Stereoselective Synthesis of Hydrindane and Hydroazulene Derivatives by Transannular Cyclization of Nine- and Ten-Membered carbocycles

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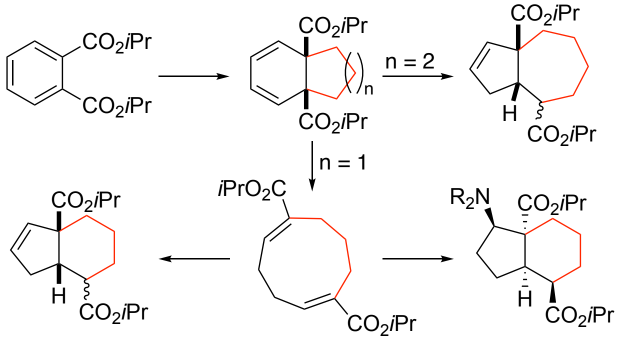
Supporting Information Placeholder



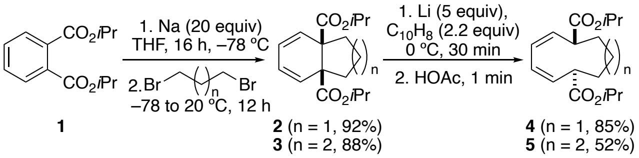
ABSTRACT: Treatment of *cis*-fused bicyclic diene dicarboxylates with Li/naphthalene triggers a tandem ring-opening and transannular cyclization process that stereoselectively yields hydroazulenes and hydrindanes derivatives. Cyclononadienyl diesters, which can be isolated after the ring opening step by judicious choice of the reaction conditions, undergo a tandem conjugate addition/intramolecular Michael addition upon treatment with chiral lithium amides, to give bicyclic β-amino esters in a process where 4 contiguous stereocenters are formed with high diastereocontrol. A concise route towards the highly enantioenriched AEF ring core of the aconitine-type alkaloids has been developed as an application of this methodology. The starting *cis*-fused bicyclic dicarboxylates are easily prepared in one step by reductive alkylation of diisopropyl phthalate (Na/THF, followed by the appropriate *bis*-electrophiles).

INTRODUCTION

Transannular reactions of medium or large sized-ring systems constitute a useful synthetic tool for building bi- and polycyclic frameworks present in many natural products.[1,2] Different types of transannular approaches have been developed over the years, the most popular being based on Diels-Alder cycloadditions, Michael-type additions, aldol reactions, and radical cyclizations.[3] The main difficulty for the application of this type of strategies is often the synthesis of the required, suitably functionalized, starting medium or large-ring cyclic substrates.[4,5]

Our group has described a two-step preparation of 9 and 10-membered cyclic unsaturated diesters (**4** and **5**) from phthalates (Scheme 1), via a Li-mediated ring-opening reaction of unsaturated fused-bicyclic diesters **2** and **3** obtained from the reductive-alkylation of phthalates (Scheme 1).[6] The functionality present in these medium-sized carbocycles makes them ideally suited for the exploration of Dieckmann condensation or Michael addition-based transannular cyclizations. Herein we report an efficient, stereoselective synthetic route to hydroazulene and hydrindane derivatives based on this concept. Thus, treatment of cyclonona- or cyclodecadiene diesters **4** and **5** with appropriate bases or nucleophiles provided for the efficient construction of hydrindane and hydroazulenes with up to four new contiguous stereocenters with excellent stereocontrol.

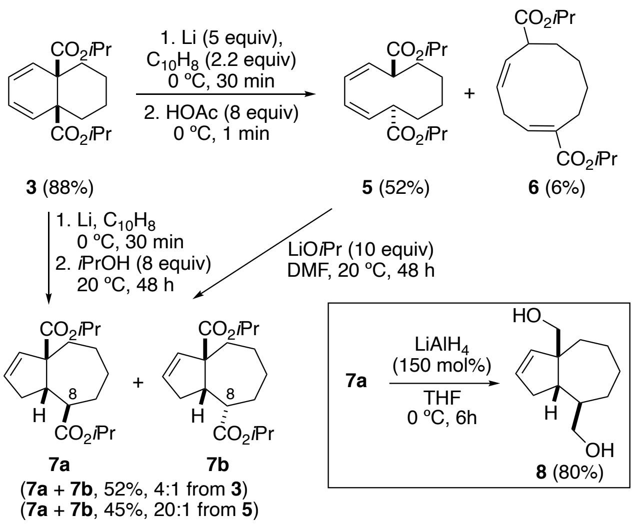
SCHEME 1. Synthesis of 9- and 10-membered rings from diisopropyl phthalate[6]



RESULTS AND DISCUSSION

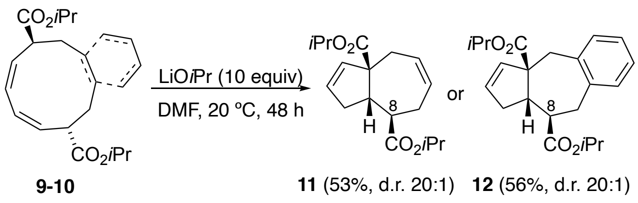
As previously described by our group, the reductive alkylation of diisopropyl phthalate (**1**) with sodium in THF and 1,4-dibromobutane afforded *cis*-bicyclo[4.4.0]decane **3** (n = 2) in 88% yield (Scheme 1). Ring-opening[6] of the 6,6-fused bicycle **3** with Li/naphthalene in THF at 0 ºC for 30 min, followed by kinetic protonation through the least hindered side of the intermediate *bis*-enolate with HOAc, afforded cyclodecadiene **5** in 52% yield, along with a small amount of its monoconjugated isomer **6** (6%) (Scheme 2). The main ring-opened product **5** derives from the protonation at the α-position of both enolates of the ring-opening intermediate. However, when we added *i*PrOH to the reaction at 20 ºC for 48 h (in an attempt to obtain the corresponding thermodynamic ring-opened product, which would have both C-C double bonds conjugated with the ester moieties), we isolated a recyclized hydroazulene product **7** instead, through the formation of sodium isopropoxide which catalyzed a proton abstraction and Michael addition of the resulting enolate, in 52% yield (as a 4:1 mixture of epimers at carbon 8, **7a** and **7b**, Scheme 2). Clearly, hydroazulenes **7a**,**b** had formed from **3** by a tandem reductive ring-opening/transannular Michael addition. We tried to improve the stereoselectivity of this transformation by modifying the quenching conditions and the reaction solvent, to no avail. However, when cyclodecadiene **5** was first isolated and then treated with LiO*i*Pr in DMF at 20 ºC for 48 h, hydroazulene **7** was obtained in 45% yield as an improved 20:1 mixture of epimers. To confirm the structure of **7**, the major diastereoisomer **7a** was isolated and reduced with LiAlH$_4$ at 0 ºC to give the corresponding crystalline diol **8** in 80% yield. The structure of diol **8**, and therefore the relative configuration of the newly created stereocenters of diester **7a**, was established as a *cis*-fused hydroazulene by X-ray crystallographic analysis.

SCHEME 2. Synthesis of hydroazulene 7



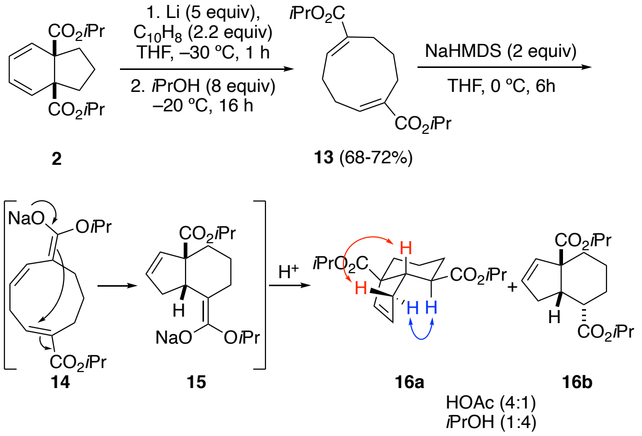
Similarly, transannular cyclizations of 10-membered rings diesters bearing an additional double bond (**9**) or a phenyl group (**10**) took place stereoselectively as well, to give the corresponding hydroazulenes **11** or **12** in 53% and 56% yield, respectively, as 20:1 mixtures of epimers at carbon 8 (Scheme 3).

