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Attempted Resolution and Racemization of Beckmann-derived CTV-Lactam and the use of Chirabite-AR® to Determine Optical Purity of the Supramolecular Scaffold

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Abstract

Chirabite-AR was employed to differentiate enantiomers of the axially chiral cyclotriveratrylene (CTV)-derived macrocyclic lactam with baseline separation of most of the proton NMR resonances enabling enantiomeric purity determination of this supramolecular scaffold. Attachment of menthyloxy acetic acid as a chiral auxiliary to the CTV-Beckmann derived lactam afforded diastereomers that were enriched to a ratio of 87:13, as confirmed by both ^{1}H NMR and single-crystal X-ray diffraction. Basic hydrolysis of the enriched diastereomeric mixture proceeded with rapid bowl inversion to yield racemic CTV-lactam as confirmed by Chirabite-AR

NMR analysis. Density functional theory (DFT) calculations (M06 2X /6-31G*) were performed on the crown and saddle conformers of the CTV-lactam.

Introduction

Chiral cyclophanes have applications in enantiodiscrimination processes including catalysis, recognition and sensing, determination of enantiomeric excess, and signaling chiral information of guests,[1, 2] as with chiral molecular tweezers that exhibit selective binding and chiral recognition of specific guests.[3] Cyclotriveratrylene (CTV, **1**)[4] is a natural product and was first isolated from the bark of *Zanthoxylum conspersipunctatum* found in New Guinea.[5] CTV and its [1.1.1]cyclophane congeners in their rigid crown conformation are unique bowl-shaped molecules that have applications in sensors, self-organized materials, liquid crystals, and metallosupramolecular chemistry.[6] CTV and its cryptophane derivatives are of great interest in molecular recognition.[7] They are members of a larger family of inherently axially chiral concave molecules that have applications in chiral recognition and asymmetric synthesis.[2] A chiral CTV derivative bearing Kemp's triacid was shown to induce triple helix formation of collagen peptides.[8] A dynamic thermodynamic resolution strategy was recently reported of racemic CTV units by addition of remote stereogenic centers.[9] Helically chiral CTV units have been employed to construct enantiopure molecular cages,[10] along with a host of elegant CTV-derived coordination cages.[11] Some of the fascinating supramolecular structures of self-assembled cages derived from CTV-type scaffolds have recently been reviewed,[12] such as a racemic C3-symmetric bipyridyl-bearing CTV ligand with zinc shown to self-assemble into triply interlocked chiral catenanes within an overall chiral crystal.[13] CTV-based host

compounds bearing three binaphthol moieties have been reported as chiral sensors with recognition of sugar derivatives.[14]

The crown form of cyclotriveratrylene can undergo umbrella inversion that inverts chiral derivatives into their enantiomeric counterpart, as Collet demonstrated by observing the slow racemization of structurally chiral cyclotriveratrylene derivatives.[15] Resolution and NMR studies have been performed on the crown and saddle conformers of a CTV derivative toward chiral liquid crystals.[16]

While most work with CTV has focused on peripheral functionalization, we have focused on apical functionalization, enabling attachment of CTV "bowl-out" receptors on surfaces,[17] including desymmetrized C1-symmetric derivatives that are also of interest.[18] The parent 9-membered cyclophane **1** (Figure 1) is under ambient conditions locked into the bowl-shaped crown conformer. Elegant high temperature melt and quench experiments by Zimmerman first enabled isolation of the saddle conformer of CTV.[19] In contrast, the corresponding CTV monoketone **2** exists exclusively as the saddle conformer,[4] and resolves upon crystallization in a chiral conformation, as a racemic mixture of enantiomerically pure chiral crystals.[20] We discovered that the corresponding oxime **3** exists as a slowly equilibrating mixture of crown and saddle conformers that are separable,[21] and reported the kinetics and thermodynamics of their interconversion.[20] Furthermore, oxime **3** undergoes facile Beckman rearrangement to afford the macrocyclic lactam **4**[22] which is axially chiral and thus potentially resolvable into its atropisomers.

Current interest in synthetic macrocyclic receptors includes applications in chiral analysis and separation,[23] as well as in supramolecular chirality in self-assembled systems.[24] Ema has developed chiral selectors with multiple H-bonding sites in macrocyclic cavities[25-27] including the commercially available Chirabite-AR. While the macrocycle of CTV-lactam **4** contains a larger 10-membered ring, amide resonance[28] reduces flexibility through restricting rotation around the carbonyl C-N bond. We were interested if Chirabite-AR, which is designed for determining the enantiomeric purity of small molecules that can ideally be contained within its macrocycle, might be usable to determine the enantiomeric purity of larger supramolecular axially chiral scaffolds such as CTV-derived lactam **4**. Furthermore, we addressed the possibility that lactam **4** might be resolvable *via* attachment of a chiral auxiliary through N-functionalization of lactam **4**, given its ability[29] to undergo acylation in high yield to imide derivative **5**.

