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Enantiomerically Pure Tribenzotriquinacenes through Stereoselective Synthesis

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Abstract: *Inherently chiral acetophenones and benzaldehydes bearing the large, bowl-shaped framework of tribenzotriquinacene (TBTQ) were synthesized in enantiomerically pure form employing enzyme catalysis. Five-step sequences involving lipase CAL-B lead to the (M)-enantiomers, (+)-2-acetyl-TBTQ (M)-**5** and (+)-2-formyl-TBTQ (M)-**6**, whereas use of lipase PS leads to the (P)-enantiomers, (−)-2-acetyl-TBTQ (P)-**5** and (−)-2-formyl-TBTQ (P)-**6**, with at least 99 % ee in each case. The absolute configuration of these rigid 3D building blocks was determined by X-ray diffraction analysis of the ketones **5** and by comparison of their chiroptical properties with those of the aldehydes **6**.*

The polycyclic molecular framework of tribenzotriquinacene (**1**, TBTQ, Figure 1)[1–3] provides a unique and highly interesting combination of structural and chemical properties: Structurally, the mutual fusion of the three indane wings generates a C_{3v}-symmetrical and conformationally rigid scaffold, the three wings point into the three-dimensional space at almost right angles, and the TBTQ bowl adopts a pronounced concavity.[4–7] Chemically, the four bridgehead positions and the six outer positions of the aromatic periphery can be functionalized independently and in various ways and the electronic interaction of the three benzene units is negligible.[1b,4b–d,8] As a consequence, TBTQ derivatives have been considered promising building blocks for three-dimensional extensions to generate novel voluminous covalent or supramolecular assemblies.[1b,3a,b,d–f,h,i,9] Of particular interest are orthogonal arrangements bearing several TBTQ units since, from a geometrical point of view, the three indane wings may represent the edges of a cube or a tetrahedron consisting of eight or four TBTQ units, respectively, at their tips.[1b,3a,b,4b,8]

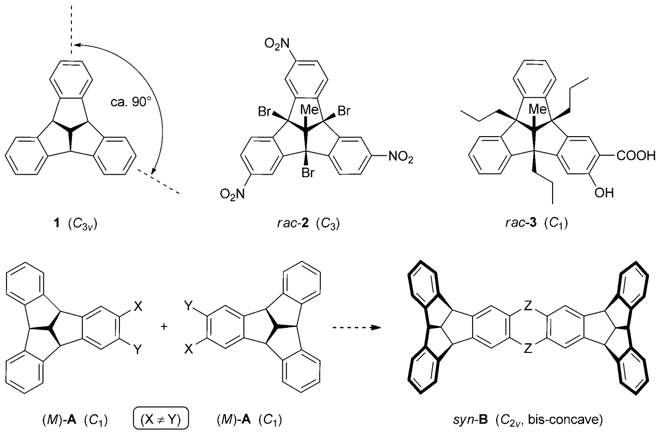

Figure 1. Tribenzotriquinacene (**1**), chiral TBTQ derivatives *rac*-**2** and *rac*-**3**, and the concept of the condensation of two identical difunctionalized enantiomers, (*M*)-**A**, that would lead to bis-concave scaffolds. The axes of the indane wings of **1** and its derivatives are oriented at right angles to each other.

A covalent cubic assembly of eight achiral TBTQ units has been constructed recently by use of an achiral (C_{3v}-symmetrical) derivative in a reversible condensation process,[3b] paralleling a previously reported reversible condensation of eight cycloveratrylene units.[10] A similar approach has led to covalently bound bipyramidal and tetrahedral TBTQ-based cage compounds.[3a] Conceptually, however, chiral TBTQ derivatives bearing three (or six) functional groups in a C_3-symmetrical collocation at the outer molecular periphery promise an alternative and possibly more versatile approach—provided that they are available as pure enantiomers. The C_3-symmetrical TBTQ derivative **2** was found to self-assemble, in the solid state, into supramolecular cubes that consist of either eight (*M*)- or eight (*P*)-enantiomers.[9] Since then, an increasing number of mono-, di-, and trifunctionalized TBTQ derivatives with a chiral pattern of functional groups at the outer periphery have been reported.[2b,8,11–17] However, only a few of them were made available in enantiomerically pure form, and all methods applied so far are based on either the use of chiral auxiliaries[11,12,15] or chromatography on a chiral support.[16–18] The C_1-symmetrical TBTQ-based salicylic acid **3** represented the first example of this series.[11] Most recently, enantiomerically pure, C_1-symmetrical TBTQ building blocks were used to construct a molecular square.[17] It is noteworthy that, in spite of a myriad of asymmetric catalytic procedures, up to now no method has been developed that provides access to such compounds in enantiomerically (and, if relevant, diastereomerically) pure form through a stereoselective synthesis. The main reason may be the fact that the chirality of such compounds is based on only a minimum differentiation of three out of the four substituents at the chiral center (Scheme 1). However, a synthetic method for the elegant and easy-to-apply preparation of substantial amounts of enantiomerically pure TBTQ building blocks would facilitate

