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Synthetic studies on the icetexones: enantioselective formal syntheses of icetexone and *epi*-icetexone

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Abstract

Two strategies for the synthesis of the icetexane diterpenoids icetexone and *epi*-icetexone that rely on Ga(III)-catalyzed cycloisomerization of alkynyl indene substrates to yield fused [6-7-6] tricycles have been explored. In the first approach, access to a tricycle bearing a *gem*-dimethyl group paved the way for explorations of C–H functionalization of one of the methyl groups in close proximity to a hydroxyl-directing group. This approach was ultimately unsuccessful and led only to ring cleaved products. In the second approach, an alkynyl indene substrate bearing a cyano substituent was utilized, which was effective in providing a functional handle to access the icetexone subclass of diterpenoids. A key epoxide opening/diazene rearrangement sequence was utilized to complete a formal synthesis of icetexone and *epi*-icetexone, which is discussed in detail. Furthermore, the cyano-containing substrate has been prepared in enantioenriched form using a Rh-catalyzed conjugate addition reaction, which now provides a route to the enantioselective synthesis of these natural products.

Keywords

Icetexanes; Total synthesis; Ga(III) cycloisomerization; Cycloheptadienes; Diterpenes; Enantioselective conjugate addition

1. Introduction

The icetexane family of diterpenoids is a diverse group of natural products that exhibit a unique structural skeleton and a wide range of biological activity (see Fig. 1). Members of this diterpenoid family possess a [6-7-6] tricyclic motif, which has the systematic name 9(10–20)-*abeo*-abietane. Congeners vary by the level of oxidation in each ring and the degree of oxygenation of the arene portion. In a recent review, a classification scheme was proposed that divided this family into five groups on the basis of the oxygenation at the C3, C11, C12, and C14 positions (see Fig. 1 for numbering).¹ Of these groups, the icetexones are the most complex, exhibiting oxygenation at the C11, C12, and C14 positions, as well as possessing a lactone or ether linkage between C19 and either the C10 or C6 position. Members of the highly oxygenated icetexone subclass have been isolated from different plants of the *Salvia* genus. Icetexone (**1**) was the first compound in this family to be isolated and characterized from the aerial parts of *Salvia ballotaeflora* Benth in 1976 along with the *ortho*-quinone tautomer, romulogarzone (**3**).² X-ray crystallographic analysis enabled a

determination of the absolute configuration of **1**, the name of which has been used to represent this family of natural products.³ Other members of the icetexone subclass, such as 7,20-dihydroanastomosine (**4**), 19-deoxyisoicetexone (**5**), and 19-deoxyicetexone (**6**) have subsequently been isolated from the same source.⁴

In 2000, Nieto et al. reported the isolation of *epi*-icetexone (**2**) from the aerial parts of *Salvia gillessi* Benth and later, Sanchez et al. reported activity of this compound against *Trypanosoma cruzi* (IC₅₀ of 6.5±0.75 µM).⁵ The trypanocidal activity of these diterpenoids has been postulated to arise from a redox cycling process of the quinone moiety, a structural motif that is shared with other trypanocidal agents.⁶ Of note, in the account pertaining to the biological activity of **2**, Sanchez et al. reported the spectral data for isolated *epi*-icetexone, which matches the data for synthetic icetexone (and not synthetic *epi*-icetexone) reported by Majetich.⁷ As such, the Nieto et al. report on the isolation of these compounds may have switched the assignment of the two structures and therefore the reported biological activity for *epi*-icetexone may in fact be that of icetexone.

The biological activity and interesting structures of the icetexone subclass have garnered interest from the synthetic community. Majetich and Grove completed the first enantioselective syntheses of icetexone, *epi*-icetexone, and 19-deoxyicetexone in 2009 using a 'cyclialkylation' strategy to form the [6-7-6] tricyclic core.⁷ As noted above, the Majetich synthesis led to reassignment of the spectral data reported in the literature for both icetexone and *epi*-icetexone. In 2010, we reported formal syntheses of racemic icetexone and *epi*-icetexone.⁸ In this full account, we present the details of our studies that led to formal syntheses of icetexone and *epi*-icetexone as well as the development of a route that accomplishes the formal enantioselective syntheses of these natural products.

