 g, 0.0725 mol). After standing at room temperature for 3 days, protected from moisture, the reaction mixture was extracted with H_2O (100 mL). The organic phase was isolated, filtered, and then concentrated (rotary evaporator). The residue was crystallized from 100% ethanol (80 mL). Yield: 14.49 g (0.0204 mol, 67.9%); mp 108.5−110.5 °C; optical rotation $[\alpha]^{20}_{589}$ −65.41, $[\alpha]^{20}_{578}$ −68.87, $[\alpha]^{20}_{546}$ −78.92 (*c* 10.01324, toluene); ^{1}H NMR ($CDCl_3$) δ 0.76 (6H, d, J = 6.85 Hz), 0.86 (6H, d, J = 6.98 Hz), 0.91 (6H, d, J = 6.45 Hz), [2 H, m: obscured by methyl doublets], 0.94−1.23 (4 H, m), 1.36−1.58 (4H, m), 1.63−1.77 (4H, crude d), 1.80−1.94 (2H, quintet of d), 2.04−2.15 (2H, crude d of t), 4.84−4.97 (2H, t of d, J = 10.88 and 4.43 Hz), 5.33 and 5.41 (calc.) (4H, ABq, J = 12.35 Hz), 7.32−7.52 (10H, m), 8.02 (2H, s); ^{13}C NMR ($CDCl_3$ at 77.1) δ 166.2, 165.0, 135.1, 134.5, 134.4, 129.4, 128.6 (4C), 128.4, 128.3 (4C), 76.5, 67.9, 47.0, 40.4, 34.1, 31.4, 26.2, 23.3, 22.0, 20.8, 16.2 (two carbons per peak unless otherwise noted). Anal. Calcd for $C_{44}H_{54}O_8$: C, 74.34; H, 7.66. Found: C, 74.55; H, 7.61.

2,5-Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxycarbonyl]terephthalic Acid (Para-di-*l*-menthyl Pyromellitate) (11b) from the Dibenzyl Ester (20b). Para-dibenzyl-di-*l*-menthyl pyromellitate (**20b**) (3.57 g, 5.02 mmol) and 10% Pd/C (0.35 g) were stirred in tetrahydrofuran (70 mL) under H_2 (1 atm, ambient temperature). Gas uptake was complete after 23 min, but stirring was continued for 2 h. The catalyst was filtered off. The filtrates were concentrated in vacuo. Yield: quantitative. The crude solids were crystallized from minimal MeOH. Yield (first crop): 1.07 g (2.02 mmol, 40.1%). Mp 251.5−255.0 °C (dec).

1,2,4,5-Tetrakis-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] Benzene-1,2,4,5-tetracarboxylate (Tetra-*l*-menthyl Pyromellitate) (26b).[16,17] A solution of tetraethyl pyromellitate[4] (**25**) (110.21 g, 0.3008 mol) and (1*R*,2*S*,5*R*)-(−)-menthol (**4**) (234.46 g, 1.5004 mol) in *p*-xylene (603 mL) was prepared. About one-third of it was heated to reflux under N_2 (*a safety precaution since hydrogen is to be evolved as the NaH is added*) in a 4 L heavy wall standard taper 29/42 erlenmeyer flask on a hot plate with magnetic stirring. Small portions of NaH slurry in *p*-xylene were added ***dropwise*** until ethanol began to be vigorously evolved. Thereafter, alternating portions of solution and catalyst were added to the boiling mixture, to keep the reaction under control. (*Warning: ethanol, unlike methanol, azeotropes with xylene, so that boiling can become quite threatening in ethyl ester systems, even in a large flask. The ingredients cannot all safely be in the flask initially, on this scale.*) Further small portions of catalyst continued to be added periodically, until no further effect was noted, and the vapor temperature remained above 139 °C. The dark brown reaction mixture was allowed to cool for 10 min, before being treated with HOAc (50 mL), which caused the color to fade considerably. The reaction mixture was washed with H_2O (1000 mL), which was back-extracted with EtOAc (100 mL). The combined organic phases were filtered (with addition of CH_2Cl_2 as needed to prevent crystallization) and then concentrated (rotary evaporator). The residue was crystallized from 100% ethanol. Seeding was essential to prevent oiling. Yield: 214.26 g (0.265 mol, 88.2%). A recrystallization from 100% EtOH afforded 200.39 g (0.248 mol, 82.5%) of pale cream dense granules. Mp 120−123.5 °C [lit. mp 123.5−124.5 °C]; optical rotation $[\alpha]^{20}_{589}$ −95.38, $[\alpha]^{20}_{578}$ −99.98, $[\alpha]^{20}_{546}$ −114.24 (*c* 10.18, toluene) [lit.[16] $[\alpha]^{20}_{589}$ −102.5 (*c* 1.1, benzene)]; [NMR and microanalysis are reported in Supporting Information.]