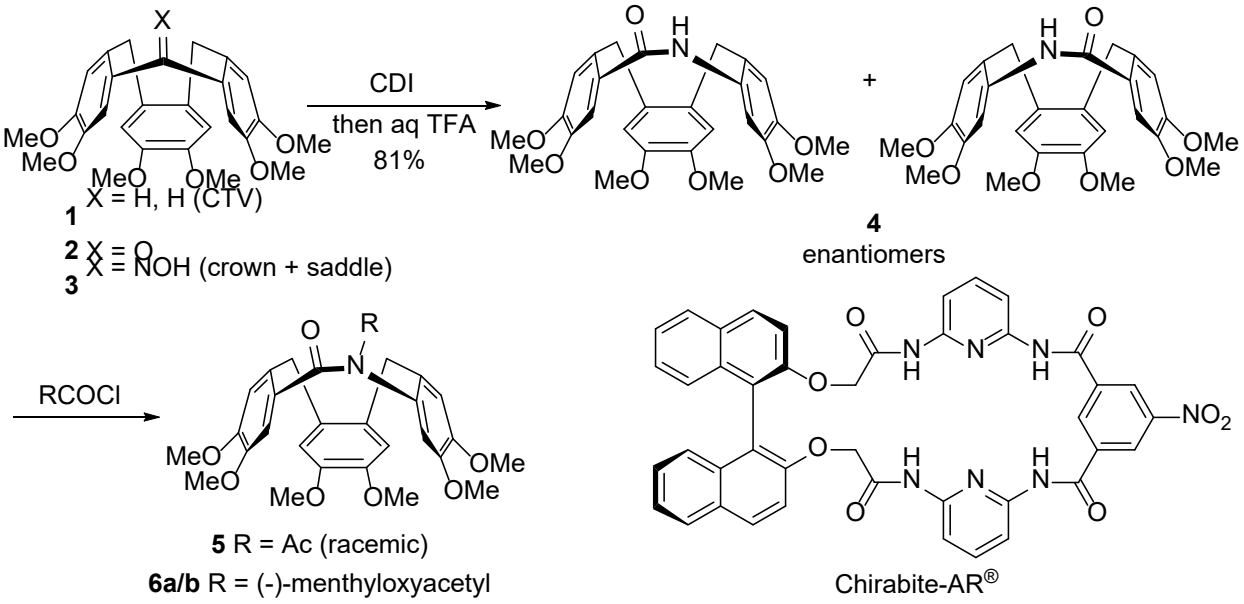

Figure 1. Synthesis *via* Beckmann rearrangement of the 10-membered CTV-derived lactam **4** enantiomers and conversion to N-acyl imide derivatives **5** and **6**, and the structure of Chirabite-AR

Results and Discussion

Toward the possible resolution of CTV-lactam **4**, we first required a method to assess enantiomeric purity. Attempts to observe the separate enantiomers of racemic lactam **4** using chiral HPLC methods were unsuccessful, so we turned to chiral shift reagents. The racemic macrocyclic lactam **4** was treated with increasing amounts of the macrocyclic chiral shift reagent Chirabite-AR in $CDCl_3$ solution and examined by ^1H NMR spectroscopy, demonstrating that the individual enantiomers could be baseline separated by NMR for optical purity determination. The ratio of Chirabite-AR to lactam **4** was examined by varying the amount of Chirabite-AR from 0.01 equivalents to 0.3 equivalents. Some separation of enantiomeric resonances in the proton NMR was already evident with only 0.01 equivalents of Chirabite-AR, and 0.05 equivalents were optimal to provide baseline separation of the proton resonances in the aromatic regions of the two enantiomers, while only 0.025 equivalents were required for baseline separation of some methoxy resonances. Additional quantities of Chirabite-AR were counterproductive, leading to large chemical shift displacements and compromising the ability to assign peaks. We surmise that Chirabite-AR is interacting most strongly with the lactam carbonyl oxygen, which bears a Mulliken charge of -0.489 au, the greatest point electron density on the molecule, and should be a strong H-bond acceptor for the H-bond donor moieties of Chirabite-AR.

There are several regions of the ^{1}H NMR spectra that provide peaks to track and integrate the CTV-lactam enantiomers in the presence of Chirabite-AR. Within the aromatic region (6.5-7.3 ppm) shown in Figure 2, there were six clearly resolved Ar-H peaks that were split into twelve separate resonances when 0.125 equivalents of Chirabite-AR were added. When 0.30 equivalents of Chirabite-AR were utilized, the enantiomeric lactam NH resonances in this region can also be differentiated. Furthermore, the aromatic Ar-H peak at 6.7 ppm was clearly resolved giving near-baseline separation using a very low Chirabite-AR loading (0.05 eq). In the methoxy region from 3.7 to 4.05 ppm, shown in Figure 3, signals of nearly all methoxy moieties from both enantiomeric lactams were split into separate peaks, especially when using 0.175-0.20 equivalents of Chirabite-AR. Importantly, the NMR resonances for Chirabite-AR itself did not overlap with any of the peaks for the CTV-lactam as most of the Chirabite-AR resonances appear beyond 7.27 ppm, a region which contains no peaks relating to CTV-lactam **4**.

