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Synthesis, Enantiomer Separation, and Absolute Configuration of 2,6-Oxygenated 9-Azabicyclo[3.3.1]nonanes

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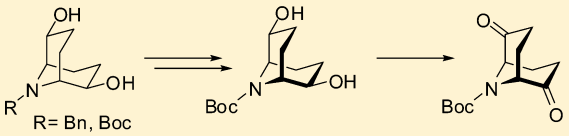
Supporting Information

ABSTRACT: The synthesis of the enantiomerically pure *N*-Boc 9-azabicyclo[3.3.1]nonane-2,6-dione (**4b**), a potentially useful chiral building block, from *N*-Bn and *N*-Boc 9-azabicyclo[3.3.1]nonane-2,6-diols **2a** and **2b** was accomplished. The enantiomer resolution of diols **2a** and **2b** was achieved by crystallization of their diastereomeric esters or by kinetic resolution of the racemic diol **2a** using lipase from *Candida rugosa* (CRL). Both enantiomers of *N*-Boc protected diol **2b** were converted into the corresponding enantiomerically pure diones **4b**, the absolute configuration of which was determined by comparison of the experimental and simulated circular dichroism (CD) spectra, obtained by ab initio time-dependent density functional theory (TDDFT) calculations. The (−)-(1*R*,5*R*)/(+)-(1*S*,5*S*) absolute configuration of **4b** inferred from the TDDFT calculations was confirmed via analysis of the CD spectrum of *endo*,*endo*-dibenzoate (+)-**7** derived from diol (+)-**2b** and application of the benzoate exciton chirality method. The assigned absolute configuration was further supported by the results of kinetic resolution of diol **2a** using *Candida rugosa* lipase, which exhibited kinetic preference toward the (1*R*,2*R*,5*R*,6*R*)-enantiomer in agreement with the Kazlauskas' rule.



INTRODUCTION

The bicyclic skeleton of 9-azabicyclo[3.3.1]nonane (granatane) is common to numerous macroline, sarpagine and ajmaline-related indole alkaloids, an important class of natural products with diverse biological activity.[1] These three structurally similar classes of alkaloids possess an indole-annulated azabicyclo-[3.3.1]nonane (cycloocta[b]indole) scaffold, which has recently been a subject of biology-oriented synthesis (BIOS).[2] Macroline-like compounds, obtained using the BIOS approach, have been identified as promising targets for developing a novel class of potent and selective antibiotic agents with activity against *Mycobacterium tuberculosis*.[3]

To date, the Pictet−Spengler reaction of tryptophan derivatives remains a key strategic transformation for the stereospecific synthesis of macroline, sarpagine and ajmaline-related indole alkaloids.[1,4] As a consequence, the synthesis of congeners possessing oxygenated indole ring requires the optimization of enantioselective routes to the relevant oxygenated tryptophan analogues.[1,5] By contrast, the potential of the 9-azabicyclo[3.3.1]nonane synthons for de novo construction of the indole moiety of cycloocta[b]indole core is considerably less explored. Moreover, while 2,6-oxygenated 9-azabicyclo[3.3.1]nonanes attracted attention as suitable precursors for the synthesis of ajmaline and sarpagine alkaloids,[6] their synthesis in an enantiomerically pure form has never been reported, and in general, literature examples of simple enantiopure 9-azabicyclo[3.3.1]nonane derivatives remain scarce.[7]

We have demonstrated the utility of the enantiomerically pure bicyclo[3.3.1]nonane-2,6-dione[8] for the synthesis of chiral C_2-symmetric cleft molecules, incorporating self-complementary hydrogen bonding heteroaromatic moieties. Such monomeric units with inherent geometric features responsible for controlled spatial aggregation provide access to various supramolecular structures, such as cages,[9] helical tubular oligomers[10] and belts.[11] The three-dimensional structure of the supramolecular assemblies was profoundly governed by the enantiomeric purity of the building blocks, whereas long alkyl chains were prerequisite to attain the sufficient solubility in nonpolar solvents.[10,11]

In connection with our ongoing research on the synthesis of novel supramolecular synthons, we focused on the derivatives of 9-azabicyclo[3.3.1]nonane, which offer a unique advantage to introduce solubilizing groups at the position not accessible in case of carbocyclic congeners, i.e., on the apical nitrogen atom. As the synthetic methodologies to access the enantiomerically pure compounds of this framework are unavailable, we focused on the synthesis and enantiomer separation of 2,6-oxygenated 9-azabicyclo[3.3.1]nonane derivatives and determination of their absolute configuration. CD spectroscopy today is a well-established technique for determination of the absolute configuration of chiral compounds.[12] A variety of methodologies, ranging from empirical rules to ab initio quantum mechanical methods, have been devised for the correlation of the observed sign and magnitude of Cotton effects (CEs) in the CD spectra with the absolute configuration. In recent years, high-level quantum mechanical calculations have emerged as a general and convenient method for the determination of absolute stereochemistry. In particular, the time-dependent density functional theory (TDDFT)[13] has become a practicable tool in theoretical CD spectroscopy due to a reasonable balance

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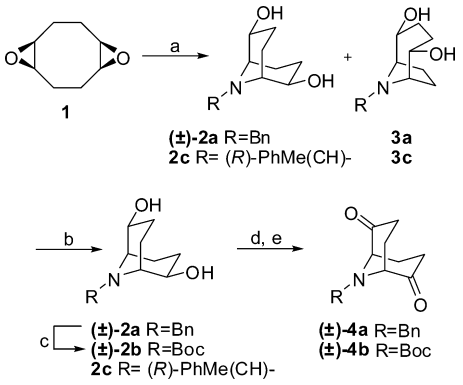
between accuracy and computational efficiency. As the chiroptical properties depend on the contribution of all populated conformers, theoretical calculations provide an efficient method for the determination of the absolute configuration of the conformationally flexible molecules.[14]

In this work, the enantiomer resolution of 2,6-oxygenated 9-azabicyclo[3.3.1]nonane derivatives by crystallization of diastereomeric salts and camphanate esters as well as enzymatic kinetic resolution were investigated, and synthesis of the potentially useful chiral building blocks was accomplished. The chiroptical properties of the obtained enantiomerically pure compounds were studied, and the absolute configuration was inferred from the TDDFT calculations and application of the benzoate exciton chirality method.

RESULTS AND DISCUSSION

Synthesis of Racemic 9-Azabicyclononanes. Racemic *N*-benzyl 9-azabicyclo[3.3.1]nonane-2,6-diol (**2a**) was obtained from *syn*-diepoxide **1** following the reported procedure.[15] The reaction of diepoxide **1** with benzylamine in water under reflux produced a 1:1 mixture of isomeric 9-azabicyclo[3.3.1]- and [4.2.1]nonanediols **2a** and **3a** in a quantitative yield (Scheme 1).

Scheme 1[a]



[a]Conditions: (a) $BnNH_2$ or (*R*)-1-phenylethylamine, H_2O, reflux. (b) (i) TFAA, DCM, −60 °C; (ii) TEA, DCM, reflux; (iii) 2.5 N NaOH, THF, rt, 95−98%. (c) (i) H_2, Pd/C, AcOH, MeOH, rt; (ii) Boc_2O, TEA, MeOH, reflux, 70−71%. (d) R = Bn: *t*-BuOK, PhH, Ph_2CO, rt, 68%. (e) R = Boc: cat. RuO_2, $NaIO_4$, CCl_4−MeCN−H_2O, rt, 80%.

The interconversion of **3a** to the desired thermodynamically more stable diol **2a** was accomplished via trifluoroacetylation of the obtained mixture, followed by isomerization in refluxing dichloromethane. Subsequent saponification of the resulting bistrifluoroacetate afforded diol **2a** in 95−98% overall yield solely as *endo*,*endo* diastereomer.[15]

For a large scale synthesis of **2a**, the use of rather expensive commercial diepoxide **1** was not practical, and the convenient method for preparation of **1** from cheap 1,5-cyclooctadiene was required. According to literature, the former compound could be synthesized by epoxidation of 1,5-cyclooctadiene using either peroxyacetic acid (57% yield)[16] or $MeReO_3/H_2O_2$ (80−97% yield on a small scale).[17] We employed an alternative procedure for oxidation of 1,5-cyclooctadiene using inexpensive and safe oxidant OXONE. The two-phase procedure using an aqueous solution of OXONE and ethyl acetate in combination with acetone[18] as a mediator afforded diepoxide **1** in 60−77% yield. The crude product showed only a minute amount of impurities in the NMR spectra and could be used for the synthesis of **2a** without further purification.