SCHEME 3. Transannular ring closure of substituted 10-membered diesters



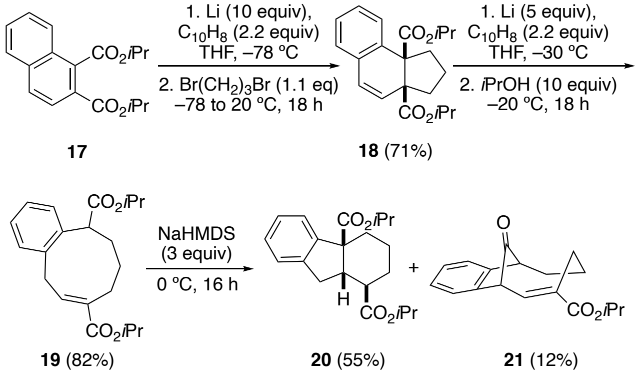
Next, we studied the transannular cyclization of the homologous 9-membered carbocyclic diesters. Fully conjugated cyclonona-1,5-diene diester **13** was obtained in 68-72% yield by ring-opening of [4.3.0] bicycle **2** with Li/naphthalene, followed by addition of *i*PrOH at –20 ºC for 12 h (Scheme 4).[6] In contrast to the behavior of its 10-membered ring counterpart, we did not observe products arising from an in situ transannular cyclization in this case. Cyclononadiene diester **13** showed a lower tendency to give a transannular cyclization than its higher homologue upon treatment with LiO*i*Pr/THF, and long reaction times were required to obtain the desired bicyclo[4.3.0]nonane **16** in reasonable yields (up to 6 days of stirring at rt to achieve a 52% yield of the desired product). Thus, we decided to explore the cyclization of **13** using stronger non-nucleophilic bases, such as NaHMDS, to accelerate the formation of the required intermediate enolate **14**. Under these conditions, monoenolate formation and subsequent transannular Michael condensation proceeded rapidly affording, after aqueous work-up, a 1:1 mixture of two cyclized hydrindanes, **16a**:**16b** (Scheme 4). Being aware that enolate **15** should be the final reaction intermediate after cyclization, we decided to investigate the effect of different protonating agents on the stereoselectivity of the formation of the third stereocenter formed in the reaction. Thus, when we added HOAc to the reaction, a mixture of **16a**:**16b** in a 4:1 ratio was obtained. However, when *i*PrOH was added instead of HOAc, a 1:4 mixture of **16a**:**16b** was formed. The relative configuration of the stereocenters in **16a** and **16b** was established by NMR. The major product obtained from the reaction quenched with HOAc shows a vicinal coupling constant of 10 Hz for the H adjacent to the ester group with the H of the ring juncture ($^{3}J_{ax\text{-}ax}$= 10 Hz) indicative of axial-axial disposition.[7] Accordingly, structure **16a** has been assigned to this product. Moreover, NOE effects are consistent with this structure (arrows in Scheme 4 show hydrogen which showed strong NOE effects upon irradiation).[8]

SCHEME 4. Transannular Michael cyclizations to give hydrindanes 16



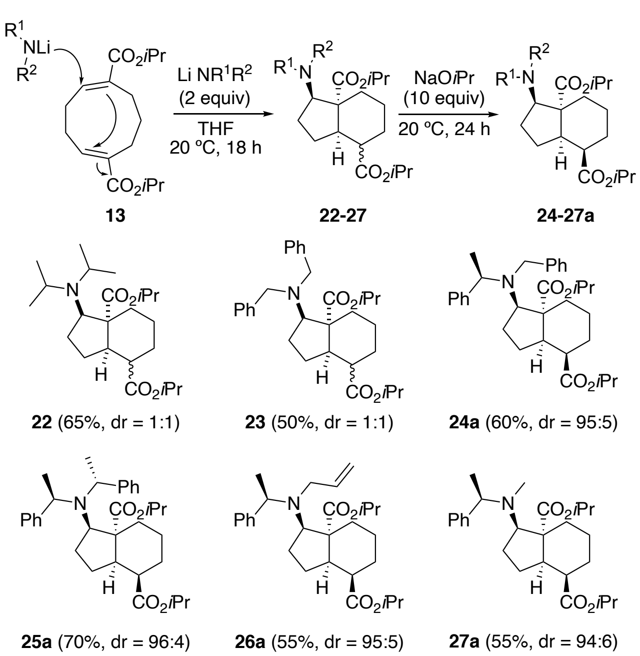
To study the transannular cyclizations on non-symmetric substrates we prepared the phenyl-fused 9-membered ring substrate **19** (Scheme 5). Reductive alkylation of diisopropyl naphthalen-1,2-dicarboxylate (**17**) with lithium/naphthalene and 1,3-dibromopropane afforded tricycle **18** in 71% yield. Ring-opening of **13** with Li/naphthalene at –78 ºC, followed by addition of *i*PrOH and stirring at –20 ºC for 16 h, led to the desired **19** in 82% yield. Cyclononane diester **19** has two different relatively acidic positions, the deprotonation of which would lead to different reaction products. In the event, proton abstraction from the α-carbon to the ester group with NaHMDS followed by conjugate addition of the intermediate enolate to the unsaturated ester was favored since tricycle **20** (55% yield) was the major isolated product. A minor product, bridged ketone **21**, derived from a Dieckmann condensation after deprotonation had taken place at the benzylic/allylic carbon, was also isolated (12% yield).

SCHEME 5. Transannular ring closure of a non-symmetrically substituted substrate



While studying the scope of the bases that can be used in the deprotonative transannular cyclization of 9-membered ring diesters, we made the perhaps not surprising observation that LDA preferentially adds in a conjugate fashion[9] to the unsaturated ester moiety of **13** instead of abstracting a proton (Scheme 6). The product of this amide Michael addition is an enolate that can undergo a further transannular Michael addition to afford bicyclic amine **22**, which in the event could be isolated in 65% yield, as a 1:1 mixture of diastereomers. At this point we turned our attention towards further exploring this transannular cyclization through a double conjugate addition started by lithium amides. Thus, when we used lithium dibenzylamide as the nucleophile, the expected cascade double Michael addition was observed and dibenzylaminohydrindane **23** was isolated in 50% yield (1:1 d.r.).

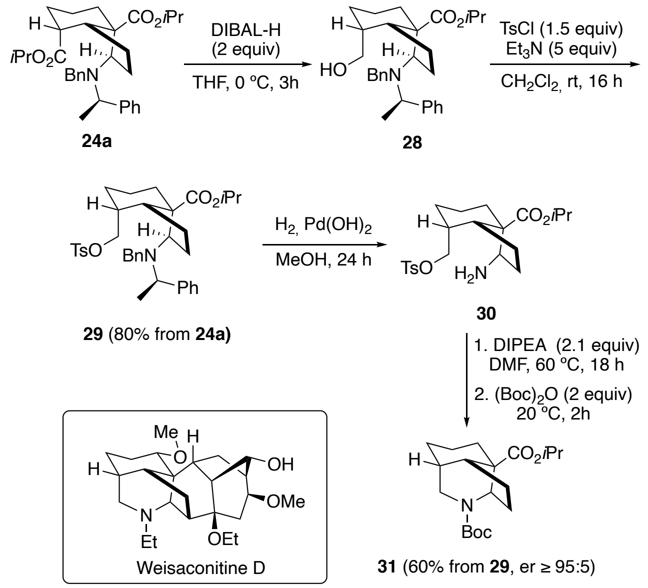
SCHEME 6. Stereoselective tandem conjugated addition of lithium amides/intramolecular Michael addition



Chiral lithium amides have been successfully used as nucleophiles in conjugate addition reactions for the asymmetric synthesis of β-amino acid derivatives.[10] Consequently, we explored the conjugate addition of a series of chiral lithium amides to cyclononadiene diester **13** at room temperature.[11] A smooth formation of bicyclic β-amino esters **24**-**27** in moderate to good yields (as a 1:1 mixtures of diastereomers) was observed (Scheme 6). Analogously to the case of hydroazulene **16**, the two diastereomers obtained were thought to be epimers derived from the protonation of the final intermediate enolate. This idea was confirmed because it was possible to separate the two diastereomers of amine **25** and to crystallize each one of them separately. X-ray crystallography showed that both compounds only differ in the configuration of the tertiary carbon attached to an ester group, which implies that three of the four newly created stereocenters have been generated with complete stereocontrol. A work-up modification consisting of adding NaO*i*Pr/*i*PrOH to the reaction and stirring at 20 ºC for 24 h, allowed the control of the stereochemical course of the protonation of the enolate responsible of generating the fourth stereocenter. This treatment allowed us to improve the diastereomeric ratios of the aminohydrindanes from 1:1 to approx. 95:5 (Scheme 6). The whole sequence thus generates four contiguous stereocenters in a highly stereoselective fashion.