Our foray into the synthesis of the icetexone family began with the development of a Ga(III)-catalyzed cycloisomerization reaction of alkynyl indenenes (e.g., **9**, Scheme 1B) to form benzannulated cycloheptadienes (e.g., **10**). This transformation was inspired by a report from Chatani and Murai on the Ga(III)-catalyzed skeletal reorganization of enyne substrates that appeared in 2002 (Scheme 1A).⁹ By using an appropriate tether for our substrates, a [6-7-6] tricyclic motif could be synthesized selectively and efficiently. Other transition metal salts and complexes commonly utilized for the cycloisomerization of enynes (e.g., PtCl₂, PtCl₄, [Ru(CO)₃Cl]₂, [Rh(CO)₂Cl]₂)¹⁰ led to the competing formation of a [7-5-6] tricyclic isomer (e.g., **11**). These isomeric byproducts, as well as the starting material, are difficult to separate from the desired products and so it was important that the cycloisomerization reaction was highly selective and proceeded to completion. This demanding criteria was met by the Ga(III) salts that we employed as catalysts. Our initial reports in this area demonstrated that various arene substitution patterns and a *gem*-dimethyl group on the alkyl tether were well tolerated. The selectivity observed in the formation of the benzannulated cycloheptadiene products utilizing substrates with varying substitution on the benzenoid portion of the indene substrate demonstrated that transposition of the indene double bond (which would ultimately lead to isomeric products) was not a significant competing process. This methodology was subsequently applied to the total synthesis of several members of the icetexane diterpenoid family.¹¹

As outlined in Scheme 2, with icetexone as the target, we envisioned a similar strategy for the synthesis of the highly oxygenated icetexone subclass of the icetexane diterpenoids. This reasoning led to our first approach to icetexone and *epi*-icetexone, which would capitalize on substrates closely related to others that we had prepared previously.

2. Results and discussion

2.1. A first approach to icetexone and *epi*-icetexone

Retrosynthetically (Scheme 2), icetexone (**1**) could arise from lactone **12** by a concluding oxidation of the hydroquinone moiety to the corresponding quinone as well as cleavage of the lactone ring in **12** and a translactonization. Lactone **12** would be formed from oxime **13** or the corresponding aldehyde, which could be oxidized to the carboxylic acid. Specifically, lactone **12** would arise from the acid derived from oxime **13** using a Mitsunobu displacement to forge the lactone. The oxime (**13**) was envisioned to be accessible from alcohol **14** using a Barton nitrite ester reaction.^{12a} This classical and powerful C–H functionalization method has been used previously for the functionalization of a range of remote C–H bonds in complex molecule synthesis.^{12b} The hydroxy group of alcohol **14** could be installed through an epoxidation of the tetrasubstituted double bond of diene **15**, isomerization to the corresponding dihydrofuran, and hydroboration of the resulting alkene from the α -face. Cycloheptadiene **15** could be obtained from **16** using the Ga(III)-catalyzed cycloisomerization method.

To arrive at alkynyl indene **16**, indanone **21** (Scheme 3) was first prepared. This commenced with known alcohol **17**,^{8,13} which was converted to aldehyde **18** using Parikh–Doering oxidation conditions. Aldehyde **18** was subsequently subjected to Horner–Wadsworth–Emmons conditions to provide α,β -unsaturated ester **19**. Hydrogenation of **19** (H₂, Pd/C) followed by saponification led to the formation of carboxylic acid **20** in 89% yield over the two steps. Indanone **21** arose from an intramolecular Friedel–Crafts acylation of the acid chloride derived from acid **20**. The overall sequence for the preparation of indanone **21** is robust and can be scaled to prepare 5 g of **21** in one pass.

Formation of α -ketoester **22** (Scheme 4) was accomplished using NaHMDS and Mander's reagent to favor the desired C-alkylation of indanone **21**. Subsequent alkylation of α -ketoester **22** with alkyl iodide **23**^{11a} at 65 °C led to adduct **24** in 66% yield over the two steps.