Initial attempts to obtain dione **4a** by oxidation of diol **2a** using a number of standard oxidizing reagents met little success. The benzyl protecting group was therefore replaced with more convenient *tert*-butyloxycarbonyl (Boc) group to give **2b**,[15] which could be oxidized to the corresponding dione **4b** in high yields by using Swern or RuO_2 catalyzed oxidation with sodium periodate (Scheme 1). Room temperature ruthenium-catalyzed oxidation gave higher yields, was operationally simpler than Swern oxidation and could be easily adapted to a large-scale synthesis. On the other hand, by using Oppenauer oxidation[19] of **2a**, *N*-benzyl dione **4a** could be obtained in 68% yield but proved to be rather unstable. This is consistent with the similar disappointing results of the oxidation of the *N*-methyl congener of **2a**, reported earlier.[6b] All attempts to synthesize *N*-unsubstituted dione by deprotection of **4b** under standard conditions (TFA/DCM) were equally unproductive.

In order to attain the enantiomerically enriched azabicyclic derivatives, a few catalytic asymmetric methodologies for enantioselective opening of *meso*-epoxides were briefly investigated. From this point of view, diepoxide **1** represents a particularly challenging substrate, as the reaction with benzylamine (or any other achiral nucleophile) has to be both enantio- and regioselective to avoid the formation of the achiral diol **3**. In addition, skeletal isomerization of *meso*-**3** to the desired diol **2** is in principle reversible and proceeds via formation of the transient aziridinium intermediate, thus providing a pathway for racemization at the same time.[20] A very efficient titanium isopropoxide/BINOL catalyzed enantioselective desymmetrization of a few *meso*-epoxides with benzylamines as nucleophiles has been reported;[21] coordination of the substrate to the catalyst in a bidentate fashion was found to be prerequisite for high stereoselectivity. We reasoned that diepoxide **1** could provide such coordination to Ti/BINOL complex via oxygen atoms of both epoxide moieties. Nevertheless, Ti(*i*-PrO)$_4$/(*R*)-BINOL (1 mol %) catalyzed reaction of diepoxide **1** with benzylamine or (*R*)-1-phenylethylamine in the presence of water[21a] afforded only trace amounts of both diols **2** and **3**. On the other hand, ring-opening reaction of **1** with (*R*)-1-phenylethylamine in water under standard conditions (Scheme 1) produced corresponding azabicyclo[3.3.1]- and [4.2.1]nonanediols **2c** and **3c** approximately in a 1:1 ratio as an inseparable mixture, which could be isomerized to the required azabicyclo[3.3.1]nonane diol **2c** via the corresponding bistrifluoroacetate. The ^{1}H NMR of the crude reaction product (ca. 50% yield), however, indicated the formation of the two diastereomeric *endo*,*endo*-diols **2c** in roughly 1:1 ratio. The results of ytterbium(III) triflate/(*R*)-BINOL catalyzed[22] ring-opening reaction of **1** with *p*-anisidine, derivatives of which can be oxidatively deprotected,[23] were equally disappointing.

Enantiomer Resolution. With racemic compounds **2a**,**b** and **4b** in hand, we focused on their resolution into enantiomers. Because of the basic nature, amino alcohol **2a** seemed to be perfectly suited for enantiomer resolution via fractional crystallization of diastereomeric salts with chiral acids. Nevertheless, attempts to resolve racemic diol **2a** with a number of enantiomerically pure acids afforded only partially enantiomerically enriched alcohols (ca. 20% ee), as determined by chiral HPLC of the corresponding benzoate **7** (Scheme 2, vide infra).

Encouraged by a successful enantiomer resolution of numerous spirocyclic,[24] bicyclic[25] and polycyclic alcohols[26]

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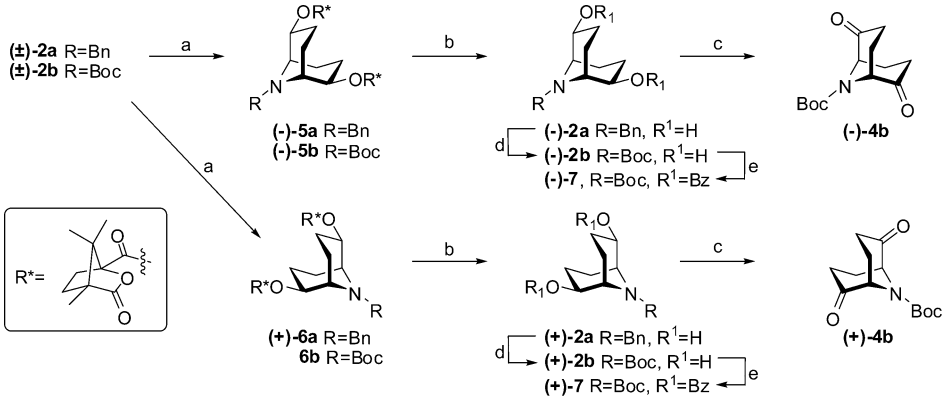
Scheme 2[a]



[a]Conditions: (a) (i) Camphanic chloride, DMAP, TEA, DCM, rt, 93−96%; (ii) fractional crystallization, 18−37%. (b) K_2CO_3, MeOH, rt, quant. (c) cat. RuO_2, $NaIO_4$, CCl_4−MeCN−H_2O, rt, 72−86%. (d) (i) H_2, Pd/C, AcOH, MeOH, rt; (ii) Boc_2O, TEA, MeOH, reflux, 70−71%. (e) PhCOCl, DMAP, TEA, DCM, rt, 69−94%.

via camphanate esters, we investigated the resolution of esters **5** and **6**, obtained in 93−96% yields from racemic diols **2a**,**b** and enantiomerically pure (−)-(1*S*)-camphanic chloride (Scheme 2). Fractional crystallization of the diastereomeric mixture of *N*-Boc diesters **5b** and **6b** from methanol afforded diastereomerically pure **6b** in 31% yield. Interestingly, solutions of **6b** in chloroform exhibited no measurable specific rotation angle. The second diastereomer (−)-**5b** (20% yield) was obtained by concentration of the mother liquor and fractional crystallization of the residue from dichloromethane−diethyl ether mixtures. The diastereomeric purity of the resolved diastereomers was determined from their ^{1}H NMR spectra, where the diagnostic resonance signals corresponding to the methyl groups of the camphanate moieties were sufficiently resolved. Subsequent hydrolysis of the individual diastereomers (−)-**5b** and **6b** afforded practically enantiomerically pure diols (−)-**2b** (99% ee) and (+)-**2b** (98% ee), respectively, as determined by chiral HPLC of the corresponding benzoates **7** (Scheme 2). The resolution was reproducible on both small and relatively large (7 mmol) scale, and the resolving reagent could be recovered as camphanic acid after hydrolysis of the camphanate esters in 82% average yield.

Analogously, diastereomerically pure camphanates (−)-**5a** (18%) and (+)-**6a** (37%) were obtained via fractional crystallization of the diastereomeric mixture of *N*-Bn diesters **5a** and **6a**. Subsequent saponification of the individual diesters (−)-**5a** and (+)-**6a** afforded enantiomerically pure diols (−)-**2a** and (+)-**2a**, respectively. The obtained (−)-**2a** and (+)-**2a** were converted to diols (−)- and (+)-**2b**, respectively, via an exchange of the *N*-protecting group by hydrogenolysis and subsequent Boc protection.[15] The latter chemical correlation relates the absolute configurations of the *N*-Bn and *N*-Boc series; i.e., camphanates (−)-**5a**, (−)-**5b**, diols (−)-**2a**, (−)-**2b** and dibenzoate (−)-**7** possess the same absolute configuration of the azabicyclic framework at the C_1, C_2, C_5 and C_6 stereogenic centers (Scheme 2). While the separation and subsequent saponification of *N*-Boc and *N*-Bn diastereomeric camphanates afforded the corresponding enantiomerically pure diols in a comparable overall yields, the resolution of *N*-Bn protected camphanates **5a** and **6a** was found to be more difficult to reproduce, especially in the case of (−)-**5a**. Subsequent RuO_2 catalyzed oxidation of diols (−)-**2b** and (+)-**2b** (Scheme 2) proceeded uneventfully to give enantiomerically pure diones (−)-**4b** and (+)-**4b**, respectively.