Hydrindamines **24a**-**27a** obtained from the tandem conjugate addition of chiral amines/transannular Michael addition constitute a framework found in many relevant bioactive compounds. As an application of our methodology and to quantify the degree of stereoinduction coming from the chiral lithium amide, we explored the use of this highly functionalized framework bearing four contiguous stereocenters as an intermediate towards the synthesis of the A-E-F ring system of aconitine type alkaloids (Scheme 7).[12-13] To this end, we chose to start from amino diester **24a**.

SCHEME 7. Synthesis of highly enantioenriched AEF core system of aconitine-type alkaloids



Reduction of the less hindered carboxylate group of **24a** with DIBAL-H in THF at 0 ºC, efficiently led to primary alcohol **28** without affecting the ester attached to the quaternary carbon. Subsequent treatment of **28** with tosyl chloride and triethylamine afforded tosylate **29** in 80% combined yield from the initial ester **24a**. Removal of the chiral amino protecting groups of **29** was effectively achieved by catalytic hydrogenolysis ($Pd(OH)_2/C$, 10 atm of H_2) to give amine **30** quantitatively, which upon heating in the presence of base (iPr$_2$NEt) in DMF smoothly cyclized to afford a tricyclic amine, which was treated with di-*t*-butyldicarbonate to provide the Boc-protected tricycle **31** (60% yield from **29**). The enantiomeric purity of **31** was determined by chiral HPLC to be 95:5 er. Recrystallization from hexane afforded suitable crystals for X-ray structural determination. The structure of tricycle **31** was confirmed by single-crystal X-ray analysis.

In summary, we have developed a base-catalyzed stereoselective transannular Michael addition of cyclodecadiene and cyclononadiene diesters to give bicyclic[5.3.0]decanes and bicyclic[4.3.0]nonanes, respectively, and in just 2 or 3 steps starting from diisopropyl phthalate. When the transannular cyclization was initiated by the conjugated addition of a chiral lithium amide to cyclononadiene diester **13**, amino hydrindanes containing four contiguous stereocenters are created with high diastereoselectivity. As an application of this methodology, we have synthesized the tricyclic core of a family of aconitine alkaloids in 6 stages from commercial diisopropyl phthalate with a 15% overall yield and in a highly enantioenriched form (95:5 er).

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed in flame- or oven-dried (120 ºC) glassware under an atmosphere of argon. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. High reaction temperatures were maintained using DrySyn® multi-position heating blocks. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use; methylene chloride (CH_2Cl_2) and *N*,*N*-dimethylformamide (DMF) were distilled from CaH_2, and isopropanol (iPrOH) from CaO and Mg/iodine.[14] Thin layer chromatography (TLC) was performed on pre-coated silica gel GF-254 Merck plates, and visualized by UV light or staining with 10% ethanolic solution of phosphomolybdic acid followed by heating. For column chromatography, silica gel 60 Å (40-60 mm) from Acros Organics was used. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500MHz/125MHz on AMX-500 MHz spectrometer and at 300MHz/75MHz on Varian Mercury 300 at 300 K unless otherwise noted. Chemical shifts are reported in parts per million (ppm) with the residual chloroform solvent peak (δ 7.26) as an internal standard. Chemical shifts for ^{13}C NMR are reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) or $C_2D_2Cl_4$ (δ 73.78 ppm) with complete proton decoupling. Mnova software was used for data processing routines. Infrared (IR) spectra were recorded on a BRUKER FT-IR IFS-66V or Agilent Technologies Cary 630 FTIR spectrophotometers. High-resolution mass spectra (HRMS) were acquired on a Bruker Microtof mass spectrometer or a Q-TRAP mass spectrometer. Optical rotations were measured on Jasco P-2000. Melting points were recorded on a Büchi Melting Point B-540. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC), DAICEL CHIRALPAK® IE-3, in comparison with racemic sample. Compounds **3**-**6**, **9**, **10** and **13** were prepared as described previously in the literature.[6]

Diisopropyl cis-2,3-dihydro-1H-indene-3a,7a-dicarboxylate (2). Modified procedure for gram-scale reactions (80 mmol scale reaction): A suspension of sodium (36.8 g, 1.6 mol, 20 equiv) in THF (300 mL) at –50 ºC was treated with a solution of phthalate **1** (20 g, 80 mmol, 1 equiv) in THF (50 mL), and the reaction mixture was stirred for 24 h. The resulting solution was transferred via cannula to a –50 ºC flask, washed with THF (50 mL), and 1,3-dibromopropane (9 mL, 88 mmol, 1.1 equiv) was added. The reaction mixture was allowed to warm to rt and stirred for 24 h. The reaction was quenched with pH 7 phosphate buffer (50 mL) and then partitioned between CH_2Cl_2 (100 mL) and pH 7 phosphate buffer (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried and concentrated in vacuo. Purification by flash column chromatography (EtOAc/Hexane, 1:15) afforded **2** as a colorless oil (18 g, 78%). Yields of 92% were obtained with up to 8 mmol scale reactions. Spectral data are identical to those previously reported.[6, 15]

Preparation of hexahydroazulene 7 from bicycle 3. A suspension of small pieces of lithium (17 mg, 2.45 mmol, 5 equiv) and naphthalene (140 mg, 1.09 mmol, 2.2 equiv) in THF (3 mL) was sonicated for 30 minutes at rt. The resulting dark purple solution was cooled to 0 ºC and treated with a solution of bicycle **3** (150 mg, 0.49 mmol, 1 equiv) in THF (2 mL). After being stirred for 30 minutes, iPrOH (0.30 mL, 3.92 mmol, 8 equiv) was added, and the resulting mixture was stirred for 48 h at rt. Then, pH 7 phosphate buffer (8 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and phosphate buffer of pH 7 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried and concentrated *in vacuo*. The crude product was obtained as a 4:1 diastereomeric mixture and was purified by flash column chromatography (EtOAc/Hexane, 1:15) to afford **7** (78 mg, 52% yield) as a colorless oil. Main diastereoisomer **7a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (dt, *J* = 5.2, 2.4 Hz, 1H), 5.47 (m, 1H), 5.00 (dhept, *J* = 12.5, 6.1 Hz, 2H), 3.45 (ddd, *J* = 11.6, 9.2, 6.6 Hz, 1H), 2.61 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.31 (t, *J* = 10.5 Hz, 1H), 2.06 (m, 2H), 1.75 (m, 4H), 1.43 (t, *J* = 13.5 Hz, 1H), 1.22 (m, 14H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 175.8, 175.5, 135.6, 129.4, 68.0, 67.3, 64.0, 51.7, 43.2, 39.8, 34.2, 31.4, 30.1, 26.1, 21.9, 21.9, 21.9, 21.8. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{28}O_4Na$ 331.1880, found: 331.1879.

Preparation of 7 from cyclodecadiene 5. A suspension of lithium hydride (28 mg, 3.5 mmol, 10 equiv) and iPrOH (320 μL, 4.2 mmol, 12 equiv) in DMF (2 mL) was stirred at 0 ºC for 1 h, and a solution of cyclodecadiene **5** (108 mg, 0.35 mmol, 1 equiv) in DMF (1.5 mL) was added. The reaction mixture was stirred for 48 h at room temperature. Then, pH 7 phosphate buffer (5 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and phosphate buffer of pH 7 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed repeatedly with brine to remove DMF, dried and concentrated *in vacuo*. The crude product was obtained as a 20:1 diastereomeric mixture and purified by flash column chromatography (EtOAc/Hexane, 1:15) to afford **7** (48.6 mg, 45% yield) as a colorless oil.