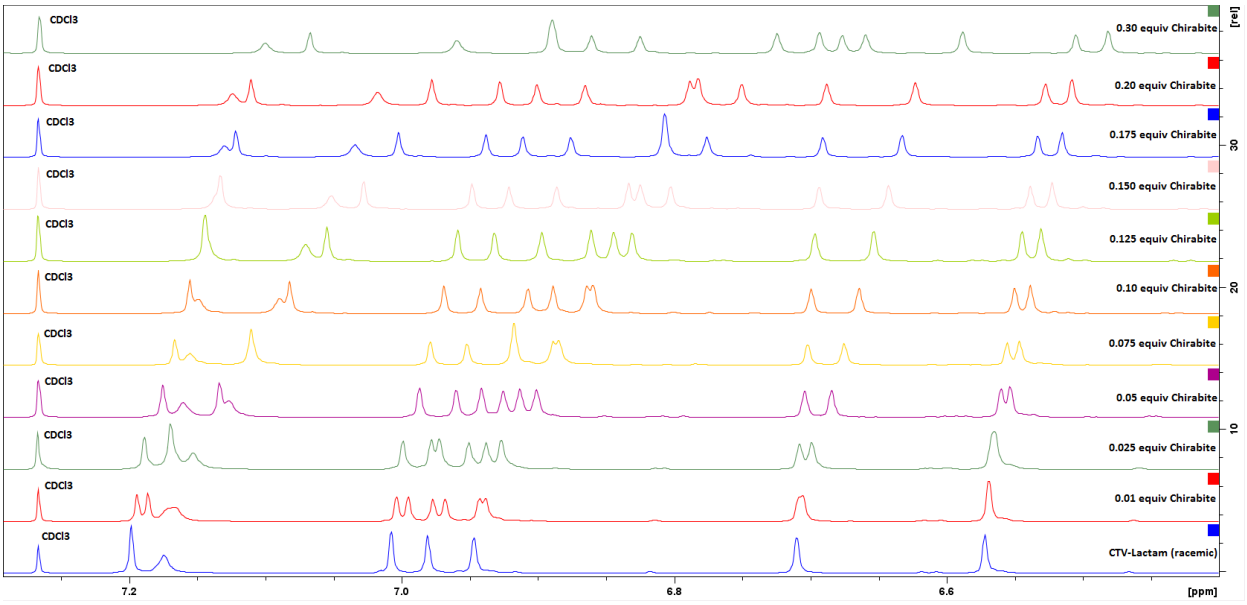

Figure 2. The aromatic region of the proton NMR spectra (400 MHz, $CDCl_3$) of CTV-lactam **4** with increasing quantities of Chirabite-AR (0.01 to 0.30 equivalents).

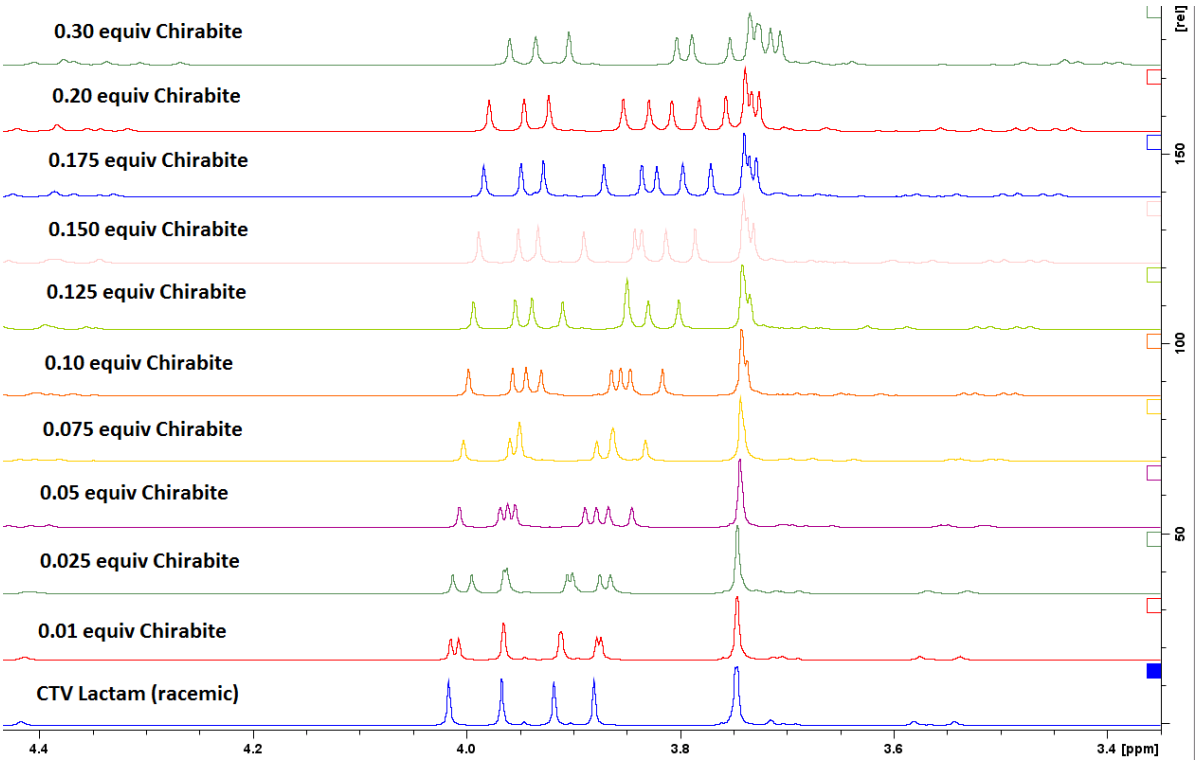

Figure 3. The methoxy-containing region of the proton NMR spectra (400 MHz, $CDCl_3$) of CTV-lactam **4** with increasing quantities of Chirabite-AR (0.01 to 0.30 equivalents).

Toward the possible resolution of CTV-lactam **4**, several different chiral auxiliaries were explored for reaction with the lactam N-H of **4**, including (1S)-(-)-camphanic chloride, (S)-(+)-α-methoxy-a-trifluoromethylphenylacetyl chloride, diacetyl-L-tartaric anhydride, (S)-(+)-alpha-methoxy-alpha-trifluoromethylphenylacetate, and ketopinic acid chloride, several of which did not provide N-acylated adducts under a number of conditions explored. However, reaction of (-)-menthyloxyacetic acid chloride was successful in providing diastereomeric imide adducts in good yield when using an excess of (-)-menthyloxyacetic acid chloride in pyridine at reflux,