Enzymatic Kinetic Resolution. Although the enantiomers of **2a**,**b** could be obtained via resolution of the corresponding camphanates, the separation procedure required several fractional crystallizations and involved additional esterification/saponification synthetic steps. Therefore alternative methodologies based on the enzymatic kinetic resolution of enantiomers were explored, including the Baker's yeast mediated reduction of racemic dione **4b**. The latter method was found to be a very efficient way for resolution of the racemic bicyclo[3.3.1]nonane-2,6-dione, a carbocyclic analogue of **4b**, providing enantiomerically pure (+)-2,6-dione[8] after two consecutive fermentations. Despite the bulky Boc protecting group at ninth position of bicyclic framework, a rather fast reduction of dione **4b** with Baker's yeast occurred, but the enantiomeric purity of the recovered dione (+)-**4b** was below 30% even after the repeated fermentation or fermentation under high dilution conditions.[27]

An alternative pathway is the differentiation of the enantiomers of alcohols by hydrolytic enzymes, either by stereoselective esterification of the racemic alcohols or by hydrolysis of the corresponding esters.[28] Lipases are particularly useful in organic synthesis, because they are efficient, simple to use and can function in organic solvents,[29] thus substantially simplifying the purification procedures. Resolution of bicyclic diols both by lipase-catalyzed hydrolysis of the corresponding diacetates[30] and transesterification[31] has been reported, including the enantiomer resolution of 9-oxabicyclo[3.3.1]-nonane-2,6-diol using lipases from *Candida antarctica* (CAL) or *Candida rugosa* (CRL).[32]

We investigated the kinetic resolution of racemic diols **2a** and **2b**, using CRL and vinyl acetate as an irreversible acyl donor. Initial experiments revealed that the acetylation of *N*-Boc diol **2b** was extremely sluggish, giving negligible conversion after one week. By contrast, *N*-Bn protected diol **2a** underwent a very fast acetylation in pure vinyl acetate at 20 °C producing mixture of unreacted diol (+)-**2a** and corresponding mono- and diacetates **8** and **9** (Scheme 3).

To elucidate the efficiency of the lipase catalyzed resolution, a detailed kinetic study (Figure 1) was performed by taking aliquots from the reaction mixture and monitoring the reaction progress by GC−MS. For ee determination, the unreacted diol

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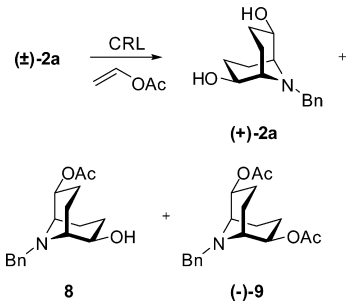
Scheme 3



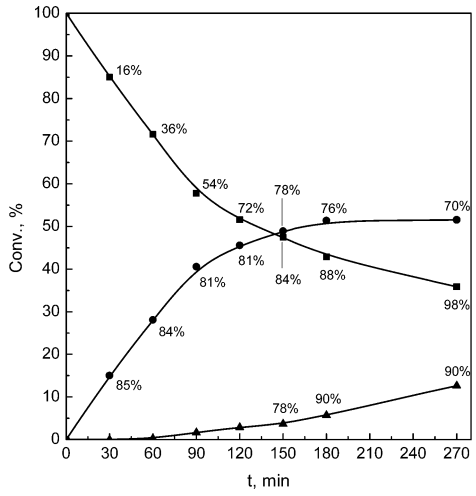


Figure 1. Conversion (**2a** (■); **8** (●); **9** (▲)) and enantiomeric excesses of the CRL catalyzed acetylation of (±)-**2a** at 20 °C.

2a, monoacetate **8** and diacetate **9** were separated by column chromatography; **2a** and **8** were converted to the corresponding diacetates **9** by a standard acetylation with acetic anhydride in the presence of DMAP and analyzed by chiral HPLC.

Thus, in pure vinyl acetate approximately 53% conversion of **2a** was reached in 2.5 h (Figure 1). At this point, the remaining diol (+)-**2a** had the enantiomeric purity of 84%, whereas the corresponding monoacetate **8** exhibited a rather modest enantiomeric excess (78% ee). The latter steadily decreased as the reaction proceeded further (Figure 1) because of the subsequent acetylation of **8** to give diacetate **9**. After 4.5 h, 64% of the diol was consumed to produce a 36:51:13 mixture of **2a** (98% ee), **8** (70% ee) and **9** (90% ee), respectively. Attempts to improve the efficiency of the kinetic resolution by performing the acetylation in organic solvents met little success, probably due to a very limited solubility of **2a**. For example, negligible conversions were attained in methyl *tert*-butyl ether in the presence of 2, 3, or 4 equiv of vinyl acetate after one week. Fortunately, the enantiomeric purity of the enantioenriched **2a** (78−84% ee) could be readily improved by a single recrystallization to give enantiopure material.

Preparative scale resolution of racemic **2a** was conducted in pure vinyl acetate, and the reaction was quenched after 2.5 h by filtering off the enzyme and evaporation. Separation of the unreacted diol from acetates **8** and **9** and subsequent recrystallization afforded enantiomerically pure (+)-**2a** (27%). The other enantiomer, (−)-**2a**, was obtained in 23% yield by single crystallization of the enantioenriched diol, obtained after saponification of the combined fractions, containing acetates **8** and **9**. Although CRL mediated kinetic resolution proceeded with moderate enantioselectivity, the described procedure provides convenient and fast method to attain both enantiomers of **2a** in 50% combined yield. The remaining practically racemic diol **2a** (47%) could be recovered from the combined mother liquors and reused in the subsequent resolutions.

Chiroptical Properties and Absolute Configuration. For determination of the absolute configuration, the chiroptical properties of the obtained enantiomerically pure diones **4b** were studied. The absolute configuration of chiral ketones can be assigned from the analysis of CD spectra using the octant rule for the n → π^* transition of the carbonyl chromophore. While numerous successful applications have proved the octant rule as a practicable tool for determination of the absolute configuration of many saturated ketones,[33] the prediction of the CE sign should be made with caution when molecular conformation is ambiguous. Moreover, the validity of the octant rule may become even more disputable when two nonequivalent carbonyl chromophores are present in the molecule.[34] Although compounds of both *N*-Bn and *N*-Boc series lack molecular symmetry, *N*-Bn derivatives behave as pseudo C_2-symmetric due to a rapid inversion of trigonal pyramidal nitrogen atom. By contrast, the presence of coplanar carbamate moiety and hindered rotation around (O═)C—N(sp^2) bond renders the two halves of the bicyclic framework nonequivalent in the *N*-Boc series. This is evident from the ^{1}H and ^{13}C NMR spectral data of **2b**, **4**−**6b** and **7**, where the two separate resonance signals corresponding to H−C_1/H−C_5 (and H−C_2/H−C_6) are observed.

In the experimental CD spectrum of (+)-**4b**, a bisignate CE centered at 306 nm (negative at 319 nm and positive at 292 nm), attributable to the n → π^* transitions of the C═O groups, is observed, and the positive CE at 232 nm is assigned to the n → π^* transition of the carbamate chromophore. As expected, (−)-**4b** exhibited the mirror-image CD spectrum (Figure 2).