1,2,4,5-Tetrakis[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl] Benzene-1,2,4,5-tetracarboxylate (Tetra-*d*-menthyl Pyromellitate) (26a). This was prepared similarly from **25**[4] (37.97 g, 0.1036 mol) and (1*S*,2*R*,5*S*)-(+)-menthol (**3**) (95.34 g, 0.6101 mol) in *p*-xylene (250 mL). Yield: 69.50 g (0.0861 mol, 83.1%). Mp 116.5−117.5 °C; recrystallized and melted 122.0−125.5 °C. Another preparation had mp 119.5°−121.5 °C, recrystallizing in part to crystals which melted sharply at 125.5−126.0 °C. A 10 g sample was recrystallized from *n*-butanol (21 g), in 85.1% recovery. Optical rotation: $[\alpha]^{20}_{589}$ +92.96, $[\alpha]^{20}_{578}$ +97.33, $[\alpha]^{20}_{546}$ +111.34 (*c* 10.49, toluene). A 50 g sample, recovered in 88.7% yield from *n*-butanol (75.4 g), had corresponding rotations of +91.20, +95.84, and +109.26 (*c* 9.775, toluene). This (43 g) was then recrystallized from toluene (43 g), with only 40.9% recovery. The optical rotations were now respectively +94.08, +98.89, and +112.72 (*c* 10.62, toluene), for an estimated optical purity of 98.6%. ^{1}H NMR ($CDCl_3$) δ 0.82 (12 H, d, J = 7.00 Hz), 0.91 (12 H, d, J = 6.94 Hz), 0.95 (12 H, d, J = 6.54 Hz), (2D NMR and integrals suggest 4 H, m are obscured under the methyl doublets), 1.06−1.17 (8 H, m), 1.44−1.59 (8 H, m), 1.71−1.74 (8 H, d, J = 11.72 Hz), 1.90−1.97 (4 H, quintet of doublets, J = 2.6 and 7.0 Hz), 2.18−2.22 (4 H, m), 4.90−4.97 (4 H, t of d, J = 4.4 and 10.8 Hz), 7.94 (2 H, s); ^{13}C NMR ($CDCl_3$ at 77.0) δ 165.5, 134.6, 129.3 (2 C), 76.3, 47.1, 40.4, 34.2, 31.5, 26.3, 23.4, 22.0, 20.8, 16.4 (4 carbons per peak

unless otherwise noted). Anal. Calcd for $C_{50}H_{78}O_8$: C, 74.40; H, 9.74. Found: C, 74.10; H, 9.70.

Resolution of (*R*,*S*)-Nicotine by Manual Triage. Para-di-*l*-menthyl pyromellitate (**11b**) (26.55 g, 0.05 mol) and (*R*,*S*)- nicotine[5] (**1** + **14**) (8.10 g, 0.05 mol) were dissolved in hot methanol (150 mL), and the resulting solution was allowed to crystallize undisturbed to provide the results of "round 1" (Table 1). The decanted mother liquors were permitted to evaporate over a month in an open erlenmeyer flask in the refrigerator, depositing an admixture of large transparent chunks and crusts of small feathery crystals which became opaque while drying out, while the chunks remained transparent. From this was obtained by manual triage the quantities reported for "round 2" (Table 1). Total recovery of solids: 30.90 g (89%).