providing an 86% yield of the desired imide **6** as an approximately 87:13 mixture of diastereomers based on ^{1}H NMR integration. After aqueous workup and filtration through a bed of alumina, crystallization from hexane/DCM afforded a mixture of diastereomers in an 87:13 ratio (Figure 4). Attempts to separate the diastereomers and to improve the diastereomeric purity by further recrystallization and/or achiral column chromatography techniques were unsuccessful. Recrystallization from DCM/hexane provided X-ray quality crystals but did not alter the diastereomeric ratio from 87:13, which was the same ratio obtained from ethyl acetate/heptane. Interconversion and equilibration of the diastereomers is not possible, since umbrella inversion of the bowl-shaped macrocycle would require the menthyloxyacetyl substituent to pass through the center of the bowl, which is not possible. The crystal structure obtained through X-ray crystallography of crystals from DCM/hexane (Figure 5) showed that the two diastereomers co-crystallize as a solid solution in a ratio of 83.2 ± 0.3% to 16.8 ± 0.3% based on electron density, with very similar ratios of diastereomers in the solid state and in solution. The absolute configuration of the two bowl moieties is inverted and the two sections are related by a non-crystallographic pseudo-mirror plane. As expected, the menthyloxyacetate units have identical absolute configurations, 1R,2S,5R, but are slightly shifted against each other (Fig. S1, S2). The structures obtained for both diasteromers are consistent with the molecular structures and absolute configurations expected.

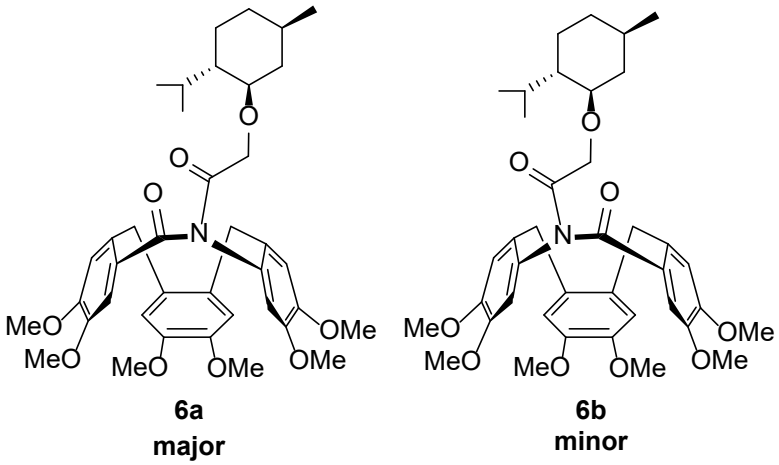

Figure 4. Structures of menthyloxyimide **6a** (major diastereomer) and **6b** (minor diastereomer)

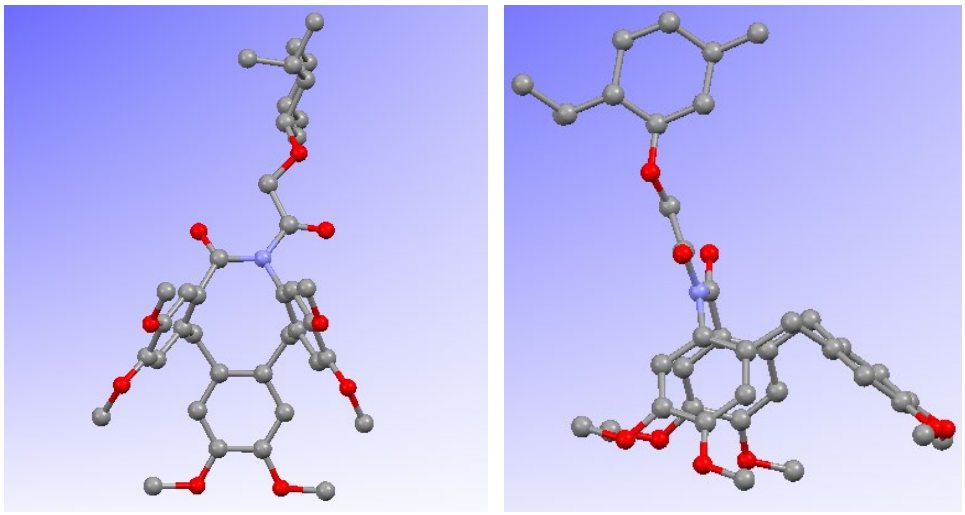

Figure 5. Two views of the X-ray crystal structure of major diastereomer **6a** (H atoms omitted).

Ortep plots and figures showing disorder of **6a** and **6b** are given in the SI (Fig. S1 – S3).

The type of disorder observed for **6** is not unprecedented. A similar behavior had been previously observed for the acetyl-substituted counterpart of **6**, N-acyl imide derivative **5**.[29] The latter had been crystallized as a racemic mixture, with molecules located on and bisected by a crystallographic mirror plane, thus inducing whole molecule disorder not too dissimilar from that

observed for **6**. The geometry and conformation of the CTV-imide section in **5** and **6** closely resemble each other. Both molecules have the bowl shaped appearance typical for CTV and its derivatives,[4, 6] and the CTV-imide sections are virtually superimposable (Figs S4), with only slight deviations for the outer substituents, mostly torsion angles of the methoxy groups. In menthyloxy-substituted lactam **6**, all methoxy groups are in plane with the benzene rings to which they are substituted, as is usual for sterically unencumbered polymethoxy benzene derivatives.[30] In N-acetyl lactam **5**, on the other hand, one of the methoxy substituents is twisted out of plane, to avoid an otherwise unfavorable close contact with the methyl group of a neighboring molecule in the crystal. The menthyloxyacetate chain in **6** has an all-trans extended conformation, and the menthyl group is aligned with its long axis roughly perpendicular to the plane of the N-acyl imide segment. The positions of the menthyl units in major **6a** and minor **6b** diastereomers are quite similar, with a slight shift induced by the different positions of the connecting oxygen atom in **6a** and **6b**. Intermolecular interactions and packing in N-acetyl lactam **5** and in menthyloxyacetyl lactam **6** are similar (Fig S1, S2). Packing interactions are dominated by intra- and intermolecular CH···O interactions, augmented by a small number of CH···π contacts, involving the aromatic C-H groups, the bridging methylene CH_2 units, the methoxy CH_3 groups, and, for **6**, the C-H, CH_2 and CH_3 moieties of the menthyl substituents. The positions of the menthyl groups in **6a** and **6b** are close enough to each other to not seriously affect packing interactions between neighboring molecules, and no additional disorder induced by the unequal disorder onto neighboring molecules is resolved. Molecules in N-acetyl lactam **5** as well as in N-menthyloxyacetyl lactam **6** can both be described to be arranged in stacked-cup arrays, with the acetyl or menthyl group of one molecule located in the cavity of the bowl of another, leading to columnar assemblies. The larger