With α -ketoester **24** in hand, a saponification/decarboxylation protocol was effected to afford indanone **25** (Scheme 5), which underwent reduction using diisobutylaluminum hydride and elimination of the resulting hydroxyl using methanesulfonic anhydride to generate the key alkynyl indene (**16**) in 79% yield over three steps. Utilizing the previously optimized conditions for cycloisomerization established by our group (20 mol % GaCl₃ and 4 Å molecular sieves at 40 °C), cycloheptadiene **15** was formed in 87% yield. With a route to **15** in place, we initiated a survey of conditions to achieve the remote functionalization of one of the geminal methyl groups (C19).

Formation of the substrate for methyl group functionalization (alcohol **26**, Scheme 6) was initiated through selective epoxidation of the tetrasubstituted double bond of diene **15** using *m*-chloroperbenzoic acid (*m*-CPBA), followed by isomerization of the vinyl epoxide to the dihydrofuran. Hydroboration of the resulting dihydrofuran double bond from the α -face afforded hydroxy tetrahydrofuran **26** in 73% yield over the two steps. Although we were able to synthesize the nitrite ester of **26**, an attempted Barton nitrite ester functionalization¹⁴ upon irradiation led only to decomposition products. A second attempt at remote functionalization using a Norrish type II protocol was then undertaken. There was cause for optimism with this procedure because of the existing precedent of Jeger, who has demonstrated the formation of a cyclobutanol product by functionalization of an angular methyl group using a Norrish type II procedure.¹⁵ Synthesis of Norrish substrate **27** was accomplished by oxidation of alcohol **26** to the corresponding ketone followed by epimerization of the C5 stereocenter. However, upon irradiation of ketone **27**, the only

identifiable products appeared to arise from the fragmentation of the seven-membered ring to form trace amounts of aldehyde **28**.

2.2. A second, successful approach to icetexone

The myriad challenges encountered with the remote functionalization strategy led us to devise a new plan to access the icetexone core. We elected to pursue a pre-functionalization of the alkynyl indene cycloisomerization substrate, which would provide a benzannulated cycloheptadiene (e.g., **30**, Scheme 7) already possessing a functional handle at C19. Preliminary studies using a range of alcohol derivatives proved futile, but eventually led to the identification of a cyano group as a masked carboxylic acid group that was tolerated by our cycloisomerization conditions as well as subsequent steps.

In accord with this plan (Scheme 7), icetexone would arise from primary amide **29** by oxygenation of the C10 position and subsequent lactone formation. The amide group could form from hydrolysis of nitrile **30**, which in turn could come from the Ga(III)-cycloisomerization of alkynyl indene **31**. This key substrate could be synthesized by the alkylation of **32** with alkyl iodide **33**. Importantly, the use of a nitrile substrate would extend the scope of the Ga(III)-catalyzed cycloisomerization chemistry to prepare [6-7-6] ring systems. Finally, because **33** possesses a stereocenter that would direct the installation of the two additional stereocenters in **1**, the preparation of alkyl iodide **33** in enantioenriched form would set the stage for an enantioselective synthesis of icetexone and *epi*-icetexone.

The synthesis of alkyl iodide **33** (Scheme 8) commenced with commercially available 3-bromo-1-propanol (**34**). Protection of the hydroxy group with triisopropylsilyl chloride and displacement of the bromide with methyl cyanoacetate in the presence of K₂CO₃ gave **35** in 90% yield over the two steps. Formation of the quaternary center was accomplished using a standard methylation reaction with methyl iodide and a subsequent chemoselective reduction of the ester group in the presence of the nitrile group was achieved with an excess of sodium borohydride to provide alcohol **36**. Oxidation of the alcohol group using Swern conditions followed by an Ohira–Bestmann homologation¹⁶ gave rise to alkyne **37** in 85% yield over the two steps. Finally, deprotection of the primary alcohol followed by mesylation and displacement of the mesylate with sodium iodide completed the synthesis of alkyl iodide **33**. Using this scalable sequence, 25 g of iodide **33** can be routinely prepared in one pass.

Synthesis of the desired cycloisomerization substrate (**31**, Scheme 9) commenced with a Claisen condensation of indanone **21** with diethyl carbonate to give ketoester **32**. Ketoester **32** underwent alkylation with alkyl iodide **33** to give adduct **38** in 86% yield over the two steps. A saponification/decarboxylation sequence gave rise to indanone **39**, which was reduced with sodium borohydride to afford the indanol as an inconsequential mixture of alcohol diastereomers. Dehydration using KHSO₄ completed the synthesis of alkynyl indene **31** in 63% yield over the latter two steps.