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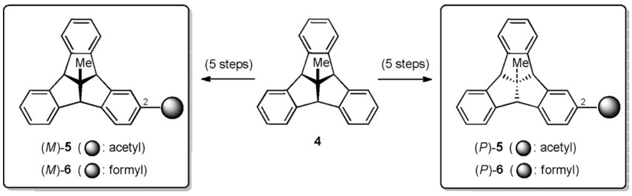
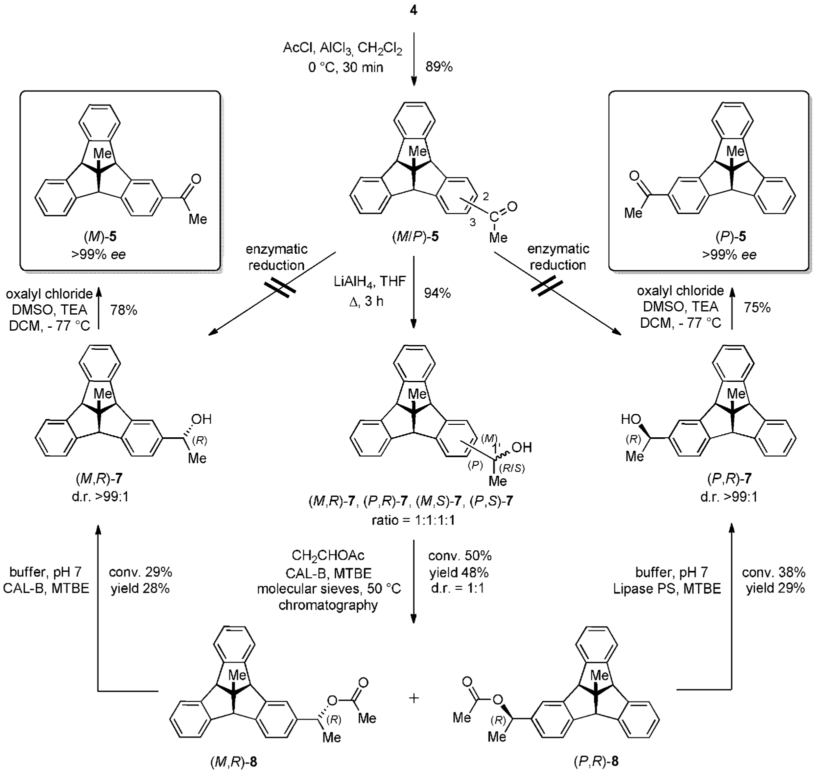


Scheme 1. Access to enantiomerically pure TBTQ-aldehydes **5** and methyl ketones **6**.

the systematic construction of globular (all-concave) structures. This is illustrated in Figure 1 for the simplest case, the condensation of two identical enantiomers, arbitrarily termed (*M*)-**A**, giving the concave–concave dimer *syn*-**B**.[19]

In the present report, we disclose the first preparation of optically pure monofunctionalized TBTQ derivatives that is based on a synthetic stereoselective approach. This methodology is demonstrated for the synthesis of the 2-acetyl- and 2-formyltribenzotriquinacenes (*M*)-**5** and (*P*)-**5** as well as (*M*)-**6** and (*P*)-**6**, respectively, from the achiral 12d-methyl derivative **4** (Scheme 1).[1a,20] It turned out to be straightforward and highly practical, thus enabling the rapid synthesis also of larger lab-scale amounts of such TBTQ target products. A key feature in this stereoselective total synthesis of the two enantiomers is the use of a readily available commercial biocatalyst.