size of the menthyl substituent in **6** extends the distance between the bowl segments within columns, from ca. 8.5 Å in **5** to 13.4 Å in **6**.

Toward the possible isolation of an enriched enantiomer of **4**, cleaving the chiral menthyloxyacetyl auxiliary of the 87:13 mix of diastereomers of **6a/b** was performed using aqueous LiOH in THF. Attempts to determine the rate of racemization (from ~87:13 to 50:50) of isolated lactam by optical rotation showed a rotation of 0° at the first time point reading, indicating rapid complete racemization within less than 15 minutes. This was confirmed by NMR methods using again Chirabite-AR as a chiral resolution aid. Hydrolysis of the chiral auxiliary was carried out on enriched CTV-menthyloxyacetic imide in aqueous THF using lithium hydroxide (3.5 eq) at < 5 °C for 15 minutes, then the reaction mixture was sampled, rapidly concentrated, redissolved in $CDCl_3$ containing Chirabite-AR (0.30 equiv), and analyzed by ^1H NMR. Examination of peaks of interest to monitor enantiomeric purity (Figure 6), specifically at 6.63/6.69 ppm and 6.51/6.53 ppm as indicated by the black circles correspond to the singlets in the racemic CTV lactam without Chirabite-AR as denoted in (A), and indicated a 1:1 ratio of enantiomers, thus complete racemization. The chemical shifts of the separated enantiomers in (A) are noted to correspond closely to the shifts observed for lactam **4** with 0.175 eq Chirabite-AR (C), rather than with 0.30 eq Chirabite-AR (D), presumably due to the excess hydroxide present in the reaction mixture that is competing with Chirabite and its interaction with lactam **4**. These results indicate that once the chiral auxiliary is cleaved, the bowl inversion is quite rapid furnishing lactam **4** as a racemate, with a barrier to interconversion of less than 21-25 kcal/mol, which was the barrier to interconversion determined for the crown and saddle conformers of CTV-oxime **3**.[20]

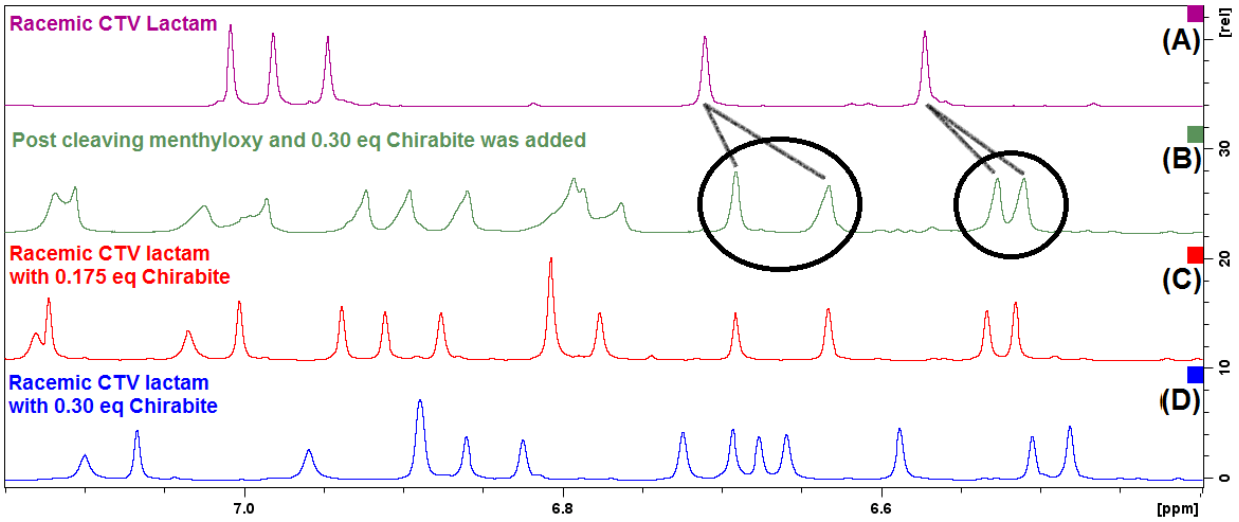

Figure 6. ^{1}H NMR spectra for (**A**) in purple, lactam **4** without Chirabite; (**B**) in green, the lactam **4** derived from basic cleavage of enriched **6a/b** with 0.30 eq Chirabite with excess hydroxide showing a 1:1 ratio of singlets indicating racemic lactam **4**; (**C**) lactam **4** in the presence of 0.175 eq Chirabite; and (**D**) in blue, racemic lactam **4** with 0.30 eq Chirabite.