With a route to the key alkynyl indene substrate in hand, several cycloisomerization conditions were surveyed (Table 1). The standard conditions employed in our earlier cycloisomerization studies (entry 1) yielded a mixture of starting material and the desired product in a ratio of 1.36:1.0. It was gratifying to observe only trace decomposition or isomeric byproducts. A study of other Ga(III) salts under the same conditions yielded similar conversion ratios, with GaI₃ faring slightly better (compare entries 1–3). In one experiment, complete conversion of alkynyl indene **31** to cycloheptadiene **30** was achieved using 50 mol % GaI₃ with heating at 65 °C over 4 days (entry 4). The temperature was then increased in an attempt to decrease the catalyst loading and reaction time. At 80 °C, the catalyst loading could be decreased to 25 mol %, and complete conversion was observed

after 4 days (entry 5). Ultimately, it was determined that the reaction time could be decreased to 2 days by heating at 100 °C in toluene (entry 6).

Using the optimized sequence, cycloisomerization of alkynyl indene **31** proceeded in 91% isolated yield to afford cycloheptadiene **30** as the sole product (Scheme 9). Hydrolysis of the tertiary nitrile group was initially attempted using standard acid and base-mediated protocols. However, these proved to be ineffective and either led to no reaction or the non-specific decomposition of the starting material. Perusal of the literature brought to our attention a platinum-based catalyst (see **40**) developed by Ghaffar and Parkins,¹⁷ which accomplishes the conversion of nitrile groups to primary carboxamides in excellent yields under mild conditions. Gratifyingly, hydrolysis of nitrile **30** using Ghaffar and Parkins' platinum complex (**40**) as a catalyst afforded amide **29** in 87% yield.

On the basis of our previous synthetic studies on the icetexane diterpenoid salviasperanol,^{11a} we anticipated that oxygenation at the C10 position of diene **29** could occur through a chemoselective epoxidation of the tetrasubstituted olefin. We were pleased to observe exclusive formation of vinyl oxirane **41** (as a single diastereomer) when diene **29** was treated with *m*-CPBA. Presumably, epoxidation is directed by the amide functional group to the face bearing the amide group. Initial attempts to open the vinyl epoxide moiety of vinyl oxirane **41** included the use of DIBAL and Red-Al®, as well as the use of Pd(0) catalysts in an attempt to form an intermediate π -allyl species. These efforts simply returned the starting material. Also, on the basis of our previous studies, camphorsulfonic acid was expected to effect an acid-catalyzed isomerization of the vinyl epoxide to the corresponding dihydrofuran, but instead, lactone **42** was isolated. This unexpected, yet fortuitous, outcome could arise from opening of the vinyl epoxide under acidic conditions, followed by trapping of an intermediate allylic carbocation by adventitious water and lactonization with the primary amide.

Although lactone **42** was merely a deoxygenation away from a per-methylated precursor to icetexone and *epi*-icetexone, all attempts to directly remove the hydroxy group resident at C5 were unsuccessful. For example, we were unable to transform the hydroxy group to a xanthate group in preparation for a Barton deoxygenation, presumably because of the high steric congestion at C5. An attempted ionic reduction of the allylic alcohol with BF₃·OEt₂ and triethylsilane led only to non-specific decomposition. Because of the potential role of sterics in the lack of reactivity of the hydroxy group of **42**, transposition of the hydroxyl using chromium reagents was attempted, but this also led to decomposition products. A stepwise transposition of the hydroxy group of **42** could be achieved by first hydrogenating the double bond followed by elimination using thionyl chloride, which yielded trisubstituted alkene **43** (Scheme 11). Attempted isomerization of the trisubstituted double bond in alkene **43** into conjugation with the arene only returned starting material. Oxidation of the doubly activated benzylic and allylic position of **43** with manganese triacetate gave a stable peroxide intermediate that could be converted to an alcohol (not shown) using an aluminum/mercury amalgam procedure developed by Yu and Corey.¹⁸