***cis* (4,5,6,7,8,8a-hexahydroazulene-3a,8(1*H*)-diyl)dimethanol (8).** A 0 ºC suspension of $LiAlH_4$ (26 mg, 0.70 mmol, 150 mol%) in THF (0.6 mL) was treated with a solution of **7a** (150 mg, 0.46 mmol, 1 equiv) in THF (1 mL). The reaction mixture was stirred for 6 h at 0 ºC. EtOAc (0.5 mL) was then slowly added, followed by sat Na_2CO_3 (1 mL), $CHCl_3$ (2 mL), KH_2PO_4 and Na_2SO_4. The resulting mixture was stirred for 1 h, filtered over celite and washed with $CHCl_3$. The combined, clear filtrate and washings were evaporated to give a white solid. Recrystallization from CH_2Cl_2:Hexane afforded **8** as white crystals (78 mg, 80% yield). M.p. 117-119 ºC (CH_2Cl_2:Hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dt, *J* = 5.8, 2.3 Hz, 1H), 5.30 (dt, *J* = 5.8, 2.2 Hz, 1H), 3.71 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.63 (d, *J* = 10.4 Hz, 1H), 3.55 (dd, *J* = 10.7, 5.7 Hz, 1H), 3.42 (dd, *J* = 10.7, 7.2 Hz, 1H), 2.64 (ddt, *J* = 16.4, 8.8, 2.2 Hz, 1H), 2.20 (ddt, *J* = 16.4, 7.5, 2.2 Hz, 1H), 2.14 (m, 1H), 1.86 (dd, *J* = 11.8, 7.3 Hz, 1H), 1.78 (m, 1H), 1.72-1.31 (m, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 137.5, 130.3, 70.5, 67.4, 57.1, 47.7, 42.8, 40.6, 33.3, 30.2, 29.7, 24.3. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{20}O_2Na$ 219.1356, found 219.1345.

Preparation of compound 11 from cyclodecatriene 9. A suspension of lithium hydride (26 mg, 3.3 mmol, 10 equiv) and iPrOH (303 μL, 3.96 mmol, 12 equiv) in DMF (2 mL) was stirred at 0 ºC for 1 h, and a solution of cyclodecatriene **9**[6] (100 mg, 0.33 mmol, 1 equiv) in DMF (1.3 mL) was added. The reaction mixture was stirred for 48 h at room temperature. Then, pH 7 phosphate buffer (5 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and phosphate buffer of pH 7 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were repeatedly washed with brine, dried, and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/Hexane, 1:15) to afford **11** (20:1 diastereomeric mixture) as colorless oil (53 mg, 53% yield). Main diastereoisomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (dt, *J* = 5.2, 2.4 Hz, 1H), 5.50 (m, 3H), 5.02 (dhept, *J* = 12.5, 6.2 Hz, 2H), 3.47 (dt, *J* = 11.7, 8.7 Hz, 1H), 2.85 (td, *J* = 11.9, 1.7 Hz, 1H), 2.59 (m, 2H), 2.39 (m, 1H), 2.28 (m, 2H), 2.17 (ddt, *J* = 16.9, 8.6, 2.4 Hz, 1H), 1.25-1.16 (m, 12H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.8, 174.8, 135.1, 130.6, 129.9, 126.2, 68.0, 67.6, 64.6, 47.8, 43.5, 38.4, 32.7, 31.7, 21.9, 21.9, 21.8, 21.8. IR (KBr): 1730 cm^{-1} (C=O). HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{26}O_4Na$ 329.1723, found 329.1728.

Preparation of tetrahydrobenzo[*f*]azulene 12. A suspension of LiH (28 mg, 3.5 mmol, 10 equiv) and *i*PrOH (320 μL, 4.2 mmol, 12 equiv) in DMF (1 mL) was stirred at 0 ºC for 1 h, and a solution of **10**[6] (80 mg, 0.35 mmol, 1 equiv) in DMF (1.3 mL) was added. The reaction mixture was stirred for 48 h at room temperature. Then, pH 7 phosphate buffer (5 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and phosphate buffer of pH 7 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were repeatedly washed with brine, dried, and concentrated to dryness. Flash column chromatography of the crude product (EtOAc/Hexane, 1:15) afforded **12** (20:1 diastereomeric mixture) as a colorless oil (45 mg, 56% yield). mixture. Main diastereoisomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (m, 4H), 5.75 (dt, *J* = 5.2, 2.4 Hz, 1H), 5.63 (ddd, *J* = 5.7, 2.5, 1.6 Hz, 1H), 5.06 (hept, *J* = 6.2 Hz, 1H), 4.76 (hept, *J* = 6.3 Hz, 1H), 3.51 (dt, *J* = 11.0, 8.5 Hz, 1H), 3.39 (dd, *J* = 16.8, 11.5 Hz, 1H), 3.09 (d, *J* = 15.4 Hz, 1H), 2.99 (m, 3H), 2.64 (ddt, *J* = 17.0, 8.8, 2.1 Hz, 1H), 2.21 (ddt, *J* = 16.9, 8.2, 2.4 Hz, 1H), 1.26 (dd, *J* = 6.3, 4.2 Hz, 6H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.77 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.8, 174.4, 137.5, 136.0, 135.1, 131.8, 131.0, 130.3, 126.5, 125.8, 68.1, 67.8, 62.6, 46.7, 44.0, 39.0, 38.2, 36.7, 22.0, 21.9, 21.7, 21.3. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{28}O_4Na$ 379.1885, found 379.1888.

Diisopropyl (1*E*,5*E*)-cyclonona-5,9-diene-1,5-dicarboxylate (13). Modified procedure for gram-scale reactions. A suspension of small pieces of lithium (1.19 g, 171 mmol, 5 equiv) and naphthalene (9.64 g, 75.2 mmol, 2.2 equiv) in THF (200 mL) was sonicated at room temperature for 45 minutes. The dark purple solution was cooled to –30 ºC and a solution of **2** (10 g, 34.2 mmol, 1 equiv) in THF (30 mL) was added. The reaction mixture was stirred for 2 h, then *i*PrOH (21 mL, 275 mmol, 8 equiv) was added and the reaction mixture was warmed to –20 ºC and stirred for 16 h. Then, pH 7 phosphate buffer (100 mL) was added, and the mixture was partitioned between CH_2Cl_2 (300 mL) and pH 7 buffer (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL), and the combined organic layers were dried and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/Hexane, 1:20) to afford cyclononadiene **13** (6.82 g, 68% yield) as a colorless oil. Yields of 72% were obtained for 0.34 mmol scale reactions.[6] Spectral data are identical to those previously reported.[6]

Preparation of compound 16a. A 0 ºC solution of **13** (100 mg, 0.34 mmol, 1 equiv) in THF (3 mL) was treated with NaHMDS (680 μL, 1M in THF, 0.68 mmol, 2 equiv). The reaction mixture was stirred for 6 h and then HOAc (200 μL, 3.4 mmol, 10 equiv) was added. After just 1 minute, pH 7 buffer (8 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and pH 7 phosphate buffer (15 mL). The aqueous layers were extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried and concentrated to dryness. The crude product was obtained as 4:1 diastereomeric mixture. Purification by flash column chromatography (EtOAc/Hexane, 1:15) afforded **16** (10:1 diastereomeric mixture) as a colorless oil (60.1 mg, 60% yield). Main diastereoisomer **16a**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (dt, *J* = 5.1, 2.4 Hz, 1H), 5.54 (ddd, *J* = 5.6, 2.6, 1.5 Hz, 1H), 5.02 (hept, *J* = 6.3 Hz, 1H), 4.95 (hept, *J* = 6.3 Hz, 1H), 2.94 (ddd, *J* = 9.9, 6.5, 2.3 Hz, 1H), 2.64 (ddt, *J* = 16.4, 6.5, 2.3 Hz, 1H), 2.14 (ddd, *J* = 11.4, 9.9, 4.0 Hz, 1H), 2.02 (dtd, *J* = 16.4, 2.5, 1.5 Hz, 1H), 1.90 (m, 1H), 1.74 (m, 3H), 1.66 (m, 2H), 1.23 (t, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.5, 175.3, 134.6, 132.4, 67.8, 67.6, 58.0, 46.0, 41.7, 38.8, 30.2, 26.5, 22.0, 21.9, 21.8, 21.8, 20.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{27}O_4$ 295.1904, found 295.1906.