Assessment of the relative energies of the crown and saddle conformers of lactam **4** were assessed through calculations on model structures **7a-c** lacking the six methoxy groups (Figure 7), since a saddle conformer must be an intermediate in inversion and racemization of the chiral crown conformer.[4] Density functional theory (DFT) calculations (M06 2X /6-31G*) on lactams **7a-c** were performed using Spartan '16 (Wavefunction, Inc., Irvine, CA). It was found that the saddle conformer **7b** is 7.1 kcal/mol higher in energy than the crown conformer **7a**, and the side-saddle **7c** is 8.6 kcal/mol higher in energy than the crown **7a**, consistent with the observation of only the crown conformer in the crystal structure of **5**. We reported earlier for the 9-membered ring CTV oxime **3** that the saddle conformer is 3.15 to 5.23 kcal/mol (13.2 to 21.9 kJ/mol) higher in energy than the more stable crown conformer.[20] Thus the saddle conformers for the model lactam **7** that were examined are higher in energy than for the smaller macrocycle CTV oxime **3**,

yet the transition state to the saddle conformer must be easily surmountable at room temperature to enable racemization of CTV lactam **4**.

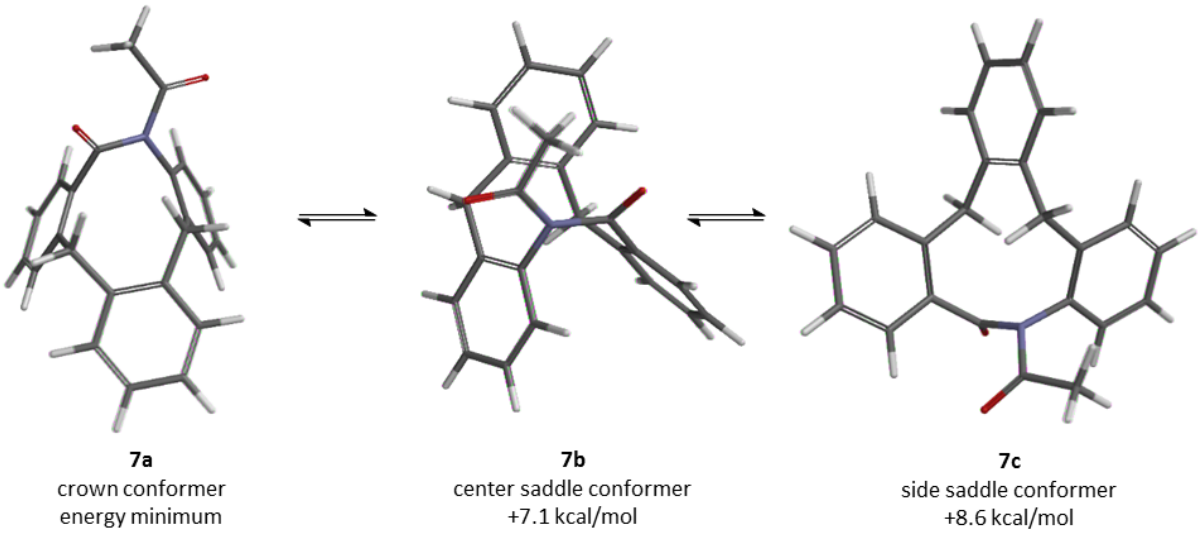

Figure 7: DFT energy minimized structures for lactam **7** crown and saddle conformers as a model for CTV-lactam **4**

In summary, we have demonstrated that Chirabite-AR can be used to differentiate the enantiomers of inherently axially chiral supramolecular scaffolds such as CTV-derived lactam **4**, and have succeeded in attaching (-)-menthyloxy acetic acid as a chiral auxiliary to lactam **4** and enriching the diastereomeric ratio through crystallization, as confirmed by NMR spectroscopy and X-ray crystallography. Hydrolytic cleavage of the chiral auxiliary, however, returned racemic lactam **4**, based on optical rotation and NMR analysis in the presence of Chirabite-AR.

Experimental Section

DFT Calculations

Calculations at the density functional level of theory were performed using Spartan ‘016 by Wavefunction, employing the M06 2X functional and the 6-31G* basis set according to a previously-described protocol.[31]

10,15-Dihydro-2,3,7,8,12,13-hexamethoxy-5H tribenzo[a,d,g]cyclononen-5-one (CTV-Monoketone) 2

The procedure was improved from the previously-reported synthesis.[21] A 5-liter glass reactor (3-necked), equipped with an overhead mechanical stirrer, J-Kem thermocouple, heating mantle, reflux condenser, and nitrogen inlet was charged in the following order with CTV **1** (76.22 g, 0.17 moles, 18 eq), ethyl acetate (2 L), activated manganese dioxide (264.7 g, 3.05 moles), ground potassium permanganate (241.1 g, 1.53 moles, 9 eq) and lastly ethyl acetate (0.29 L) as a rinse. The reaction was stirred at room temperature to ensure that there was no exotherm reaction. The mixture was then heated to reflux and stirred overnight. After 18 hours, TLC and HPLC analysis indicated that the reaction was complete. The reaction solution was colorless once solids settled indicating that all $KMnO_4$ had reacted. The reaction mixture was cooled to 50°C, filtered over a pad of Celite (70.6 g), and the Celite Cake was rinsed with ethyl acetate (3 x 500 mL) and DCM (2 x 500 mL). The filtrate was concentrated under reduced pressure at 40-50°C to give crude CTV-monoketone **(**61.91 g) as a pale yellow solid. The crude monoketone (51.00 g) was placed into a 250-mL glass reactor (2-necked), equipped with a large magnetic stir bar, J-Kem thermocouple, heating mantle, and reflux condenser. To the reactor was added acetonitrile (150 mL, HPLC grade). The mixture was heated to 70 °C and the slurry was stirred (250-300 rpm) at 70 °C for 18 hours. The slurry mixture was allowed to gradually cool to room temperature over 4 hours, then continued to stir at room temperature for approximately 3 hours. The slurry was filtered over a fitted funnel (medium porosity), the wetcake was washed with acetonitrile (60 mL), dried by suction, and further dried *in vacuo* at 60 °C overnight to give purified CTV monoketone **2** (32.54 g white solid, 65% yield). The mother liquor was partially

concentrated to remove about 75% of the solvent to provide a slurry. The slurry was filtered and the wetcake was washed with ethyl acetate/heptane (50/50, 10 mL) and dried to give a second crop (15.8 g, 31% yield, white solids) of purified CTV-monoketone **2**. The ^{1}H NMR data are in accordance with those reported in the literature.[20]