As the octant rule is clearly inapplicable in this case, the absolute configuration of **4b** was inferred from the comparison of experimental and TDDFT calculated CD spectra. Conformational analysis of arbitrarily chosen (1*R*,5*R*)-enantiomer of **4b** using MMFF94 force field, followed by optimization using DFT at B3LYP/6-31G(d) level identified chair−chair (*c*−*c*),

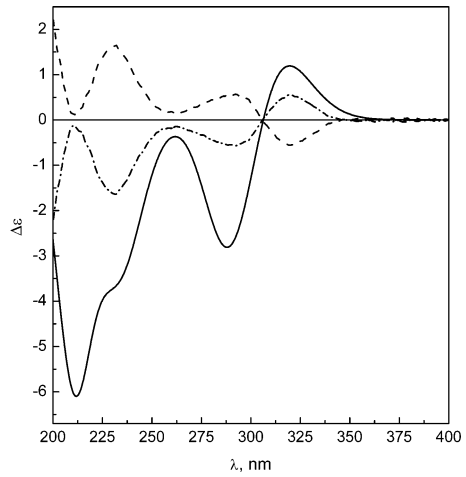


Figure 2. CD spectra of diones (+)-**4b** (− −) and (−)-**4b** (−·−·) in ethanol; wavelength corrected, Boltzmann-averaged CD of (1*R*,5*R*)-**4b** (—), calculated at B3LYP/6-311++G(2d,2p) level.

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two chair−boat (*c*−*b* and *c*−*b1*) and double twistboat (*tb*−*tb*) conformations within a 1 kcal/mol window (Figure 3).

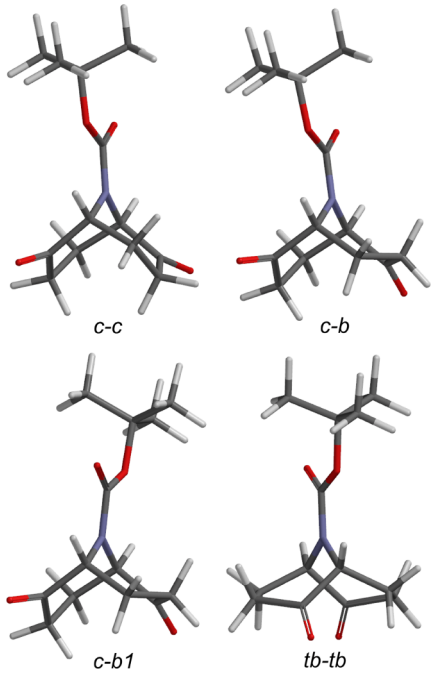

Figure 3. Structures of the low energy conformers of **4b** optimized at B3LYP/6-311++G(d,p) level of theory.

The obtained structures were further optimized at B3LYP/6-311G++(d,p) level, and harmonic vibrational frequencies were then calculated to confirm the stability of all conformations and to permit the calculation of their relative free energies (Table 1). At the B3LYP/6-311G++(d,p) level, *c*−*c* conformation is predicted to be lower in energy than the *c*−*b* conformer only by 0.15 kcal/mol. The two chair−boat conformers (*c*−*b* and *c*−*b1*) are comparably populated, and together with the *c*−*c* conformer they constitute ∼88% of the equilibrium mixture.

Table 1. (1*R*,5*R*)-4b: Conformational Energies and Circular Dichroism

conformer	ΔG^a	$P(\Delta G)^b$	λ, nm	$R_{vel}{}^c$
c−*c*	0	37.0	324, 312	7.30, −13.57
c−*b*	0.15	28.6	318, 307	18.26, −18.69
c−*b1*	0.31	22.0	319, 307	12.71, −16.84
tb−*tb*	0.65	12.4	332, 298	0.30, 0.29

[a]B3LYP/6-311G++(d,p) relative free energies in kcal/mol. [b]Populations obtained from ΔG values, using Boltzmann statistics and T = 298 K. [c]B3LYP/6-311++G(2d,2p) calculated n → π^* C═O transitions; R values in 10^{-40} esu^2 cm^2.

Excitation energies, oscillator strengths and rotational strengths were predicted for the conformations of (1*R*,5*R*)-**4b**, at their B3LYP/6-311++G(d,p) equilibrium geometries, using B3LYP and the 6-311++G(2d,2p) basis set. The calculated rotatory strengths (R_{vel}) were simulated into the CD curves assuming a Gaussian band shape[35] with a half-width at 1/e of the peak maximum (σ) value of 0.26 eV, approximately matching the broadening of the CD bands in the experimental spectra (see Supporting Information, Figure S1). For the determination of the absolute configuration of **4b**, the signs of the Cotton effects for the n → π^* transition of the carbonyl chromophores were diagnostic. For each conformer two low-energy transitions are predicted within the range 332−298 nm, attributable to n → π^* excitations of the C═O groups, well-separated from the next-highest excitations. For the three most populated *c*−*c*, *c*−*b* and *c*−*b1* conformers, calculations uniformly predict a bisignate n → π^* CD, positive at the longer wavelengths and negative at shorter wavelengths, whereas for the *tb*−*tb* conformer a very weak positive CD is predicted (Table 1). The Boltzmann-averaged CD spectrum of the equilibrium mixture of conformers, blue-shifted by 13 nm to match experimental λ_{max} of the CE at 319 nm, is plotted in Figure 2. Qualitatively, the calculated CD spectrum well reproduces the shape and relative intensity of the CEs in the experimental CD spectra of **4b**. The predicted CD spectrum of (1*R*,5*R*)-**4b** exhibits a bisignate CE (positive at 320 nm and negative at 290 nm) followed by negative CE below 250 nm, in agreement with the experimental spectrum of (−)-**4b**. The DFT calculations thus lead to the conclusion that the absolute configuration of dione **4b** is (−)-(1*R*,5*R*)/(+)-(1*S*,5*S*). As a result, (−)-(1*R*,2*R*,5*R*,6*R*)/(+)-(1*S*,2*S*,5*S*,6*S*) absolute configuration can be assigned to diols **2a** and **2b** on the basis of the chemical correlation described above (Scheme 2).

The absolute configuration of dione **4b** inferred from the TDDFT calculations was confirmed via analysis of the CD spectrum of dibenzoate (+)-**7** derived from diol (+)-**2b** and application of the benzoate exciton chirality method.[36] The benzoate chromophores with intense $\pi \rightarrow \pi^*$ absorptions are well-studied excitons that give rise to a characteristic pair of CD bands with opposite signs originating from the ^1L_a transitions. In the experimental CD spectrum of the (+)-**7**, the negative exciton couplet located at the benzoate chromophore ^1L_a transition wavelength at 231 nm was observed (Figure 4). In concordance with the exciton-type coupling, the strong absorption maximum at the same wavelength was observed in the UV spectrum of (+)-**7**.

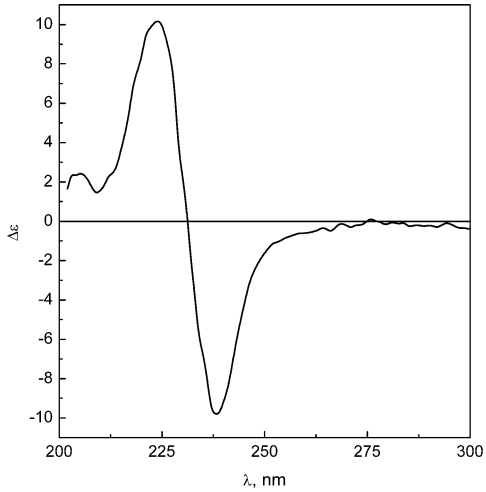

Figure 4. CD spectrum of dibenzoate (+)-**7** in ethanol.