Preparation of compound 16b. A solution of **13** (100 mg, 0.34 mmol, 1 equiv) in THF (3 mL) was cooled to 0 ºC and treated with NaHMDS (680 μL, 1M in THF, 0.68 mmol, 2 equiv). The reaction mixture was stirred for 6 h and then *i*PrOH (260 μL, 3.4 mmol, 10 equiv) was added. After just 1 minute, pH 7 phosphate buffer (8 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and pH 7 buffer (15 mL). The aqueous layers were extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried and concentrated to dryness. The crude product was obtained as 1:4 diastereomeric mixture. Purification by flash column chromatography (EtOAc/Hexane, 1:15) afforded **16** (1:15 diastereomeric mixture) as a colorless oil (63.1 mg, 63% yield). Main diastereoisomer **16b**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (dt, *J* = 5.8, 2.0 Hz, 1H), 5.74 (dt, *J* = 5.7, 2.4 Hz, 1H), 5.03 (dhept, *J* = 8.8, 6.3 Hz, 2H), 2.88 (m, 2H), 2.22 (t, *J* = 2.2 Hz, 1H), 2.20 (t, *J* = 2.2 Hz, 1H), 2.13 (m, 1H), 1.82 (m, 1H), 1.59 (m, 1H), 1.48 (qd, *J* = 12.7, 3.5 Hz, 1H), 1.24 (m, 13H), 1.11 (td, *J* = 13.5, 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.2, 174.6, 137.1, 129.8, 67.9, 67.4, 57.0, 41.6, 32.8, 31.8, 23.1, 22.0, 22.0, 21.9, 21.9, 21.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{27}O_4$ 295.1904, found 295.1907. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.75; H, 9.24.

Diisopropyl *cis*-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-3a,9b-dicarboxylate (18). A suspension of small pieces of lithium (115 mg, 16.6 mmol, 10 equiv) and naphthalene (470 mg, 3.66 mmol, 2.2 equiv) in THF (12 mL) was sonicated for 30 minutes. The dark purple solution was cooled to –78 ºC and a solution of **17** (500 mg, 1.67 mmol, 1 equiv) in THF (4.6 mL) was added. The reaction mixture was stirred for 2 h, and the resulting solution was transferred via canula to a –78 ºC round-bottomed flask and treated with 1,3-dibromopropane (190 μL, 1.87 mmol, 1.1 equiv). The reaction mixture was stirred for 18 h while gradually warming to rt. Then, pH 7 buffer (20 mL) was added, and the mixture was partitioned between CH_2Cl_2 (40 mL) and phosphate buffer of pH 7 (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic layers were dried, filtered, and evaporated. The crude product was purified by flash column chromatography (CH_2Cl_2/Hexane, 2:1) to afford **18** (405 mg, 71% yield) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 1H), 7.17 (m, 2H), 7.05 (m, 1H), 6.37 (s, 2H), 5.01 (hept, *J* = 6.2 Hz, 1H), 4.82 (hept, *J* = 6.2 Hz, 1H), 3.01 (ddd, *J* = 13.5, 9.7, 7.2 Hz, 1H), 2.53 (ddd, *J* = 13.5, 8.6, 5.0 Hz, 1H), 2.25 (ddd, *J* = 13.2, 8.4, 4.9 Hz, 1H), 1.86 (ddd, *J* = 13.1, 9.3, 7.8 Hz, 1H), 1.74 (m, 1H), 1.49 (m, 1H), 1.23 (dd, *J* = 6.3, 2.5 Hz, 6H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.9, 173.5, 135.5, 131.9, 130.5, 127.9, 127.4, 127.2, 126.8, 124.6, 68.5, 67.9, 59.1, 57.4, 41.5, 38.1, 21.7, 21.6, 21.5, 21.4, 21.3. IR (neat): 1722 cm^{-1} (C=O). HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{26}O_4Na$ 365.1723, found 365.1724.

Diisopropyl (*E*)-6,7,8,11-tetrahydro-5*H*-benzo[9]annulene-5,9-dicarboxylate (19). A suspension of small pieces of lithium (40.5 mg, 5.84 mmol, 5 equiv) and naphthalene (330 mg, 2.57 mmol, 2.2 equiv) in THF (9 mL) was sonicated for 30 min at room temperature. The resulting dark purple solution was cooled to –78 ºC and treated with a solution of **18** (400 mg, 1.17 mmol, 1 equiv) in THF (2.7 mL). After 30 min, *i*PrOH (900 µL, 11.7 mmol, 10 equiv) was added and the reaction mixture was stirred for 18 h while gradually warming to –20 ºC. Then, pH 7 buffer (20 mL) was added, and the mixture was partitioned between CH_2Cl_2 (40 mL) and pH 7 phosphate buffer (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic layers were dried, filtered, and evaporated. The crude product was purified by flash column chromatography (EtOAc/Hexane, 1:10) to afford **19** (330 mg, 82% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dt, *J* = 7.2, 1.7 Hz, 1H), 7.24 (m, 2H), 7.13 (dt, *J* = 7.3, 1.8 Hz, 1H), 7.00 (dd, *J* = 11.2, 6.5 Hz, 1H), 5.19 (hept, *J* = 6.3, 1H), 5,08 (hept, *J* = 6.3, 1H), 4.14 (d, *J* = 7.0 Hz, 1H), 4.08 (t, *J* = 12.2 Hz, 1H), 3.35 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.91 (m, 1H), 2.70 (dt, *J* = 13.9, 4.2 Hz, 1H), 2.50 (m, 1H), 1.77 (m, 2H), 1.38-1.25 (m, 13H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 174.0, 167.1, 141.3, 140.7, 135.9, 131.1, 131.1, 127.4, 127.2, 126.0, 68.4, 67.9, 44.6, 33.9, 30.0, 26.6, 23.2, 22.0, 22.0, 22.0, 21.6. IR (neat): 1725, 1703 cm^{-1} (C=O). HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{21}H_{29}O_4$ 345.2060, found 345.2060.

Preparation of hexahydrofluorene 20. A solution of **19** (150 mg, 0.44 mmol, 1 equiv) in THF (3.1 mL) was cooled to 0 ºC and treated with NaHMDS (1.3 mL, 1M solution in THF, 1.31 mmol, 3 equiv). The reaction mixture was stirred for 16 h and HOAc (250 µL, 4.36 mmol, 10 equiv) was added. After 1 min, pH 7 buffer (8 mL) was added, and the mixture was partitioned between CH_2Cl_2 (15 mL) and pH 7 phosphate buffer (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried, filtered, and concentrated to dryness. Purification by flash column chromatography (EtOAc/Hexane, 1:15) afforded **20** (83 mg, 55%) and **21** (15 mg, 12%), both as colorless oils:

Compound 20: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (m, 4H), 5.03 (hept, *J* = 6.2 Hz, 1H), 4.90 (hept, *J* = 6.3 Hz, 1H), 3.21 (m, 2H), 2.55 (m, 1H), 2.36 (m, 1H), 2.02 (ddd, *J* = 11.7, 10.0, 3.8 Hz, 1H), 1.91 (ddd, *J* = 14.1, 11.9, 4.0 Hz, 1H), 1.73 (m, 2H), 1.46 (m, 1H), 1.24 (m, 7H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 175.3, 174.4, 143.3, 142.9, 127.5, 126.7, 125.6, 123.9, 68.2, 67.7, 57.7, 45.7, 44.1, 37.3, 30.0, 27.4, 22.0, 21.9, 21.7, 21.6, 20.9. IR (neat): 1722 cm^{-1} (C=O). HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{21}H_{29}O_4$ 345.2060, found 345.2061.

Compound 21: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.04 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.97 (hept, *J* = 6.2 Hz, 1H), 4.14 (d, *J* = 9.0 Hz, 1H), 3.63 (t, *J* = 4.4 Hz, 1H), 2.67 (ddd, *J* = 16.6, 11.2, 1.7 Hz, 1H), 2.32 (m, 1H), 2.04 (m, 2H), 1.66 (m, 1H), 1.24 (m, 7H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 220.8, 167.6, 141.1, 140.8, 137.3, 136.4, 128.5, 128.2, 124.8, 124.7, 68.6, 53.8, 52.8, 36.7, 24.6, 23.8, 22.0, 22.0. IR (neat): 1751, 1699 cm^{-1} (C=O). HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{18}H_{21}O_3$ 285.1485, found 285.1488.

General Procedure A. Conjugate Addition-Transannular Cyclization. Synthesis of β-aminoesters. A 0 ºC solution of the appropriate amine (0.68 mmol, 2 equiv) in THF (2 mL) was treated dropwise with *n*-BuLi (470 µL, 0.68 mmol, 2.0 equiv), and the mixture was stirred for 20-60 min. A solution of **13** (100 mg, 0.34 mmol, 1 equiv) in THF (1.5 mL) was added, and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h. Then, pH 7 phosphate buffer (8 mL) was added, and the mixture was partitioned between CH_2Cl_2 (20 mL) and pH 7 buffer solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried and concentrated to dryness. The crude product was purified by flash column chromatography (SiO_2).