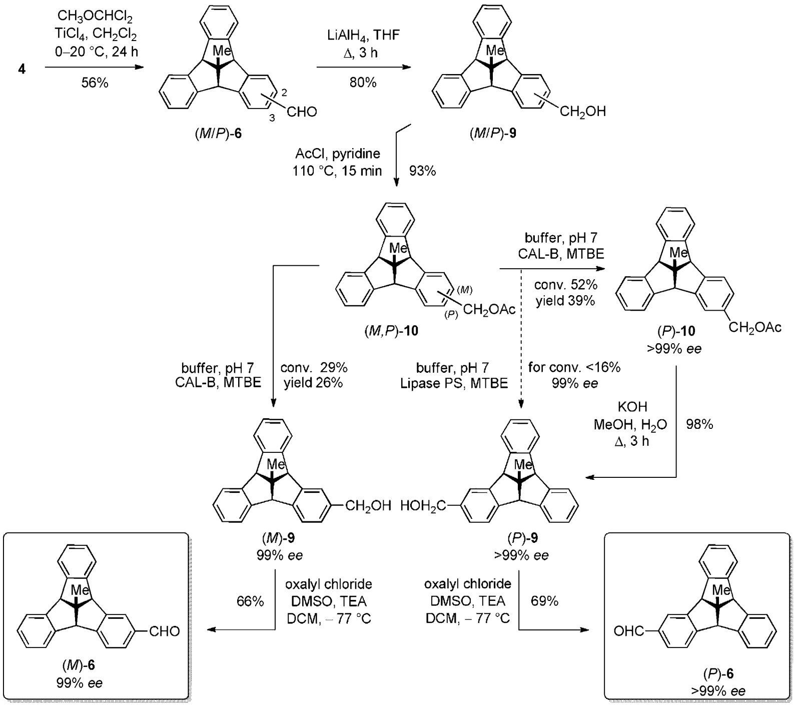
Scheme 2. Synthesis of enantiomerically pure TBTQ-based secondary benzylic alcohols (*M*,*R*)-**7** and (*P*,*R*)-**7** and acetophenones (*M*)-**5** and (*P*)-**5**.

The initial step in our synthesis was the single Friedel–Crafts acetylation of the 12d-methyl derivative **4** at 0 °C, which occurred with high regioselectivity at one of the peripheral positions, thus furnishing the racemic TBTQ-based acetophenone (*M*/*P*)-**5** in excellent yield (Scheme 2). First attempts at an asymmetric tribenzotriquinacene synthesis were based on a biocatalytic reduction of this ketone. We focused on enzymes as chiral catalysts due to their well-known excellent selectivity even when substrates with low stereodiscrimination at the chiral centers are used.[21] However, none of the applied (*S*)- or (*R*)-enantioselective alcohol dehydrogenases suitable for the enantioselective reduction of a broad range of ketones[22] showed activity for acetophenone (*M*/*P*)-**5**, indicating that the bulkiness of the TBTQ core hinders its access to the enzyme's active site.[23]

As an alternative, we envisaged the enzyme class of lipases to potentially tolerate and enantioselectively convert the bulky tribenzotriquinacenes to generate the desired target molecule **7** in enantiomerically and diastereomerically pure form. To this end, first reduction of (*M*/*P*)-**5** with lithium aluminum hydride was carried out to give the corresponding secondary benzylic alcohols as a mixture of four stereoisomers (diastereomeric racemates), (*M*/*P*,*R*/*S*)-**7**, in a ratio of 1:1:1:1, as revealed by chromatography on a chiral support.

Next, we studied lipases[24] as potential catalysts for the enantioselective esterification of the mixture of diastereomeric carbinol racemates (*M*/*P*,*R*/*S*)-**7** with vinyl acetate in methyl *tert*-butyl ether (MTBE).[25] We were pleased to find that, in the presence of the readily available commercial *Candida antarctica* lipase B (CAL-B) and molecular sieves (4 Å), a mixture of two diastereomeric esters and two diastereomeric alcohols was obtained (Supporting Information, SI). Thus, the lipase not only tolerates the bulky TBTQ framework but also enantioselectively converts both racemates of the pair of diastereomers **7**! After a conversion of 50 %, the pair of esters **8** was separated from the alcohol components and isolated in 48 % yield as a 1:1 mixture of diastereomers, to which we tentatively assigned the (*M*,*R*)- and (*P*,*R*)-configuration on the basis of Kazlauskas's rule.[26] Subsequent kinetically controlled hydrolysis of the esters (*M*,*R*)-**8** and (*P*,*R*)-**8** employing again CAL-B in MTBE and aqueous buffer at pH 7 afforded one single alcohol enantiomer, (*M*,*R*)-**7** ($[\alpha]_D^{18} = +83$ (MeOH)), with d.r. > 99:1 after 29 % conversion and in 28 % isolated yield.[27] All attempts to grow single crystals from this enantiomer failed; however, subsequent Swern oxidation furnished the enantiomerically pure TBTQ-acetophenone, (*M*)-**5**, in 78 % yield, and single crystals were obtained by use of the vapor-diffusion technique. X-ray structure analysis[28] and subsequent chiral chromatography of (*M*)-**5** ($[\alpha]_D^{18} = +137$) confirmed its optical purity and absolute configuration. Thus the precursor alcohol was identified as the (*M*,*R*)-**7** stereoisomer, again implying Kazlauskas's rule.