Subjecting the alcohol generated from Mn(OAc)₃/TBHP oxidation of alkene **43** to Myers' reductive allylic alcohol transposition conditions¹⁹ only led to the recovery of the starting material. However, it was reasoned that ionization of the allylic hydroxy group could be possible since a doubly stabilized carbocation would result. Thus, exposure of the alcohol intermediate to acidic conditions in the presence of tosyl hydrazide at elevated temperatures (ca. 80 °C) led to diastereomeric lactones **44** and **45** (**44** as the major product, >10:1 dr). Presumably this occurs by the tosyl hydrazide engaging the incipient carbocation followed by loss of sulfinic acid and an ensuing diazene rearrangement. Comparison of the ¹H NMR

and ^{13}C NMR spectra of **44** to that reported in the literature by Majetich confirmed its structure and thus a formal synthesis of *epi*-icetexone was achieved.

Although our access to **44** as described in Scheme 11 was serviceable, several attempts were made to improve the synthetic route. It was theorized that the ionization of tertiary alcohol **42** could lead directly to the same reactive carbocation intermediate that was presumed to engage the tosyl hydrazide nucleophile. To test this hypothesis, allylic alcohol **42** was exposed to camphorsulfonic acid in the presence of tosyl hydrazide. Gratifyingly, lactone **44** was obtained (Scheme 12), albeit in low yield. This observation eliminated the need to undergo the lengthy and low yielding transposition sequence previously described (see Scheme 11). Furthermore, on the basis of the formation of **42** from a CSA-catalyzed isomerization of epoxide **41**, a one-pot epoxide ring-opening followed by reductive transposition was proposed. Upon subjecting vinyl epoxide **41** to the reaction conditions described previously, a mixture of **44** and **45** (2.5:1 diastereomeric ratio) was obtained, allowing access to both icetexone and *epi*-icetexone, respectively. A brief optimization study established that this transformation could be accomplished in a 42% combined yield of lactones **44** and **45** from vinyl epoxide **41**.

The variability in diastereomeric ratio of lactones **44** and **45** obtained from vinyl oxirane **41** (Scheme 12) as compared to that obtained from allylic alcohol **42** (or alkene **43**, Scheme 11) can be rationalized by the following proposed mechanism (Scheme 13). Acid-catalyzed opening of the vinyl epoxide likely leads to tertiary carbocation **46**, which can be stabilized by the styrenyl double bond. Attack by tosyl hydrazide at the less sterically hindered benzylic position from either face can give rise to intermediate **47**. From this intermediate, a tandem lactone formation and diazene transposition yields lactones **44** and **45**, wherein the stereochemistry at C5 is determined by which face nucleophilic attack occurs from. For allylic alcohol **42** (or alkene **43**), because the lactone is formed prior to tosyl hydrazide attack, there is significant facial control in the addition step.

2.3. Enantioselective formal synthesis of icetexone and *epi*-icetexone

It is evident from our retrosynthetic analysis of icetexone and *epi*-icetexone (Scheme 7) that rendering the synthesis of alkyl iodide **33** enantioselective would complete enantioselective formal syntheses of these natural products given that the single stereocenter in nitrile **33** controls the stereoselectivity during the installation of all additional stereocenters. Our planned approach to enantioenriched nitrile **33** sought to capitalize on the remarkable enantioselective conjugate addition reaction of cyanopropionates (e.g., **49**, Scheme 14) to acrolein (**50**) using Rh(I)-2,2'-bis[1-(diarylphosphino)ethyl]-1,1'-biferrocenes (ArylTRAP) complexes (**51**) as first reported by Sawamura et al.²⁰ In accordance with the protocols developed by Sawamura et al., reacting cyanoester **49** (1 equiv) with acrolein (1.5 equiv) in benzene at 0 °C yielded the conjugate adduct, which was immediately reduced to provide alcohol **52**. The enantiomeric excess of quaternary cyanoester **52** (89% ee)²¹ was determined after its derivatization to the corresponding *p*-nitro benzoate. To convert enantioenriched **52** to alkyl iodide **33**, the hydroxy group was protected with TIPSCl and, the *tert*-butyl ester group could be reduced selectively to the corresponding alcohol in the presence of the nitrile group using sodium borohydride in EtOH/THF (4:1). Swern oxidation of the hydroxy group and alkynylative homologation of the resulting aldehyde using the Ohira–Bestmann protocol gave enantioenriched **37** (not shown in Scheme 14) in good yield. Unveiling the primary alcohol of **37** (with TBAF) set the stage for its replacement with an iodide group via the intermediacy of the mesylate. Enantioenriched **33** obtained in this way provided identical ^1H and ^{13}C NMR spectra as the racemic material that we had prepared previously. Because we began with the (*S,S*)-(*R,R*)-2,2'-bis[1-(diphenylphosphino)ethyl]-1,1'-biferrocene complex (**51**), we wanted to ensure that the