(±) Diisopropyl (3*R*,3a*R*,7a*R*)-3-(diisopropylamino)octahydro-3a*H*-indene-3a,7-dicarboxylate (22). According to general procedure A, a 0 ºC solution of *N*,*N*-diisopropylamine (95 µL, 0.68 mmol, 2 equiv) in THF was treated dropwise with *n*-BuLi (470 µL, 0.68 mmol, 2 equiv) and stirred for 20 minutes. Then, a solution of **13** (100 mg, 0.34 mmol, 1 equiv) was added and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h to give, after work-up, a 1:1 diastereomeric mixture of **22a** and **22b** (80 mg, 65% yield). Both diastereomers were separated by flash column chromatography (EtOAc/Hexane, 1:15) as colorless oils. **22a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (hept, *J* = 6.3 Hz, 2H), 3.32 (dd, *J* = 11.3, 8.5 Hz, 1H), 3.03 (hept, *J* = 6.6 Hz, 2H), 2.85 (td, *J* = 10.3, 4.5 Hz, 1H), 2.36 (dt, *J* = 12.9, 4.4 Hz, 1H), 2.10 (ddt, *J* = 12.8, 3.2, 1.7 Hz, 1H), 1.82 (m, 1H), 1.71 (dq, *J* = 13.9, 3.6 Hz, 1H), 1.63 (m, 2H), 1.52 (m, 3H), 1.32-1.12 (m, 14H), 0.92 (d, *J* = 6.6 Hz, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 175.3, 174.4, 67.5, 67.3, 65.4, 57.4, 45.8, 42.1, 40.7, 25.0, 23.7, 23.6, 23.0, 22.2, 22.1, 22.1, 22.0, 22.0, 21.6, 19.9. IR (KBr): 1728, 1708 cm^{-1} (C=O). HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{42}NO_4$ 396.3108, found 396.3112. **22b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (hept, *J* = 6.3 Hz, 2H), 3.35 (dd, *J* = 11.3, 8.2 Hz, 1H), 3.04 (hept, *J* = 6.6 Hz, 2H), 2.84 (tt, *J* = 10.0, 1.9 Hz, 1H), 2.30 (dt, *J* = 4.9, 2.5 Hz, 1H), 2.12 (dt, *J* = 13.2, 1.6 Hz, 1H), 1.96-1.69 (m, 4H), 1.68-1.41 (m, 4H), 1.34-1.17 (m, 13H), 0.91 (t, *J* = 6.7 Hz, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 175.7, 175.0, 67.5, 67.4, 67.0, 55.4, 45.9, 41.3, 40.8, 26.2, 25.4, 23.7, 23.3, 22.2, 22.1, 21.9, 21.8, 21.5, 19.6. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{42}NO_4$ 396.3108, found 396.3111.

Preparation of compound 23. According to general procedure A, a solution of *N*,*N*-dibenzylamine (130 µL, 0.68 mmol, 2 equiv) in THF at 0 ºC was treated with *n*-BuLi for 1 h. A solution of **13** (100 mg, 0.34 mmol, 1 equiv) was then added, and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h, to give a 1:1 diastereomeric mixture of **23a** and **23b** (80 mg, 50% yield) as a colorless oil, after flash column chromatography purification (EtOAc/Hexane, 1:15).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 8H), 7.20 (m, 2H), 4.94 (m, 2H), 3.73-3.53 (m, 5H), 2.83 (m, 1H), 2.33 (m, 2H), 1.95 – 1.48 (m, 8H), 1.37 (m, 1H), 1.32-1.12 (m, 12H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 176.2, 175.5, 174.5, 174.0, 140.1, 140.1, 128.6, 128.1, 128.0, 126.8, 126.7, 72.7, 70.1, 67.9, 67.8, 67.3, 67.3, 56.2, 56.1, 54.0, 41.8, 41.7, 41.7, 26.7, 24.4, 23.4, 23.0, 22.7, 22.4, 22.2, 21.8, 21.8, 21.8, 21.7, 20.2, 19.0. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{31}H_{42}NO_4$ 492.3108, found 492.3106.

Diisopropyl (3*R*,3a*R*,7a*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)octahydro-3a*H*-indene-3a,7-dicarboxylate (24). According to general procedure A, a solution of (*R*)-(+)-*N*-benzyl-1-phenylethan-1-amine (155 µL, 0.68 mmol, 2 equiv) in THF at 0 ºC was treated dropwise with *n*-BuLi and stirred for 1 h. A solution of **13** (100 mg, 0.34 mmol, 1 equiv) was then added and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h, to give, after work-up, a 1:1 diastereomeric mixture of **24a** and **24b** (103 mg, 60% yield). Both diastereomers were separated by flash column chromatography (EtOAc/Hexane, 1:15) and isolated as colorless oils. **24a**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.63 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27 (m, 5H), 7.20 (m, 1H), 4.94 (hept, *J* = 6.3 Hz, 1H), 4.57 (hept, *J* = 6.2 Hz, 1H), 3.98 (d, *J* = 14.7 Hz, 1H), 3.74 (q, *J* = 7.0 Hz, 1H), 3.69 (d, *J* = 14.7 Hz, 1H), 3.37 (dd, *J* = 10.6, 9.0 Hz, 1H), 2.66 (td, *J* = 10.4, 4.6 Hz, 1H), 2.31 (m, 1H), 2.25 (dt, *J* = 12.7, 4.5 Hz, 1H), 1.99 (m, 1H), 1.83 (m, 1H), 1.67 (dt, *J* = 13.5, 3.4 Hz, 1H), 1.57 (m, 3H), 1.47 (qd, *J* = 13.3, 3.8 Hz, 1H), 1.33 (m, 7H), 1.20 (m, 7H), 1.03 (d, *J* = 6.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, CD_2Cl_2) δ 174.7, 174.3, 144.3, 142.5, 129.2, 128.7, 128.6, 128.1, 127.3, 127.1, 68.1, 67.7, 66.7, 58.0, 57.5, 53.0, 42.1, 41.6, 24.2, 24.0, 23.2, 22.4, 22.1, 22.1, 22.0, 20.9, 13.5. IR (KBr): 1722 cm^{-1} (C=O). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{44}NO_4$ 506.3265, found 506.3265. $[\alpha]^{20}_{589nm}$= – 46.7 (c 0.1, $CHCl_3$). **24b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 (m, 5H), 7.18 (m, 1H), 4.86 (hept, *J* = 6.3 Hz, 1H), 4.58 (hept, *J* = 6.3 Hz, 1H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.80 (q, *J* = 6.9 Hz, 1H), 3.70 (d, *J* = 15.0 Hz, 1H), 3.57 (dd, *J* = 10.7, 8.3 Hz, 1H), 2.76 (td, *J* = 9.6, 3.3 Hz, 1H), 2.31 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.26 (q, *J* = 4.2 Hz, 1H), 1.87 (m, 2H) 1.76 (m, 2H), 1.65 (m, 1H), 1.55 (m, 1H), 1.46 (m, 2H), 1.32-1.24 (m, 7H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.2, 174.8, 143.4, 142.4, 128.5, 128.3, 128.2, 127.9, 126.7, 126.7, 69.2, 67.7, 67.4, 58.6, 54.9, 52.2, 41.7, 41.4, 27.2, 24.8, 23.1, 22.4, 22.0, 21.9, 21.8, 21.7, 19.2, 15.0. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{44}NO_4$ 506.3265, found 506.3261.