Conformational analysis of arbitrarily chosen (1*R*,2*R*,5*R*,6*R*)-enantiomer of **7** using MMFF94 force field, followed by further optimization of the obtained structures using DFT at B3LYP/6-31G(d) level, predicts four stable chair−chair conformations. The corresponding chair−boat conformers were found much higher in energy and thus insignificantly populated. At the B3LYP/6-31G(d) level, low energy chair−chair conformers of

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(1*R*,2*R*,5*R*,6*R*)-**7** differ principally with regard to the conformation around $HC_{2,6}$−O bonds (see Supporting Information, Figure S2). The benzoate moieties adopt conformation typical for alkyl benzoates,[14] i.e., *s-trans* conformation around the benzoate (O)C−O bond with the ester carbonyl group *syn* with the respect to bicyclic methine H−$C_{2,6}$ hydrogens. All four conformers of (1*R*,2*R*,5*R*,6*R*)-**7** are characterized by a positive helicity of the interacting transition electric dipole moments, which are polarized along the long axis of the benzoate chromophore. As a result, a positive exciton couplet is predicted for the (1*R*,2*R*,5*R*,6*R*) enantiomer of dibenzoate **7**, and consequently, an opposite (1*S*,2*S*,5*S*,6*S*) configuration can be assigned to the (+)- enantiomer of **7**, which exhibited a negative exciton couplet in the experimental CD spectrum (Figure 4). This conclusion is consistent with the experimental and TDDFT analysis of *endo*,*endo*-dibenzoate of bicyclo[3.3.1]-nonane-2,6-diol;[37] i.e., in the experimental CD spectra of (+)-(1*S*,2*R*,5*S*,6*R*)-enantiomer a positive exciton couplet is observed (note the opposite (1*S*,5*S*) notation of the absolute configuration here due to the change of Cahn−Ingold−Prelog priority in comparison with the 9-aza congener **7**). The CD analysis of the benzoate **7** thus yields the same (−)-(1*R*,2*R*,5*R*,6*R*)/(+)-(1*S*,2*S*,5*S*,6*S*) absolute configuration of **2b**, as concluded above from the TDDFT calculations of the CD spectrum of **4b** and chemical correlation (Scheme 2), and permits an unequivocal assignment of the absolute configuration.

The correctness of the assigned absolute configuration is further supported by the results of kinetic resolution of diol **2a** using *Candida rugosa* lipase (Scheme 3). According to Kazlauskas' rule,[38] CRL exhibits kinetic preference toward the (*R*)-configured secondary alcohols or their acylated derivatives, provided that the larger substituent at the diol stereogenic center has also the higher priority according to the Cahn−Ingold−Prelog (CIP) nomenclature. Hence, the (1*S*,2*S*,5*S*,6*S*) absolute configuration of the slow-reacting enantiomer (+)-**2a** (Scheme 3) predicted using the Kazlauskas' rule is consistent with, and adds support to, the previous assignment using TDDFT calculations and the exciton chirality method.

CONCLUSIONS

The synthesis of enantiomerically pure 9-azabicyclic 2,6-diols **2a**, **2b** and 2,6-dione **4b** was accomplished. The enantiomer resolution of diols was achieved by crystallization of their diastereomeric camphanates or by kinetic resolution using lipase from *Candida rugosa* (CRL). Although CRL mediated kinetic resolution proceeded with moderate enantioselectivity, the procedure described provides convenient and fast method to attain both enantiomers of **2a**. The (−)-(1*R*,5*R*)/(+)-(1*S*,5*S*) absolute configuration of enantiomerically pure diones **4b**, obtained from enantiomers of *N*-Boc diol **2b**, was determined by TDDFT calculations and unequivocally confirmed via analysis of the CD spectrum of *endo*,*endo*-dibenzoate (+)-**7** and application of the benzoate exciton chirality method. The assigned absolute configuration was further supported by the results of kinetic resolution of diol **2a** using CRL, which exhibited kinetic preference toward the (1*R*,2*R*,5*R*,6*R*)-enantiomer in agreement with the Kazlauskas' rule. This is the first example of 2,6-oxygenated 9-azabicyclo[3.3.1]nonanes, potentially useful chiral building blocks, obtained in an enantiomerically pure form. Application of these scaffolds for the synthesis of novel chiral supramolecular synthons is in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz for protons and 75 MHz for carbon, and chemical shifts are reported in ppm relative to solvent resonance signal as an internal standard (^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.0 ppm). IR spectra were recorded in KBr pellets. Optical rotations were measured at 589 nm; $[\alpha]^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}, and concentrations are given in units of g/100 cm^3. The CD and UV spectra were recorded at 20 °C in a 0.1 cm cell. The stock solutions were prepared by weighting compound into volumetric flask and diluting with UV-grade ethanol. The CD spectra were measured in millidegrees and normalized into $\Delta\varepsilon$ (dm^3 mol^{-1} cm^{-1}) units. Melting points were recorded with a Koefler melting apparatus and are not corrected. High resolution mass spectra (HRMS) were recorded on a time-of-flight (TOF) spectrometer with electrospray ionization (ESI).

The enantiomeric excesses were determined using HPLC system, equipped with diode array detector and CHIRALPAK IA-3, IB-3 and IC-3 analytical (250 × 4.6 mm) columns. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. The conversion of substrates in the lipase-catalyzed acetylation was followed by GC−MS using 30 m × 0.25 mm RESTEK Rtx-1701 column, temperature program: 200 °C (3 min), 200 → 260 °C (25 °C/min), 260 °C (6 min); the ratio of compounds was determined by integration of the peak area and was not corrected.

All solvents and reagents for the reactions were of reagent grade and were dried and distilled under argon immediately before use as follows: dichloromethane and triethylamine from calcium hydride, benzene from sodium. Thin-layer chromatography was carried out on Kieselgel 60 F254 (Merck) sheets coated with silica gel, and Kieselgel 60 silica gel (0.040−0.063 mm, Merck) was used for column chromatography. Petroleum ether refers to the fraction boiling in the range 40−60 °C. Lipase from *Candida rugosa* (Type VII, ≥700 unit/mg solid; L1754) was purchased from Sigma-Aldrich.

5,10-Dioxatricyclo[7.1.0.0^{4,6}]decane (1).[17] To a 2.0 L three-necked flask equipped with mechanical stirrer, dropping funnel and thermometer were added $NaHCO_3$ (30 g, 0.357 mol), water (400 mL), acetone (120 mL), ethyl acetate (400 mL) and cyclooctadiene (10 g, 0.093 mol). A solution of Oxone (114 g, 0.186 mol) in water (440 mL) was added dropwise over 2 h to the vigorously stirred reaction mixture at the rate to keep mixture temperature below 30 °C. After addition, the mixture was stirred for an additional 1 h, and then the organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was evaporated to afford **1** (9.97 g, 77%) as colorless oil, which solidified on standing; the product was TLC and NMR pure and was used for the next step without further purification: mp 28−30 °C; ^{1}H NMR δ 1.78−1.91 (m, 4H), 1.92−2.03 (m, 4H), 2.92−2.99 (m, 4H), in agreement with the literature data.[17]

(±)-*endo*,*endo*-9-Benzyl-9-azabicyclo[3.3.1]nonane-2,6-diol (2a) and (±)-*endo*,*endo*-*tert*-Butyl 2,6-dihydroxy-9-azabicyclo-[3.3.1]nonane-9-carboxylate (2b).[15] Obtained from diepoxide **1** following the reported procedures.[15]

(±)-9-Benzyl-9-azabicyclo[3.3.1]nonane-2,6-dione (4a). *t*-BuOK (135 mg, 1.2 mmol), benzophenone (547 mg, 3 mmol) and diol (±)-**2a** (74 mg, 0.3 mmol) were sequentially added to dry benzene (5 mL) under an argon atmosphere. The resulting mixture was stirred at room temperature for 24 h. The orange mixture was transferred to a separatory funnel and extracted with an aqueous 10% HCl (1 × 10 mL and 2 × 5 mL). Combined aqueous layer was treated with a solution of KOH (3.4 g) in water (10 mL) and extracted with dichloromethane (3 × 10 mL), combined organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. Yellow residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate mixture (7:3, R_f = 0.37) to afford **4a** (52 mg, 68%) as a colorless oil, which solidified on standing: mp 89−91 °C (DCM/hexane); ^{1}H NMR δ 1.93−2.04 (m, 2H), 2.38−2.56 (m, 4H), 2.69−2.80 (m, 2H), 3.38−3.40 (m, 2H), 3.83 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 13.4

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Hz, 2H), 7.24−7.38 (m, 5H); ^{13}C NMR δ 24.1 (CH_2), 35.3 (CH_2), 56.4 (CH_2), 62.9 (CH), 127.7 (CH), 128.6 (2 × CH), 137.0 (C), 212.1 (C=O); IR ν 3028, 2951, 1960, 1718, 1706, 1494, 1451, 1125, 1114, 992 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$ 244.1338, found 244.1344.