The (*S*)-diastereomer **13b** was recrystallized once from MeOH, forming large crystals (the largest weighed 2.54 g) and some crusts (yield in Table 1). Optical rotation: $[\alpha]_{589}^{20}$ −50.6 (*c* 10.38, methanol). Anal. Calcd for $C_{40}H_{56}N_2O_8$: C, 69.34; H, 8.15; N, 4.04. Calcd for $2C_{40}H_{56}N_2O_8.CH_3OH$: C, 68.62; H, 8.25; N, 3.95. Calcd for $C_{40}H_{56}N_2O_8.CH_3OH$: C, 67.93; H, 8.34; N, 3.86. Found: C, 68.73; H, 8.55; N, 3.94.

The (*R*)-diastereomer **15b** was recrystallized similarly and dried (Table 1). The salts were shown to lose around 10% of their mass upon drying, as they became opaque. This corresponds to ca. 2.5 mol of methanol of crystallization. Optical rotation: $[\alpha]_{589}^{20}$ −83.9 (*c* 10.70, methanol). Anal. Calcd for $C_{40}H_{56}N_2O_8$: C, 69.34; H, 8.15; N, 4.04. Found: C, 69.60; H, 8.04; N, 3.92.

Efficiency of Resolution, Starting with (90% *S*/10% *R*)-Nicotine. (90% *S*, 10% *R*)-Nicotine (16.24 g, 0.1 mol)[prepared by diluting racemic nicotine[5] with four parts of (*S*)-nicotine (**1**)] and para-di-*l*-menthyl pyromellitate (**11b**) (53.12 g, 0.1 mol) were allowed to crystallize undisturbed from MeOH (88.59 g, of which 2.3 g evaporated during the crystallization). "Transparent salt" **13b** was the only phase that crystallized. The resulting **13b** was recrystallized once from methanol. The rejected nicotine was recovered essentially quantitatively from each round of crystallization, and the optical rotation was determined (Table 2). An accounting of the (*R*)-nicotine content of the system (Table 2) suggested that after the second crystallization, **13b** contained 99.8% (*S*)-antipode. This purity was confirmed 12 years later when the contained nicotine was isolated (yield: 2.11 g, 98.8%) by the standard method from a 9.12 g sample (13.16 mmol) of the solids. [These had remained stable in the interim, stored at ambient temperature, with the exception of having at last gone opaque, presumably due to the loss of solvent of crystallization.] The contained resolving agent crystallized smartly from acidified aqueous methanol during workup, suggesting that it too was intact, yield: 6.97 g (99.8% recovery). The ^{13}C and ^{1}H NMR spectra confirmed the completely intact nature of the recovered resolving agent [mp 250.7−252.5 °C (dec)]. The resulting recovered nicotine provided the following optical rotations: $(\alpha)_{589}^{20}$ −170.315, $(\alpha)_{578}^{20}$ −179.245, $(\alpha)_{546}^{20}$ −205.215 (neat, 1.000 cm microcell, T = 19.98−20.01 °C). The corresponding values for (*S*)-(−)-nicotine (**1**), freshly isolated by the standard method from the bis-bitartrate dihydrate, using the same 1.000 cm microcell, were −170.85, −179.81, and −205.89, respectively. The same sample, using a 10.000 cm cell, afforded values of −170.614, −179.531, and −205.509, respectively. Calculations using these numbers show that the resolved sample contained 99.84−99.92% (*S*)-antipode.

Resolution of Nicotine with Para-di-*l*-bornyl Pyromellitate (11f). A. Initial Resolution with 11f. Para-di-*l*-bornyl pyromellitate (**11f**) and (*R,S*)-nicotine[5] (**1** + **14**) were dissolved in hot methanol and seeded. Overnight, a mass of interlocking needles formed. The mother liquors were drained off. The crystals were washed in place with MeOH (5 mL) and dried (Table 3, round 1A, 20.03 mmol scale).

The system was scaled up to 50.06 mmol (Table 3, round 1B). The mass of cottony needles was mashed and filtered, washed twice with small portions of MeOH, and dried. The filtrates were concentrated in vacuo to a syrup, which afforded a second crop. The combined solids (19.71 g were used) were recrystallized from MeOH, giving **13f** in 84.8% overall yield, based on the system content of **1**.