absolute stereochemistry was as is depicted for naturally occurring icetexone and *epi*-icetexone. Thus, using an analogous sequence as described in Schemes 9 and 10, enantioenriched **33** was advanced to tricyclic nitrile **30**. Reduction of the nitrile group using LAH proceeded without event to afford a primary amine, which was derivatized with *p*-bromo benzoyl chloride to give amide derivative **54**. X-ray crystallographic analysis of **54** (see ORTEP in Scheme 14) confirmed the C(4) stereocenter as R, consistent with that found in the natural product, thus completing the formal synthesis of icetexone and *epi*-icetexone.

3. Conclusion

In this article, formal syntheses of icetexone (**1**) and *epi*-icetexone (**2**) that rely on a Ga(III)-catalyzed cycloisomerization to form 6-7-6 fused tricyclic carbocycles was presented. Two distinct approaches were pursued. The first, which entailed attempts to oxygenate the carbocyclic skeleton, involved a remote functionalization strategy that ultimately led to fragmentation of the seven-membered ring. A pre-functionalization approach was then undertaken, and the synthesis of a cyano group-containing tether allowed for a successful Ga(III)-catalyzed alkynyl indene cycloisomerization. Of note, this work served as the first demonstration that a Ga(III)-catalyzed cycloisomerization is possible in the presence of a nitrile group. The presence of this functional handle was exploited in achieving a formal synthesis of icetexone and *epi*-icetexone through a tandem vinyl epoxide opening/diazene rearrangement sequence. Finally, using a Rh-catalyzed enantioselective conjugate addition, the formal enantioselective syntheses of these natural products was achieved.

4. Experimental section

4.1. General experimental details

All reagents were obtained from commercial chemical suppliers and used without further purification unless otherwise noted. All reactions were performed in round-bottomed flasks sealed with rubber septa, under an atmosphere of N₂, and stirred with a TeflonTM-coated magnetic stir bar unless otherwise noted. Temperatures above 23 °C were controlled by an IKA[®] temperature modulator. Pre-dried tetrahydrofuran (THF), benzene, toluene, acetonitrile (MeCN), methanol (MeOH), and triethylamine (Et₃N), were degassed with argon for 60 min and passed through activated alumina columns. Dichloromethane (CH₂Cl₂) was distilled over calcium hydride before use. Reactions were monitored by thin layer chromatography (TLC) using Silicycle SiliaplateTM glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) and *p*-anisaldehyde stain or KMnO₄ stain. Volatile solvents were removed using a rotary evaporator under reduced pressure. Silica gel chromatography was performed using Sorbent Technologies 60 Å, 230×400 mesh silica gel (40–63 μm). ¹H NMR and ¹³C NMR were obtained in CDCl₃ on Bruker 400, 500, or 600 MHz spectrometers with ¹³C operating frequencies of 100, 126, or 151 MHz, respectively. Chemical shifts are reported in parts per million () relative to residual chloroform (7.26 ppm for ¹H and 77.16 ppm for ¹³C). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is designated as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). IR spectra were obtained using a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and reported in frequency of absorption (cm⁻¹). High resolution mass spectral (HRMS) data was obtained from the Mass Spectral facility at the University of California, Berkeley.