***tert*-Butyl 2,6-dioxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (4b).** Diol **2b** (669 mg, 2.6 mmol) was dissolved in MeCN:CCl_4:H_2O (8:8:12 mL) mixture, and then $NaIO_4$ (2.22 g, 10.4 mmol) and RuO_2·H_2O (3.9 mg, 1 mol %) were added under constant stirring. The reaction mixture was vigorously stirred for 36 h at room temperature and then diluted with dichloromethane (52 mL) and water (26 mL). Phases were separated, and aqueous phase was extracted with dichloromethane (2 × 40 mL). Combined organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. Brown oily residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate mixture (7:3, R_f = 0.33) to give **4b** as colorless oil, which solidified on standing; yields and spectral data are given below.

*(±)-**4b***. Obtained from (±)-**2a** in 80% yield: mp 94−96 °C; ^{1}H NMR δ 1.47 (s, 9H), 2.10 (br s, 2H), 2.33−2.46 (m, 4H), 2.51−2.64 (m, 2H), 4.69 (br s, 1H), 4.82 (br s, 1H); ^{13}C NMR δ 25.5 (CH_2), 28.4 (CH_3), 35.0 (CH_2), 57.8 (CH), 59.0 (CH), 81.6 (C), 153.8 (C=O), 208.8 (C=O); IR ν 2978, 1721, 1691, 1408, 1318, 1171 cm^{-1}; Chiral HPLC (Chiralpak IC-3 column, hexane/2-propanol 75:25, 1 mL/min) t_1 = 11.59 min, t_2 = 13.13 min. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.82; H, 7.59; N, 5.81.

*(+)-(1S,5S)-**4b***. Obtained from (+)-**2a** in 76% yield: mp 78−80 °C; $[\alpha]_D$ +35 (*c* 1.0, $CHCl_3$); CD λ_{max} ($\Delta\varepsilon$) 319 (−0.56), 306 (0), 292 (+0.57), 232 (+1.65) nm; UV λ_{max} (log ε) 303 (1.89) nm; Chiral HPLC (Chiralpak IC-3 column, hexane/2-propanol 75:25, 1 mL/min) showed >99% ee (t_{major} = 13.12 min).

*(−)-(1R,5R)-**4b***. Obtained from (−)-**2a** in 83% yield: mp 78−80 °C; $[\alpha]_D$ −35 (*c* 1.0, $CHCl_3$); Chiral HPLC (Chiralpak IC-3 column, hexane/2-propanol 75:25, 1 mL/min) showed >99% ee (t_{major} = 11.50 min).

General Procedure for the Synthesis of Camphanates 5a, 6a and 5b, 6b. Triethylamine (4.2 mL, 30 mmol) was slowly added to a suspension of a corresponding racemic diol **2a** or **2b** (7 mmol), (*S*)-camphanic chloride (3.25 g, 15 mmol) and DMAP (43 mg, 5 mol %) in dry dichloromethane (50 mL), resulting in complete dissolution of starting materials and subsequent precipitation of triethylammonium chloride. The reaction mixture was stirred under an argon atmosphere at room temperature until no more diol or monoester could be detected by TLC (ca. 6 h). The resulting mixture was then diluted with dichloromethane (50 mL) and washed with water (25 mL), 0.5% aqueous HCl (25 mL) and saturated $NaHCO_3$ (25 mL). The organic phase was dried with Na_2SO_4, filtered and evaporated under reduced pressure to afford crude camphanates **5a**, **6a** (96%) and **5b**, **6b** (93%) as yellowish solids, which were used without further purification.

Fractional Crystallization of 5a, 6a. Diastereomeric mixture of *N*-Bn camphanates **5a**, **6a** (1 g) was dissolved in minimal amount of dichloromethane and diluted with warm diethyl ether (40 mL). Crystallization began a few minutes after the dilution; the precipitate was collected, and the procedure was repeated two more times using 25 and 20 mL of Et_2O, respectively, to give diastereomerically pure (+)-**6a** (369 mg, 37%) as a colorless crystalline powder. Mother liquors from first two crystallizations of (+)-**6a** were combined and evaporated under reduced pressure. The obtained solid residue was recrystallized from methanol to afford diasteromerically pure (−)-**5a** (178 mg, 18%) as colorless crystalline solid.

*(−)-**5a***. Data: mp 165−169 °C (MeOH); $[\alpha]_D$ −22 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.92 (s, 6H), 1.04 (s, 6H), 1.11 (s, 6H), 1.68 (ddd, *J* = 13.4, 9.3, 4.3 Hz, 2H), 1.86−2.16 (m, 12H), 2.38 (ddd, *J* = 13.3, 10.6, 4.2 Hz, 2H), 2.88−2.93 (m, 2H), 3.95 (d, *J* = 14.0 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 5.36−5.43 (m, 2H), 7.22−7.38 (m, 5H); ^{13}C NMR δ 9.7 (CH_3), 16.7 (CH_3), 16.9 (CH_3), 21.0 (CH_2), 26.4 (CH_2), 28.9 (CH_2), 30.6 (CH_2), 51.7 (CH), 54.2 (C), 54.8 (C), 56.3 (CH_2), 71.6 (CH), 90.9 (C), 127.2 (CH), 128.0 (CH), 128.4 (CH), 138.7 (C), 166.7 (C=O), 178.1 (C=O); IR ν 2968, 1792, 1749, 1457, 1320, 1265, 1171, 1109, 1062, 740, 701 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{46}NO_8$ $[M + H]^+$ 608.3223, found 608.3206.

*(+)-**6a***. Data: mp 217−220 °C (Et_2O/DCM); $[\alpha]_D$ +4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.95 (s, 6H), 1.03 (s, 6H), 1.11 (s, 6H), 1.62−1.71 (m, 2H), 1.85−2.15 (m, 12H), 2.40 (ddd, *J* = 12.7, 10.3, 4.3 Hz, 1H), 2.88−2.95 (m, 2H), 3.96 (d, *J* = 13.9 Hz, 1H), 4.04 (d, *J* = 13.9 Hz, 1H), 5.33−5.41 (m, 2H), 7.22−7.37 (m, 5H); ^{13}C NMR δ 9.7 (CH_3), 16.7 (CH_3), 16.8 (CH_3), 21.0 (CH_2), 26.4 (CH_2), 28.8 (CH_2), 30.5 (CH_2), 51.7 (CH), 54.2 (C), 54.8 (C), 56.4 (CH_2), 71.8 (CH), 91.0 (C), 127.2 (CH), 128.1 (CH), 128.4 (CH), 138.8 (C), 166.9 (C=O), 178.3 (C=O); IR ν 2972, 1786, 1744, 1455, 1311, 1263, 1172, 1110, 1063, 740, 700 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{46}NO_8$ $[M + H]^+$ 608.3223, found 608.3221.

Fractional Crystallization of 5b, 6b. Diastereomeric mixture of *N*-Boc camphanates **5b**, **6b** (4 g) was recrystallized twice from methanol to afford diastereomerically pure **6b** (1.26 g, 31%) as a colorless crystalline solid. The combined mother liquors were evaporated under reduced pressure, and the residue was filtered through a pad of silica gel (5 g), using ethyl acetate/petroleum ether (1:1) as eluent. The resulting solution was evaporated under reduced pressure. Solid residue (2.70 g) was dissolved in minimal amount of dichloromethane and diluted with warm diethyl ether (100 mL). Crystallization began a few minutes after the dilution; the collected crystalline material (1.17 g) was reprecipitated from DCM with Et_2O (25 mL) to give diastereomerically pure (−)-**5b** (870 mg, 20%) as a colorless crystalline solid.