In the course of our screening experiments with other lipases (see SI), we found that a lipase from *Pseudomonas cepacia* (commercially available as lipase PS) under similar conditions as those used with CAL-B also facilitated the stereoselective hydrolysis of the diastereomeric esters (*M*,*R*)-**8** and (*P*,*R*)-**8**. However, much to our surprise—since in the widely studied field of lipase biocatalysis lipase CAL-B and PS are known to have the same enantiopreference—the other diastereomeric alcohol, (*P*,*R*)-**7** ($[\alpha]_D^{18} = -35$), was formed after 38% conversion in 29% isolated yield and again with d.r. > 99:1! Subsequent Swern oxidation gave the corresponding TBTQ-acetophenone (*P*)-**5** ($[\alpha]_D^{18} = -137$), and X-ray diffraction of single crystals of this enantiomer confirmed the opposite absolute configuration.[28] The solid-state molecular structures of the two TBTQ acetophenones (*M*)-**5** and (*P*)-**5** are depicted in Figure 2.



Scheme 3. Synthesis of enantiomerically pure TBTQ-based primary benzylic alcohols (*M*)-**9** and (*P*)-**9** and benzaldehydes (*M*)-**6** and (*P*)-**6**.

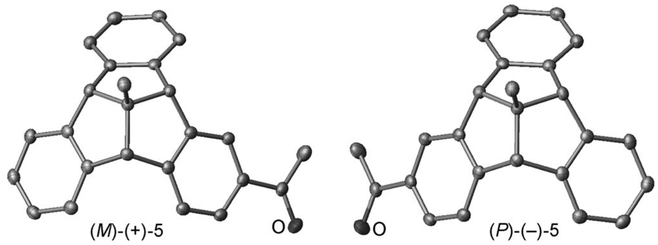


Figure 2. Molecular structures of the enantiomers (*M*)-**5** and (*P*)-**5** obtained from the esters (*M*,*R*)-**8** and (*P*,*R*)-**8** by CAL-B- or lipase-PS-catalyzed hydrolysis, respectively, and subsequent Swern oxidation (50% thermal ellipsoids, hydrogen atoms omitted for clarity).

The present results demonstrate that the enzymes used here are able to differentiate the stereochemistry not only of the carbinol functionalities of the TBTQ-based secondary alcohols containing a large, bowl-shaped hydrocarbon backbone,[29,30] but also that of the inherently chiral polycyclic framework itself.[31,32] Therefore, we were curious to examine the suitability of the corresponding primary benzylic alcohols and benzyl acetates bearing the same TBTQ backbone for enzyme catalysis. In fact, the same strategy was successful for the synthesis of enantiomerically pure TBTQ-benzaldehydes (*M*)-**6** and (*P*)-**6** (Scheme 3).