10,15-Dihydro-2,3,7,8,12,13-hexamethoxy-5H-tribenzo[a,d,g]cyclononen-5-oxime (CTV Oxime) 3, as a mixture of saddle and crown conformers

In a modification of the reported[21] procedure, to a 500-mL glass reactor (3-necked), equipped with a magnetic stir bar, reflux condenser, J-Kem thermocouple, and nitrogen inlet, was added CTV-monoketone (19.00 g), hydroxylamine hydrochloride (42.64 g), and pyridine (190 mL). The mixture was heated to reflux (110 °C) under a nitrogen atmosphere. After 16.5 hours, the reaction was deemed complete by TLC analysis (EtOAc/DCM, 20/80) and the reaction was allowed to cool. Concentration gave a crude residue to which was added USP purified water (250 mL) and the mixture was triturated at room temperature for 30 minutes. The slurry was filtered, and the wetcake was washed with USP purified water (2 x 50 mL), dried by suction, and further dried in vacuo at 50 °C overnight to provide a pure mixture of saddle and crown CTV-oximes as a white solid (17.63 g, 90%). Spectral data matched the reported literature.[21]

2,3,8,9,13,14-Hexamethoxy-11,16-dihydrotribenzo[*b*,*e*,*h*]azecin-6(5*H*)-one (CTV-lactam) 4

The previously-reported procedure[22] was modified to avoid thionyl chloride, and with good yield from a mixture of crown and saddle conformers. To a 1-liter 3-necked flask equipped with an overhead mechanical stirrer, nitrogen inlet, and J-Kem thermocouple was added CTV-oxime **2** (10.00 g, 20.85 mmol) and acetonitrile (200 mL). The mixture was stirred at ambient

temperature for 20 minutes, then carbonyldiimidazole (7.18 g, 44.28 mmol) was added. Additional acetonitrile (20 mL) was used to rinse contents off the reactor flask walls. After 1 h at rt, TLC analysis (EtOAc/DCM, 80/20) revealed that the oxime starting material was completely consumed and a new spot appeared (oxime O-acyl imidazole intermediate, Rf = 0.10). The reaction mixture was cooled to < 5 °C and de-ionized water (50 mL) was added followed by drop-wise addition of trifluoroacetic acid (TFA, 50 mL) over 20 minutes using a dropping funnel. After 20 h at room temperature, TLC analysis (EtOAc/DCM, 80/20) showed complete conversion of the acyl imidazole intermediate to CTV-lactam (Rf = 0.18). To the reaction mixture was added drop-wise de-ionized water (600 mL) over 30 minutes to provide an opaque pink slurry which was allowed to stir for 20 hours and then filtered. The wetcake was washed with water (50 mL), suction dried, and further dried in vacuo at 50 °C to provide CTV-lactam **4** (8.13 g, 81.3%). HPLC purity (220 nm): 95.2%. Spectra were identical to reported literature.[22]

5-[1,2,3,4-Tetrahydro-1-[[[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy]acetyl]-]acetyl-11,16-dihydro-2,3,8,9,13,14-hexamethoxy-tribenz[b,e,h]azecin-6(5H)-one (menthyloxyacetyl CTV-derived lactam) 6

To a solution of CTV lactam **4** (175 mg, 0.36 mmol) in pyridine (1.8 mL) was added (-)-menthyloxyacetic acid chloride (913 mg, 3.92 mmol) at room temperature and the solution was heated to reflux for 2 h. The mixture was then concentrated under reduced pressure, and the resulting residue was diluted in dichloromethane and poured onto ice. The layers were separated, and the aqueous layer was extracted two additional times with dichloromethane. The combined organic layers were washed successively with 1N hydrochloric acid (2x), saturated aqueous sodium bicarbonate, distilled water, brine, dried over sodium sulfate and concentrated to afford