*(−)-**5b***. Data: mp 203−206 °C (Et_2O/DCM); $[\alpha]_D$ −16 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 0.94 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.47 (s, 9H), 1.63−1.73 (m, 2H), 1.79−2.14 (m, 12H), 2.41 (ddd, *J* = 13.3, 10.6, 4.3 Hz, 2H), 4.18 (t, *J* = 4.4 Hz, 1H), 4.29 (t, *J* = 4.8 Hz, 1H), 5.04−5.16 (m, 2H); ^{13}C NMR δ 9.7 (CH_3), 16.7 (CH_3), 16.9 (CH_3), 22.1 (CH_2), 22.4 (CH_2), 25.8 (CH_2), 25.9 (CH_2), 28.2 (CH_3), 28.9 (CH_2), 30.6 (CH_2), 46.1 (CH), 47.7 (CH), 54.2 (C), 54.3 (C), 54.76 (C), 54.81 (C), 71.7 (CH), 71.9 (CH), 80.8 (C), 90.8 (C), 90.9 (C), 153.7 (C=O), 166.4 (C=O), 166.5 (C=O), 177.9 (C=O), 178.2 (C=O); IR ν 2971, 1795, 1746, 1701, 1313, 1264, 1168, 1107, 1060 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{47}NNaO_{10}$ $[M + Na]^+$ 640.3098, found 640.3099.

6b. Data: mp 211−213 °C (MeOH); $[\alpha]_D$ 0 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 0.94 (s, 3H), 0.95 (s, 3H), 1.04 (s, 6H), 1.10 (s, 3H), 1.11 (s, 3H), 1.46 (s, 9H), 1.67 (ddd, *J* = 13.0, 8.3, 4.0 Hz, 2H), 1.76−2.18 (m, 12H), 2.35−2.48 (m, 2H), 4.20 (t, *J* = 4.3 Hz, 1H), 4.31 (t, *J* = 4.1 Hz, 1H), 5.02−5.12 (m, 2H); ^{13}C NMR δ 9.8 (CH_3), 16.7 (CH_3), 16.8 (CH_3), 22.1 (CH_2), 22.5 (CH_2), 25.96 (CH_2), 25.99 (CH_2), 28.3 (CH_3), 28.80 (CH_2), 28.84 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 46.0 (CH), 47.6 (CH), 54.2 (C), 54.3 (C), 54.8 (C), 71.7 (CH), 72.1 (CH), 80.6 (C), 90.8 (C), 153.7 (C=O), 166.4 (C=O), 166.6 (C=O), 178.16 (C=O), 178.21 (C=O); IR ν 2971, 1790, 1748, 1702, 1315, 1262, 1170, 1106, 1063 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{47}NNaO_{10}$ $[M + Na]^+$ 640.3098, found 640.3108.

General Procedure for Hydrolysis of Camphanates 5a,b and 6a,b. A mixture of camphanate ester (2 mmol) and K_2CO_3 (2.76 g, 20 mmol) in methanol (40 mL) was stirred at room temperature for 3 h and then diluted with water (50 mL) and $CHCl_3$ (50 mL). Layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 40 mL). Combined organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. The obtained residues were purified by recrystallization or column chromatography to give the corresponding diols (−)-, (+)-**2a** and (−)-, (+)-**2b**; yields and spectral data are given below.

The remaining aqueous layer was acidified with conc. HCl (4 mL) and extracted with ethyl acetate (4 × 30 mL). Combined organic phase was dried with Na_2SO_4 and evaporated under reduced pressure to afford pure (according to ^{1}H NMR) (*S*)-camphanic acid as an off-white solid in 82% average yield: mp 198−200 °C (EtOAc), reported[39] mp 198−199 °C; ^{1}H NMR δ 1.02 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.73 (ddd, *J* = 13.4, 9.3, 4.3 Hz, 1H), 1.97 (ddd, *J* = 13.2, 10.7, 4.6 Hz, 1H), 2.09 (ddd, *J* = 13.6, 9.3, 4.5 Hz, 1H), 2.47 (ddd, *J* = 13.4, 10.7, 4.3 Hz, 1H), 8.12 (br s, 1H).

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*(−)-(1R,2R,5R,6R)-**2a***. Obtained from (−)-**5a**; purification by recrystallization from $CHCl_3$ afforded colorless crystals in 89% yield: mp 142−144 °C; $[\alpha]_D$ −30 (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.46 (br s, 2H), 1.64−2.04 (m, 8H), 2.73 (t, *J* = 4.8 Hz, 2H), 3.95 (s, 2H), 4.10−4.20 (m, 2H), 7.20−7.38 (m, 5H); ^{13}C NMR δ 20.0 (CH_2), 30.0 (CH_2), 54.7 (CH), 56.3 (CH_2), 67.9 (CH), 126.9 (CH), 128.1 (CH), 128.2 (CH), 139.8 (C). The ^1H and ^{13}C NMR spectra of racemate in CD_3OD were reported previously;[15] (−)-**2a** was converted to (−)-**2b** via an exchange of the *N*-protecting group by hydrogenolysis and subsequent Boc protection, following the procedures reported earlier.[15]

*(+)-(1S,2S,5S,6S)-**2a***. Obtained from (−)-**6a**; purification by recrystallization from $CHCl_3$ afforded colorless crystals in 88% yield: mp 142−144 °C; $[\alpha]_D$ +30 (*c* 1.0, $CHCl_3$). (+)-**2a** was converted to (+)-**2b** via an exchange of the *N*-protecting group by hydrogenolysis and subsequent Boc protection, following the procedures reported earlier.[15]

*(−)-(1R,2R,5R,6R)-**2b***. Obtained from (−)-**5b**; purification by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (2:8, R_f = 0.28) afforded a colorless glass-like solid in 98% yield: $[\alpha]_D$ −10 (*c* 2.0, $CHCl_3$); ^1H NMR δ 1.43 (s, 9H), 1.58−1.97 (m, 6H), 2.04−2.20 (m, 2H), 3.24 (br s, 1H), 3.81−3.92 (m, 2H), 4.01 (t, *J* = 4.9 Hz, 1H), 4.10 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR δ 21.4 (CH_2), 21.9 (CH_2), 28.6 (CH_3), 29.1 (CH_2), 29.7 (CH_2), 49.4 (CH), 50.7 (CH), 68.7 (CH), 69.5 (CH), 80.2 (C), 155.0 (C═O), in agreement with the literature data.[15] Chiral HPLC of the corresponding benzoate (−)-**7** (vide infra) showed 99% ee.

*(+)-(1S,2S,5S,6S)-**2b***. Obtained from **6b**; purification by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (2:8, R_f = 0.28) afforded a colorless glass-like solid in 97% yield: $[\alpha]_D$ +10 (*c* 2.0, $CHCl_3$); Chiral HPLC of the corresponding benzoate (+)-**7** (vide infra) showed 98% ee.

General Procedure for the Synthesis of 9-(*tert*-Butoxycarbonyl)-9-azabicyclo[3.3.1]nonane-2,6-diyl dibenzoates (7). For ee determination, diols **2b** obtained via fractional crystallization of camphanate esters were converted to the corresponding benzoates **7**. A mixture of diol **2b** (52 mg, 0.2 mmol), DMAP (2.4 mg, 10 mol %), TEA (141 μL, 1 mmol) and benzoyl chloride (93 μL, 0.8 mmol) in dry dichloromethane (3 mL) was refluxed for 48 h under argon atmosphere. Cooled reaction mixture was washed with water (2 × 5 mL) and dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. Oily residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate mixture (95:5, R_f = 0.24) to give the corresponding benzoate **7**.

*(±)-**7***. Obtained from (±)-**2b** in 94% yield as a colorless oil, which solidified on standing: mp 128−130 °C; ^1H NMR δ 1.50 (s, 9H), 1.88−2.33 (m, 8H), 4.36 (t, *J* = 5.0 Hz, 1H), 4.47 (t, *J* = 5.0 Hz, 1H), 5.23 (dt, *J* = 11.7, 6.0 Hz, 2H), 7.43−7.49 (m, 4H), 7.55−7.61 (m, 2H), 8.03−8.07 (m, 4H); ^{13}C NMR δ 22.5 (CH_2), 22.8 (CH_2), 26.2 (CH_2), 28.3 (CH_3), 46.4 (CH), 48.0 (CH), 71.1 (CH), 71.3 (CH), 80.5 (C), 128.4 (CH), 129.6 (CH), 130.1 (C), 130.2 (C), 133.0 (C), 133.1 (C), 153.9 (C═O), 165.4 (C═O), 165.5 (C═O); IR ν 2972, 1721, 1690, 1315, 1271, 1110, 711 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{31}NNaO_6$ $[M + Na]^+$ 488.2049, found 488.2075; Chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol 99:1, 1 mL/min) t_1 = 9.12 min, t_2 = 10.31 min.