Diisopropyl (3*R*,3a*R*,7a*R*)-3-(bis((*R*)-1-phenylethyl)amino)octahydro-3a*H*-indene-3a,7-dicarboxylate (25). According to general procedure A, a 0 ºC solution of (*R*)-(+)-*bis*-((*R*)-1-phenylethyl)amine (140 μL, 0.68 mmol, 2 equiv) in THF was treated dropwise with *n*-BuLi and stirred for 1 h. Then, a solution of **13** (100 mg, 0.34 mmol, 1 equiv) was added and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h, to give, after work-up, a 1:1 diastereomeric mixture of **25a** and **25b** (120 mg, 70% yield) as a white solid. Both diastereomers were separated by flash column chromatography (EtOAc/Hexane, 1:15). **25a**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.22 (m, 6H), 4.98 (hept, *J* = 6.2 Hz, 1H), 4.15 (hept, *J* = 6.2 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.65 (dd, *J* = 11.7, 8.1 Hz, 1H), 2.86 (td, *J* = 10.5, 4.6 Hz, 1H), 2.36 (dq, *J* = 13.4, 2.2 Hz, 1H), 2.27 (dt, *J* = 12.7, 4.4 Hz, 1H), 2.17 (qd, *J* = 12.3, 5.9 Hz, 1H), 2.00 (m, 1H), 1.64 (m, 4H), 1.51 (d, *J* = 6.8 Hz, 6H), 1.46 (m, 1H), 1.36 (m, 1H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.12 (m, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.3, 174.1, 145.2, 128.6, 127.7, 126.5, 67.7, 67.3, 66.2, 56.9, 55.1, 41.8, 41.0, 26.8, 23.6, 22.7, 22.0, 22.0, 22.0, 21.9, 21.6, 19.6, 18.7. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{33}H_{45}NO_4Na$ 542.3241, found 542.3230. **25b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.19 (m, 6H), 4.86 (hept, *J* = 6.3 Hz, 1H), 4.11 (hept, *J* = 6.2 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.73 (dd, *J* = 11.8, 7.4 Hz, 1H), 2.91 (m, 1H), 2.35 (m, 1H), 2.28 (dt, *J* = 6.2, 3.3 Hz, 1H), 2.15 (m, 1H), 2.01 (m, 2H), 1.64 (m, 4H), 1.50 (d, *J* = 6.8 Hz, 6H), 1.40 (m, 1H), 1.36 (td, *J* = 12.6, 3.7 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.7, 174.1, 145.2, 128.5, 127.7, 126.4, 67.5, 67.4, 67.4, 55.4, 55.1, 41.7, 40.9, 27.4, 26.2, 23.2, 22.1, 22.1, 21.9, 21.7, 21.6, 19.3, 18.8. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{33}H_{45}NO_4Na$ 542.3241, found 542.3237.

Diisopropyl (3*R*,3a*R*,7a*R*)-3-(allyl((*R*)-1-phenylethyl)amino)octahydro-3a*H*-indene-3a,7-dicarboxylate (26). Following general procedure A, a 0 ºC solution of (*R*)-(+)-*N*-allyl-α-methylbenzylamine (120 μL, 0.68 mmol, 2 equiv) in THF was treated with *n*-BuLi and stirred for 1 h. Then, a solution of **13** (100 mg, 0.34 mmol, 1 equiv) was added and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h, to give, after work-up, a 1:1 diastereomeric mixture of **26a** and **26b** (85 mg, 55% yield). Both diastereomers were isolated as colorless oils after flash column chromatography (EtOAc/Hexane, 1:15). **26a**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.85 (dddd, *J* = 17.5, 10.1, 7.5, 4.8 Hz, 1H), 5.11 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.96 (hept, *J* = 6.3 Hz, 1H), 4.74 (hept, *J* = 6.3 Hz, 1H), 4.00 (q, *J* = 6.8 Hz, 1H), 3.48 (t, *J* = 9.8 Hz, 1H), 3.21 (m, 1H), 3.08 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.78 (td, *J* = 10.4, 4.6 Hz, 1H), 2.29 (dt, *J* = 12.8, 4.3 Hz, 1H), 2.14 (m, 1H), 1.87 (m, 2H), 1.71-1.44 (m, 5H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.28-1.15 (m, 11H), 1.09 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.9, 174.3, 144.7, 139.2, 128.0, 127.9, 126.4, 115.9, 67.7, 67.7, 67.3, 56.9, 56.9, 51.5, 41.9, 41.3, 24.1, 23.2, 22.6, 22.1, 22.0, 21.9, 21.9, 20.6, 15.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{42}NO_4$ 456.3108, found 456.3110. **26b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.29 (m, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.81 (dddd, *J* = 17.2, 10.1, 6.9, 5.4 Hz, 1H), 5.03 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.97 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.89 (hept, *J* = 6.3 Hz, 1H), 4.80 (hept, *J* = 6.3 Hz, 1H), 4.04 (q, *J* = 6.9 Hz, 1H), 3.62 (dd, *J* = 10.6, 8.6 Hz, 1H), 3.14 (dd, *J* = 15.4, 5.5 Hz, 1H), 3.08 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.81 (m, 1H), 2.29 (q, *J* = 4.3 Hz, 1H), 2.15 (dt, *J* = 12.8, 2.3 Hz, 1H), 1.92 (m, 1H), 1.86-1.68 (m, 3H), 1.58 (m, 1H), 1.49 (m, 2H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.28-1.16 (m, 14H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.9, 174.7, 144.7, 139.5, 127.9, 127.8, 126.4, 115.4, 70.3, 67.8, 67.4, 57.3, 54.6, 51.4, 41.8, 41.4, 27.0, 25.0, 22.9, 22.5, 22.0, 22.0, 21.9, 21.8, 19.1, 16.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{42}NO_4$ 456.3108, found 456.3115.

Diisopropyl (3*R*,3a*R*,7a*R*)-3-(methyl((*R*)-1-phenylethyl)amino)octahydro-3a*H*-indene-3a,7-dicarboxylate (27). Following general procedure A, a 0 ºC solution of (*R*)-(+)-*N*-α-dimethylbenzylamine (100 μL, 0.68 mmol, 2 equiv) in THF was treated with *n*-BuLi and stirred for 1 h. Then, a solution of **13** (100 mg, 0.34 mmol, 1 equiv) was added, and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h, to give, after work-up, a 1:1 diastereomeric mixture of **27a** and **27b** (85 mg, 55% yield). Both diastereomers were separated by flash column chromatography (EtOAc/Hexane, 1:15) and isolated as colorless oils. **27a**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.07 (hept, *J* = 6.1 Hz, 1H), 4.98 (hept, *J* = 6.5 Hz, 1H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.48 (dd, *J* = 10.5, 8.2 Hz, 1H), 2.94 (td, *J* = 10.3, 4.3 Hz, 1H), 2.32 (dt, *J* = 12.3, 4.1 Hz, 1H), 2.06 (d, *J* = 13.9 Hz, 1H), 1.97 (m, 1H), 1.90 (s, 3H), 1.84-1.56 (m, 7H), 1.37 (m, 1H), 1.27-1.20 (m, 15H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 176.8, 174.0, 144.4, 127.8, 127.5, 126.3, 71.3, 67.7, 67.3, 57.5, 55.3, 44.2, 41.9, 33.6, 27.0, 22.0, 21.9, 21.8, 21.8, 21.8, 21.6, 20.6, 10.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{40}NO_4$ 430.2952, found 430.2957. **27b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.99 (hept, *J* = 6.3 Hz, 1H), 4.92 (hept, *J* = 6.3 Hz, 1H), 3.99 (q, *J* = 6.7 Hz, 1H), 3.54 (dd, *J* = 11.0, 7.4 Hz, 1H), 3.00 (m, 1H), 2.37 (m, 1H), 2.08 (m, 1H), 1.97 (m, 3H), 1.88 (s, 3H), 1.78 (m, 1H), 1.65 (m, 4H), 1.37 (td, *J* = 13.7, 4.4 Hz, 1H), 1.23 (m, 15H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 177.4, 174.4, 144.6, 128.0, 127.7, 126.4, 73.1, 67.9, 67.4, 57.8, 53.2, 43.4, 42.1, 33.6, 27.2, 26.9, 22.4, 22.3, 22.0, 21.8, 21.8, 21.6, 19.0, 11.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{40}NO_4$ 430.2952, found 430.2955.

Modification of general procedure A to improve the ratio of diastereomers of products 24-27. A 0 ºC solution of the appropriate amine (0.68 mmol, 2 equiv) in THF (2 mL) was treated dropwise with *n*-BuLi (470 μL, 0.68 mmol, 2 equiv), and the mixture was stirred for 1 h. A solution of **13** (100 mg, 0.34 mmol, 1 equiv) in THF (1.5 mL) was then added, and the reaction mixture was gradually warmed to room temperature for 2 h and stirred for an additional 16 h. The reaction mixture was added via cannula over a suspension of NaOiPr[16] (3.4 mmol, 10 equiv) in THF (1 mL) and the resulting mixture was stirred at rt for 24 h. Then, pH 7 phosphate buffer (8 mL) was added, and the mixture was partitioned between CH_2Cl_2 (20 mL) and pH 7 buffer solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried and concentrated to dryness to give a 95:5 (**24**, **26**) or 94:6 (**25**, **27**) mixture of epimers at C7. The crude product was purified by flash column chromatography (SiO_2, EtOAc/Hexane, 1:15).