the crude product as a solid (999 mg). The mixture was passed through neutral alumina (17 g) eluting with ethyl acetate/dichloromethane (20/80) to remove excess menthyloxyacetic acid, followed by elution of the cyclotriveratrylene lactam starting material that was recovered (40 mg, 25% recovered). The remaining material (477 mg) eluted from the alumina was chromatographed on silica gel (24 g) eluting with a gradient from pure dichloromethane to ethyl acetate/dichloromethane (50/50) to afford the desired imide **6** (167 mg, 69%) as a pale yellow solid. The product was crystallized using DCM and hexane yielding an 87:13 mixture of diastereomers: mp 200-203 °C; $[\alpha]_D$ = -218° (c = 2.4 g/100 mL); IR 2998.6, 2953.5, 2927.6, 2868.3, 1723.0, 1696.3, 1608.0 , 1517.9, 1463.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (bs, 2H), 6.71 (bs, 0.12H), 6.69 (bs, 0.11H), 6.68 (bs, 0.11H), 6.67 (bs, 0.13H), 6.60 (bs, 0.22H), 6.59-6.52 (complex, 3.2H), 6.47 (bs, 0.13H), 6.46 (bs, 0.13H), 6.39 (bs, 0.45H), 6.38 (bs, 0.55H), 5.07 (bs, 0.19H), 5.03 (bs, 0.26H), 4.98-4.84 (m, 0.87H), 4.80 (bs, 0.27H), 4.76 (0.20H), 4.47 (bs, 0.03H), 4.42 (bs, 0.04H), 4.37 (bs, 0.04H), 4.32 (bs, 0.31H), 4.29 (bs, 0.28H), 4.26 (bs, 0.24H), 4.23 (0.26H), 4.16 (bs, 0.04H), 4.13-4.11 (complex, 0.27H), 4.10-4.05 (complex, 0.45H), 4.04-4.02 (complex, 0.52H), 4.01-3.97 (complex, 0.43H), 3.95-3.91 (complex, 6.2H), 3.90 (bd, 1H), 3.87 (bd, 1H), 3.83 (bs, 1H), 3.81 (bs, 0.43H), 3.80-3.78 (complex, 1.2H), 3.74 (bd, 3.2H), 3.73 (bs, 3.2H), 3.71-3.60 (complex, 6.4H), 3.62-3.58 (complex, 1H), 3.55 (bd, 1H), 3.49 (bs, 0.30H), 3.45 (bd, 0.54H), 3.42 (bs, 0.28H), 3.33-3.27 (td, 1.1H), 3.20-3.07 (complex, 0.32H), 2.41-2.24 (complex, 1.35H), 2.25-2.19 (complex, 1.23H), 2.12-2.00 (complex, 0.55H), 1.68-1.58 (complex, 5.4H), 1.46-1.18 (complex, 8H), 1.08-0.71 (complex, 22.2H). ^{13}C-NMR (75 MHz, CDCl3): δ 16.1, 16.2, 16.3, 20.9, 21.0, 21.1, 21.9, 22.1, 22.3, 23.2, 23.3, 25.4, 25.5, 25.6, 29.6, 31.5, 33.8, 33.9, 34.2, 34.4, 34.5, 35.7, 35.8, 40.0, 40.2, 48.2, 48.3, 55.5, 55.6, 55.7, 55.8, 55.9, 56.0, 56.1, 56.2, 70.9, 71.2, 76.6, 77.0, 77.2, 77.4, 80.1, 80.5, 80.6, 109.2, 109.4, 111.2,

111.3, 111.5, 111.6, 111.7, 111.9, 112.1, 112.2, 112.5, 113.6, 114.2, 114.3, 115.4, 127.5, 128.1, 128.8, 129.9, 130.0, 130.5, 130.8, 131.0, 131.1, 131.3, 146.8, 147.4, 147.7, 147.8, 148.3, 148.8, 149.6, 173.4, 174.4. MS: Cald for $C_{39}H_{50}NO_9$ $[M+H]^+$: m/z 676.3, found 676.3.

Hydrolysis of CTV Lactam menthyloxy imide 6 and the use of Optical Rotation to determine resolution of CTV-Lactam 4

To the 87:13 mixture of menthyloxy CTV lactam diastereomers **6** in 3:1 THF/water (0.75 mL) at 0 °C was added lithium hydroxide (3 mg, 0.91 mmol) and the reaction was stirred for 15 minutes. The mixture was extracted three times with dichloromethane. The combined organic layers were washed once each with distilled water and brine, filtered over sodium sulfate, and concentrated to afford a solid (24 mg), which was filtered through alumina eluting with 2/8 ethyl acetate/dichloromethane to isolate the cleaved CTV lactam **4** (17 mg): $[\alpha]^{20}_D = 0°$ (c=3.4, DCM).

Hydrolysis of menthyloxy CTV lactam diastereomers 6 and the use of Chirabite-AR to determine enantiomeric purity of CTV-Lactam 4

The 87:13 mixture of menthyloxy CTV lactam diastereomers **6** (13.2 mg, 0.019 mmol) was dissolved in THF (0.75 mL) and then cooled to 0-5 °C using an ice-water bath. A solution of 0.24 M lithium hydroxide monohydrate (0.27 mL, 0.068 mmol, 3.5 eq) was added. The mixture was stirred at 0-5 °C for 15 minutes, then the reaction mixture was transferred to a 20 mL scintillation vial and concentrated under high vacuum for 5 minutes. The residue was dissolved in $CDCl_3$ (0.75 mL) followed by the addition of 0.10 M Chirabite-AR solution in $CDCl_3$ (60 µL, 0.006 mmol, 0.3 eq) and this mixture was placed in an NMR tube and an NMR was obtained

within 2 min. ^{1}H NMR analysis revealed that the mixture was racemic based on 1:1 integration of the two peaks at 6.51 and 6.53 ppm and by the 1:1 peak height.

Chirabite-AR Study with Racemic CTV-Lactam 4

To a solution of the racemic CTV-lactam **4** (20 mg, 0.042 mmol) in $CDCl_3$ (1.0 mL) in a 400 MHz tube was added a solution of 0.10 M Chirabite-AR in $CDCl_3$ prepared by mixing Chirabite-AR (38 mg, 0.05 mmol) in $CDCl_3$ (0.5 mL). The equivalents of Chirabite-AR that were evaluated were 0.01, 0.025, 0.050, 0.075, 0.10, 0.125, 0.150, 0.175, 0.20, and 0.30 eq. After addition of the specified amount of Chirabite-AR solution into the NMR sample containing racemic CTV-lactam, the sample was placed into the NMR spectrometer, analyzed, and then the next charge of Chirabite-AR solution was added followed by NMR analysis in sequential order.

Supporting Information

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/???. CCDC-1844285 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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