*(−)-**7***. Obtained from (−)-**2b** as a colorless oil in 69% yield: $[\alpha]_D$ −13 (*c* 1.0, $CHCl_3$); Chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol 99:1, 1 mL/min) showed 99% ee (t_{major} = 9.99 min, t_{minor} = 9.2 min).

*(+)-**7***. Obtained from (+)-**2b** as a colorless oil in 71% yield: $[\alpha]_D$ +13 (*c* 1.0, $CHCl_3$); CD λ_{max} ($\Delta\varepsilon$) 238 (−9.82), 231 (0), 224 (+10.23) nm; UV λ_{max} (log ε) 281 (3.08, sh), 273 (3.19), 231 (4.38) nm; Chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol 99:1, 1 mL/min) showed 98% ee (t_{major} = 9.04 min, t_{minor} = 10.44 min).

Lipase-Catalyzed Acetylation of (±)-2a. *Candida rugosa* lipase (600 mg) was added to the solution of diol (±)-**2a** (3 g, 12.1 mmol) in freshly distilled vinyl acetate (150 mL), and the mixture was stirred for 2.5 h at 20 °C. The reaction was quenched by filtering off the enzyme through a pad of Celite. After evaporation of vinyl acetate the unreacted diol **2a** was easily separated from the monoacetate **8** (R_f = 0.32) and diacetate **9** (R_f = 0.71) by column chromatography on silica gel with petroleum ether/ethyl acetate mixture (2:1). Subsequent elution with ethyl acetate afforded unreacted diol (1.448 g, 84% ee), which was recrystallized from hexane/$CHCl_3$ (1:1) mixture to afford (+)-**2a** (820 mg, 27%), $[\alpha]_D$ +31 (*c* 1.17, $CHCl_3$), 99% ee, as determined by chiral HPLC of the corresponding diacetate **9** (vide infra). Fractions containing monoacetate **8** and diacetate **9** were combined and first hydrolyzed (vide infra) to give diol **2a** (1.268 g), which was then recrystallized as described above to give (−)-**2a** (700 mg, 23%), 99% ee. Almost racemic diol **2a** (1.4 g) was recovered from the combined mother liquors left after crystallizations.

In a separate experiment, a kinetic study was performed by taking aliquots from the reaction mixture every 30 min: the enzyme was filtered off, the filtrate evaporated to dryness, and the obtained residue was analyzed by GC−MS. For ee determination, the unreacted diol **2a**, monoacetate **8** and diacetate **9** were separated by column chromatography; **2a** and **8** were converted to the corresponding diacetates **9** and analyzed by chiral HPLC (vide infra).

*9-Benzyl-6-hydroxy-9-azabicyclo[3.3.1]non-2-yl acetate (**8**)*. Yellowish oil: ^1H NMR δ 1.64−2.05 (m, 9H), 1.98 (s, 3H), 2.67 (br s, 1H), 2.82 (br s, 1H), 3.93 (ABq, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 13.9 Hz, 2H), 4.0−4.11 (m, 1H), 5.21 (dt, *J* = 11.4, 5.8 Hz, 1H), 7.16−7.33 (m, 5H); ^{13}C NMR δ 19.1 (CH_2), 21.3 (CH_3), 21.8 (CH_2), 26.5 (CH_2), 29.8 (CH_2), 52.1 (CH), 54.3 (CH), 56.3 (CH_2), 68.5 (CH), 70.0 (CH), 126.9 (CH), 128.1 (CH), 128.2 (CH), 139.5 (C), 170.6 (C═O); IR ν 3412, 2941, 1732, 1243, 1031, 892, 741, 699 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}NO_3$ $[M + H]^+$ 290.1756, found 290.1765.

General Procedure for Hydrolysis of Acetates 8 and 9. Solid K_2CO_3 (2 equiv) was added to a solution of diacetate **9** (or the monoacetate **8**; 1 equiv) in a minimal amount of methanol. The reaction mixture was stirred for 3 h at room temperature and then diluted with water, and the product was extracted with DCM. The organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the residue on silica gel with ethyl acetate gave the diol **2a** in quantitative yields.

General Procedure for the Synthesis of 9-Benzyl-9-azabicyclo[3.3.1]nonane-2,6-diyl diacetates (9). For ee determination, diol **2a** and monoacetate **8** obtained via kinetic resolution using CRL were converted to the corresponding diacetates **9**. Acetic anhydride (5 equiv) and DMAP (2 mol %) were added to the solution of diol **2a** (or monoacetate **8**; 1 equiv) in a minimal amount of dichloromethane. The reaction mixture was stirred at room temperature overnight and then neutralized with saturated aqueous $NaHCO_3$ solution. The product was extracted with dichloromethane, and the organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the residue on silica gel with petroleum ether/ethyl acetate mixture (85:15, R_f = 0.44) gave **9** as a colorless oil in quantitative yields.

*(±)-**9***. Obtained from (±)-**2a**: ^1H NMR δ 1.76−2.11 (m, 8H), 2.02 (s, 6H), 2.83−2.88 (m, 2H), 3.93 (d, *J* = 14.0 Hz, 1H), 4.03 (d, *J* = 14.0 Hz, 1H), 5.18−5.25 (m, 2H), 7.20−7.37 (m, 5H); ^{13}C NMR δ 20.8 (CH_2), 21.1 (CH_3), 26.2 (CH_2), 51.5 (CH), 56.2 (CH_2), 70.2 (CH), 126.9 (CH), 128.0 (CH), 128.1 (CH), 139.0 (C), 170.3 (C═O); IR ν 2959, 1733, 1369, 1230, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{26}NO_4$ $[M + H]^+$ 332.1862, found 332.1864; Chiral HPLC (Chiralpak IA-3 column, hexane/2-propanol 99:1, 1 mL/min) t_1 = 7.14 min, t_2 = 8.35 min.

*(−)-**9***. Obtained from (−)-**2a**: $[\alpha]_D$ −7 (*c* 1.0, $CHCl_3$); Chiral HPLC (Chiralpak IA-3 column, hexane/2-propanol 99:1, 1 mL/min) showed 99% ee (t_{major} = 7.34 min, t_{minor} = 8.43 min).

*(+)-**9***. Obtained from (+)-**2a**: Chiral HPLC (Chiralpak IA-3 column, hexane/2-propanol 99:1, 1 mL/min) showed 99% ee (t_{major} = 8.41 min, t_{minor} = 7.37 min).

Computational Details. Conformational search of **4a** and **7** was performed with SPARTAN'10[40] using Monte Carlo method and MMFF94 force field. The minimum energy conformers found by molecular mechanics were further optimized using DFT at B3LYP/6-31G(d) level. In the case of **4a**, the obtained conformers were additionally optimized at B3LYP/6-311G++(d,p) level using Gaussian

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software[41] followed by calculations of their harmonic vibrational frequencies to verify their stability and to calculate conformational free energies; population percentages were calculated using ΔG and applying Boltzmann statistics at T = 298.15 K.

The electronic circular dichroism calculations of the conformers were carried out by means of the Gaussian software employing the TDDFT approach, the B3LYP functional and the 6-311G++(2d,2p) basis set. The rotational strength calculations were carried out both in velocity (R_{vel}) and length formalism (R_{len}); the results in the two formalisms were almost identical. The CD spectra of the individual conformers were simulated by overlapping Gaussian functions for each transition[35] using SpecDis.[42] The half-width at 1/e of the peak maximum (σ) value of 0.26 eV and R_{vel} were used in this work. The calculated CD spectrum of **4b** was Boltzmann averaged according to the population percentages of individual conformers and was blue-shifted by 13 nm in relation to the experimental ones to match the experimental λ_{max} value of the long wavelength CE.

■ ASSOCIATED CONTENT

Supporting Information

Calculated CD for conformers of **4b**, geometry of low energy conformers of **7**, copies of ^{1}H NMR and ^{13}C NMR spectra, chiral HPLC traces and Cartesian coordinate geometries of molecules **4b** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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