Isopropyl (3*R*,3a*R*,7*R*,7a*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-7-(hydroxymethyl)octahydro-3a*H*-indene-3a-carboxylate (28). A solution of **24a** (1 g, 2.03 mmol, 1 equiv) in THF (20 mL) was cooled to 0 ºC and a solution of DIBAL-H (4.1 mL, 4.06 mmol, 1M in heptane, 2 equiv) was slowly added. The reaction mixture was stirred for 3 h, excess reagent was quenched with acetone (5 mL), and the mixture was partitioned between CH_2Cl_2 (20 mL) and 2 M HCl solution (10 mL). The organic layer was washed with brine, dried, and concentrated to dryness. The crude product **28** was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.26 (m, 5H), 7.18 (m, 1H), 4.52 (hept, *J* = 6.0 Hz, 1H), 3.98 (d, *J* = 14.6 Hz, 1H), 3.75 (q, *J* = 6.9 Hz, 1H), 3.68 (d, *J* = 14.7 Hz, 1H), 3.39 (m, 3H), 2.45 (td, *J* = 10.5, 4.3 Hz, 1H), 2.35 (m, 1H), 1.96 (dtd, *J* = 13.3, 10.4, 6.3 Hz, 1H), 1.83 (dtd, *J* = 13.0, 8.9, 6.7 Hz, 1H), 1.66 (dquin, *J* = 13.6, 3.6, 3.1 Hz, 1H), 1.55 (m, 3H), 1.45 (dd, *J* = 13.3, 3.5 Hz, 1H), 1.34-1.16 (m, 9H), 1.01 (m, 1H), 0.97 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.8, 143.6, 141.9, 128.7, 128.2, 128.1, 127.6, 126.8, 126.6, 67.5, 66.2, 66.1, 57.4, 57.0, 52.6, 41.1, 38.6, 24.0, 23.7, 23.2, 22.9, 21.7, 21.7, 19.6, 13.1. IR (neat): 1710 cm^{-1} (C=O). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{40}NO_3$ 450.3003, found 450.3020. $[\alpha]^{20}_{589nm}$= – 9.2 (c 0.1, $CHCl_3$).

Isopropyl (3*R*,3a*R*,7*R*,7a*R*)-3-(benzyl((*R*)-1-phenylethyl)amino)-7-(tosyloxymethyl)octahydro-3a*H*-indene-3a-carboxylate (29). A 0 ºC solution of crude **28** (2.03 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was treated with *p*-toluenesulfonyl chloride (580 mg, 3.05 mmol, 1.5 equiv) and NEt_3 (1.03 mL, 10.2 mmol, 5 equiv). After 10 min, the cooling bath was removed, and the reaction mixture was stirred overnight at rt. The reaction was quenched with pH 7 phosphate buffer (10 mL), and the mixture was washed with sat $NaHCO_3$ (2 x 10 mL) and brine (20 mL). The organic layer was dried and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/Hexane, 1:10) to give **29** as a white foam (983 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.36 (m, 4H), 7.28 (m, 5H), 7.21 (td, *J* = 6.0, 2.5 Hz, 1H), 4.51 (hept, *J* = 6.2 Hz, 1H), 3.97 (d, *J* = 14.7 Hz, 1H), 3.77 (m, 3H), 3.69 (d, *J* = 14.7 Hz, 1H), 3.40 (t, *J* = 9.8 Hz, 1H), 2.47 (s, 3H), 2.42 (td, *J* = 10.6, 4.4 Hz, 1H), 2.36 (dd, *J* = 13.1, 3.8 Hz, 1H), 1.96 (m, 1H), 1.87-1.71 (m, 2H), 1.65 (dt, *J* = 13.5, 3.2 Hz, 1H), 1.49 (dt, *J* = 10.6, 8.2 Hz, 2H), 1.42 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.30 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.18 (m, 1H), 0.99 (m, 1H), 0.95 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.1, 144.7, 143.5, 141.7, 133.1, 129.9, 128.7, 128.3, 128.3, 128.0, 127.7, 126.9, 126.7, 73.4, 67.6, 65.9, 57.4, 57.0, 52.6, 40.5, 35.5, 23.7, 23.6, 22.8, 22.6, 21.7, 21.7, 19.6, 13.0. IR (neat): 1714 cm^{-1} (C=O). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{36}H_{46}NO_5S$ 604.3091, found 604.3097. $[\alpha]^{20}_D$= –19.0 (c 0.1, $CHCl_3$).

Isopropyl (3*R*,3a*R*,7*R*,7a*R*)-3-amino-7-(tosyloxymethyl)octahydro-3a*H*-indene-3a-carboxylate (30). A mixture of **29** (450 mg, 0.74 mmol, 1 equiv) and 20% $Pd(OH)_2/C$ catalyst (52 mg, 0.1 equiv) in MeOH (3 mL) was shaken under a hydrogen atmosphere (10 atm) for 24 h at room temperature. The mixture was filtered through a short pad of Celite, washed thoroughly with MeOH, and the solvent was removed under reduced pressure to give **30**, which was used in the next step without further purification.

9-(*tert*-butyl) 7a-isopropyl (3a*R*,4*R*,7a*R*)-octahydro-7a*H*-1,4-(epiminomethano)indene-7a,9-dicarboxylate (31). A solution of **30** (300 mg, 0.73 mmol, 1 equiv) in DMF (7 mL) was treated dropwise with DIPEA (270 μL, 1.54 mmol, 2.1 equiv) and stirred at 60 ºC overnight. Boc_2O (320 mg, 1.47 mmol, 2 equiv) was added and the reaction mixture was stirred for 2 h at room temperature. Then, the reaction was quenched with pH 7 phosphate buffer and partitioned between CH_2Cl_2 (20 mL) and pH 7 phosphate buffer (20 mL). The organic layer was washed with brine (4 x 5 mL), dried with anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (SiO_2, EtOAc/Hexane 1:10) to give the product as a white solid (150 mg, 60% from **29**). Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IE-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 0.5 mL/min, 23 ºC, UV = 210 nm), t_R = 19.4 min (major) and t_R = 20.9 (minor), 96:4 er. Mp: 87-88 ºC (MeOH). $[\alpha]^{20}_{589nm}$= –76.6 (c 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 298 K, 1:1 mixture of rotamers) δ 4.95 (hept, *J* = 6.2 Hz, 1H), 4.88 and 4.78 (d, *J* = 4.4 Hz, 1H), 3.72 and 3.57 (d, *J* = 13.6 Hz, 1H), 3.09 and 3.00 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.36 (m, 1H), 2.10 (dd, *J* = 13.0, 4.6 Hz) and 2.02 (d, *J* = 8.9 Hz) (1H), 1.86-1.40 (m, 10H), 1.46 (s, 9H), 1.22 (dd, *J* = 6.3, 1.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $C_2D_2Cl_4$, 298 K, 1:1 mixture of rotamers) δ 175.2, 175.1, 153.9, 153.7, 79.1, 67.4, 67.4, 58.6, 57.4, 53.6, 53.4, 42.9, 41.5, 40.9, 40.8, 33.0, 31.1, 30.7, 29.2, 28.9, 28.5, 28.4, 27.8, 27.7, 26.7, 26.6, 21.5, 21.4, 18.7, 18.5. ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 378 K) δ 5.01 (hept, *J* = 6.2 Hz, 1H), 4.89 (d, *J* = 4.5 Hz, 1H), 3.70 (d, *J* = 13.7 Hz, 1H), 3.10 (dd, *J* = 13.5, 3.9 Hz, 1H), 2.42 (t, *J* = 4.8 Hz, 1H), 2.13 (m, 1H), 1.96 – 1.46 (m, 10H), 1.52 (s, 9H), 1.27 (dd, *J* = 6.2, 1.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $C_2D_2Cl_4$, 378 K) δ 174.9, 153.8, 79.0, 67.3, 58.4, 53.7, 42.4, 41.1, 33.3, 31.0, 29.0, 28.4, 27.8, 26.7, 21.3, 21.2, 18.6. IR (neat): 1722, 1681 cm^{-1}. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{31}NO_4Na$ 360.2145, found 360.2146.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. X-ray crystallographic data and ORTEP of **8**, **25a**, **25b** and **31**; ^{1}H and ^{13}C NMR spectra for all new compounds (PDF).

Accession Codes

CCDC 2091998-2092001 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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