Monoformylation of hydrocarbon **4** using the Rieche method[11–15] afforded the TBTQ-2-carbaldehyde (*M*/*P*)-**6** in 56% yield and subsequent reduction with lithium aluminum hydride gave the corresponding primary benzylic alcohol (*M*/*P*)-**9** in 80% yield. Interestingly, kinetically controlled CAL-B-catalyzed esterification of (*M*/*P*)-**9** with vinyl acetate in MTBE did not show any enantioselectivity with regard to the inherent chirality of the TBTQ framework. Thus, the TBTQ-based benzyl acetate (*M*/*P*)-**10** was obtained from (*M*/*P*)-**9** both by use of CAL-B and of acetyl chloride/pyridine; the latter method gave the ester in 93% yield. However, when (*M*/*P*)-**10** was hydrolyzed by use of CAL-B in MTBE/water at pH 7 under kinetic control, the benzylic alcohol (*M*)-**9** ($[\alpha]_D^{18} = +74$) was isolated in pure form (99% *ee*) and in 26% yield. Hydrolysis with lipase PS under similar reaction conditions was found to be less selective; enantiomerically highly enriched (*P*)-**9** (99% *ee*) was formed only at conversions < 16%. As a consequence, CAL-B was used for the racemic resolution of *rac*-**10** to produce the enantiopure ester (*P*)-**10** in 39% yield (> 99% *ee*). Subsequent hydrolysis with potassium hydroxide provided the second enantiomer (*P*)-**9** ($[\alpha]_D^{18} = -74$) in 98% yield and with high purity (> 99% *ee*). The primary alcohols (*P*)-**9** and (*M*)-**9** were oxidized to the corresponding enantiomerically pure TBTQ-benzaldehydes (*P*)-**6** ($[\alpha]_D^{18} = -106$) and (*M*)-**6** ($[\alpha]_D^{18} = +106$) in good yields (69% and 71%).

Since all attempts to grow single crystals for X-ray structure analysis failed, the absolute configuration of (*P*)-**6** and (*M*)-**6** was determined by comparison of their chiroptical properties with those of the TBTQ-acetophenones (*P*)-**5** and (*M*)-**5** (Figure 3). The CD spectra of the aldehyde enantiomer obtained directly by use of lipase CAL-B and that of acetophenone (*M*)-**5** obtained with the same enzyme displayed closely similar shapes and the same algebraic sign of rotation, as did the spectra of acetophenone (*P*)-**5** and the aldehyde enantiomer prepared directly by use of lipase PS or of CAL-B along the indirect route (Scheme 3). Thus, the absolute configuration of the TBTQ-benzaldehydes (*M*)-**6** and (*P*)-**6** as well as of the precursor benzylic alcohols (*M*)-**9**

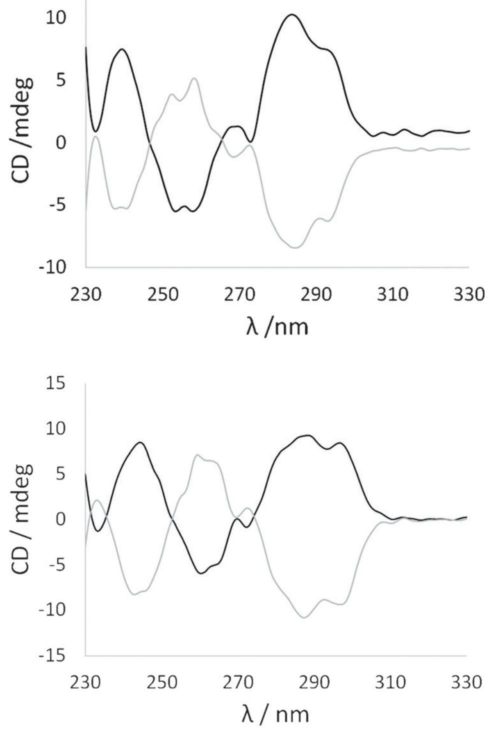


Figure 3. CD spectra of the enantiomerically pure TBTQ derivatives. Top: (*M*)-(+)-**5** (black trace) and (*P*)-(−)-**5** (grey); bottom: (*M*)-(+)-**6** (black) and (*P*)-(−)-**6** (gray), in MTBE (1.0 mM).

and (*P*)-**9** were determined unequivocally.[33] It is obvious that, in both series of TBTQ derivatives studied here, each of the lipases showed the same enantiopreference with respect to the chiral TBTQ bowl.

In conclusion, we have reported the first enantio- and diastereoselective synthesis of enantiomerically pure tribenzotriquinacene derivatives by use of two commercially available enzymes. The opposite chiral recognition of these two enzymes with respect to the bowl-shaped TBTQ framework is particularly striking, as is the finding that the convex–concave TBTQ skeleton with its hidden elements of chirality provides sufficient stereogenic information for the enzymatic discrimination of the enantiomers. We hope that such biocatalytic methodology may provide access to further enantiomerically pure TBTQ building blocks, which may be useful, for example, for the construction of novel nanoscale covalent and supramolecular assemblies.

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Keywords: bowl-shaped molecules · enzyme catalysis · inherent chirality · lipases · tribenzotriquinacenes

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