B. Isolation of (*R*)-(+)-Nicotine (14) from its Salts with a Resolving Agent ("Standard Method"). All of the mother liquors from parts A and B above were combined and evaporated to dryness. The residue, dissolved in MeOH (150 mL), was treated with concentrated HCl (6.0 mL). Water (200 mL) was added, after the resolving agent (here **11f**) began to crystallize. The solids were filtered off, rinsed with H_2O, and recovered. Concentrated HCl (4.0 mL) was added to the filtrates, which were then concentrated in vacuo to a syrup. Pellets of NaOH (8.64 g, 0.216 mol) were added to the residue, followed by H_2O (10 mL) with ice cooling. The alkaloid was extracted three times with CH_2Cl_2−Et_2O [Note: petroleum ether bp 30/60 °C or hexane(s) are also satisfactory, used alone] and isolated by evaporation of solvent, followed by Kugelrohr distillation. Yield: 5.51 g (4.85 g was the expected yield, assuming that the previously isolated salts were not solvated); the optical rotation is presented in Table 3.

C. Resolution Continued with 11a. The above crude (*R*)-(+)-nicotine (**14**) and para-di-*d*-menthyl pyromellitate (**11a**) were dissolved in MeOH and seeded, forming elongated flat prisms (further details in Table 3). Twelve years later, the contained nicotine was isolated from 9.07 g (13.09 mmol if unsolvated) of the above solids, using the standard method. Yield of (*R*)-(+)-nicotine (**14**) after Kugelrohr distillation was 2.03 g (95.6% yield). Optical rotation: $(\alpha)_{589}^{20}$ +164.93, $(\alpha)_{578}^{20}$ +173.535, $(\alpha)_{546}^{20}$ = +198.66 (neat, 1.000 cm microcell, T = 19.98 °C). This computes to 96.51% optical purity or 98.26% (*R*)- and 1.74% (*S*)-antipode. The yield of recovered resolving agent, isolated by simple filtration, was 6.67 g (96.0% yield). The intact nature of the resolving agent was confirmed by ^{13}C and ^{1}H NMR and by melting point [mp 253.5−255.0 °C (dec)].

Resolution of the Contained Terpene Alcohols. A. Purification of Di-*d*-menthyl Pyromellitate (11a). Material (**11a**) as isolated by method A was estimated to be 97.56% optically pure or to contain *d*-menthol (**3**) of 98.8% chiral purity. A sample (10.08 g) was recrystallized from MeOH (31.34 g) to give 7.21 g (71.5%). The optical purity at this stage was 99.1%, corresponding to *d*-menthol (**3**) of 99.55% absolute purity. The resulting solids (6.70 g) were crystallized again from MeOH (20.11 g), to give 4.99 g (74.5% recovery, 53.3% overall). The optical purity was now 99.9%, corresponding to 99.95% absolute purity for the contained *d*-menthol (**3**). The optical rotations for the starting material and the two recrystallized fractions are reported with the data for method A.

B. Isolation of the Contained *d*-Menthol (3). Thus purified para-di-*d*-menthyl pyromellitate (**11a**) (2.72 g, 5.13 mmol) and NaOH (5.05 g, 0.126 mol) were dissolved in H_2O (100 mL), and the mixture was distilled into an overhead solvent-still head receiver, until no further oily *d*-menthol (**3**) appeared in the condensate. Dichloromethane was cautiously added to the hot still-pot contents to distill over and rinse the product from the condenser and extract it from the distillate. The organic phase was isolated and concentrated in vacuo, and the residue was distilled (Kugelrohr). Yield: 1.59 g (10.18 mmole, 99.3%). Mp 40.0−41.5 °C (uncorr); optical rotation $[\alpha]_{589}^{20}$ +47.84, $[\alpha]_{578}^{20}$ +50.09, $[\alpha]_{546}^{20}$ +56.49, (*c* 10.4475, toluene). Corresponding rotations for natural *l*-menthol (**4**) were −47.89, −50.14, and −56.53, respectively (*c* 11.5915, toluene), so that the *d*-menthol (**3**) calculated to have been 99.9% optically pure (99.95% absolute purity).

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Supporting Information Available: General experimental methods, experimental procedures, and full characterization for compounds **11c**, **11d**, **11e**, **12a** (^{13}C NMR), **18g**, **22b**, **23b**, **24a**, **24b**, **26c**, **26d**, and **26f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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