4.1.1. 4-Isopropyl-2,3,5-trimethoxybenzaldehyde (18)—To a solution of 4-isopropyl-2,3,5-trimethoxybenzyl alcohol^{8,13} (**17**, 4.09 g, 17.0 mmol) in 4:1 CH₂Cl₂/DMSO (45 mL) at 0 °C were added SO₃-pyr (4.73 g, 29.8 mmol) and Et₃N (11.8 mL, 85 mmol). The resulting mixture was stirred at 0 °C and allowed to warm to rt over 18 h. The reaction

mixture was poured into a mixture of saturated aq NaHCO₃ (25 mL) and water (25 mL), then extracted with Et₂O (3×100 mL). The combined organic layers were washed with saturated aq NaHCO₃ (100 mL), and brine (100 mL), dried over MgSO₄, and concentrated. The crude product was passed through a plug of silica gel to give 3.49 g (14.6 mmol, 86%) of **18** as an orange oil. *R*_f 0.66 (2:1 hexanes/EtOAc); ¹H NMR (600 MHz, CDCl₃) 10.28 (s, 1H), 6.99 (s, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.52 (m, 1H), 1.26 (d, *J*=7.2 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃) 189.2, 155.0, 152.0, 151.5, 138.8, 127.3, 103.1, 62.3, 60.9, 55.6, 25.7, 20.7; IR (film) _{max} 2959, 1688, 1595, 1465, 1414, 1384, 1348, 1273, 1235, 1208, 1136, 1063, 1024 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₈O₄ ([M]⁺): *m/z* 238.1205, found 238.1205.

4.1.2. Ethyl(4-isopropyl-2,3,5-trimethoxy)cinnamate (**19**)—Triethyl

phosphonoacetate (3.19 mL, 16.1 mmol) was added to a solution of **18** (3.49 g, 14.6 mmol) and LiCl (643 mg, 15.2 mmol) in CH₃CN (52 mL) under N₂ at 0 °C. After the addition of DBU (2.40 mL, 16.1 mmol), the resulting mixture was allowed to warm to rt and was stirred for 13 h. The mixture was poured into water (100 mL) and extracted with CHCl₃ (3×50 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, and concentrated. Flash chromatography (9:1 hexanes/EtOAc) gave 3.95 g (12.8 mmol, 88%) of **19** as a thick yellow oil. *R*_f 0.48 (4:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) 7.92 (d, *J*=16.1 Hz, 1H), 6.73 (s, 1H), 6.43 (d, *J*=16.1 Hz, 1H), 4.24 (q, *J*=7.1 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.53–3.46 (m, 1H), 1.31 (t, *J*=7.1 Hz, 3H), 1.28 (d, *J*=7.1 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) 167.6, 155.1, 152.6, 147.5, 139.7, 134.1, 126.1, 118.7, 104.3, 61.6, 61.2, 60.7, 55.9, 25.8, 21.4, 14.7; IR (film) _{max} 2958, 1713, 1633, 1471, 1410, 1346, 1284, 1230, 1175, 1134, 1055, 1026 cm⁻¹; HRMS (ESI) calcd for C₁₂H₂₅O₅ ([M+H]⁺): *m/z* 309.1697, found 309.1701.

4.1.3. 4-Isopropyl-2,3,5-trimethoxydihydrocinnamic acid (**20**)—A mixture of **19**

(2.83 g, 9.18 mmol) and 10% Pd/C (283 mg) in EtOH (95%, 30 mL) was placed under an atmosphere of H₂ (balloon) and stirred rapidly at rt for 12 h. The mixture was then filtered through Celite and concentrated to give 2.53 g (8.15 mmol, 89%) of a light yellow oil, which was used without further purification. To a solution of ethyl(4-isopropyl-2,3,5-trimethoxy)dihydrocinnamate (3.96 g, 12.8 mmol) in 3:1 THF/water (60 mL) was added LiOH·H₂O (1.34 g, 31.9 mmol). The resulting mixture was stirred at rt for 18 h. The mixture was acidified with 1 N HCl (50 mL) and extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, and concentrated to give 3.6 g (12.8 mmol, 100%) of **20** as a thick yellow oil, which was used without further purification. *R*_f 0.45 (2:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) 6.45 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.47 (m, 1H), 2.92 (t, *J*=7.8 Hz, 2H), 2.68 (t, *J*=7.8 Hz, 2H), 1.29 (d, *J*=7.1 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) 179.3, 154.4, 151.7, 145.3, 130.8, 128.9, 107.5, 60.6, 60.4, 55.7, 34.8, 25.5, 25.0, 21.2; IR (film) _{max} 2956, 2835, 1710, 1603, 1578, 1452, 1409, 1340, 1286, 1231, 1130, 1072, 1028 cm⁻¹; HRMS (EI) calcd for C₁₅H₂₂O₅ ([M]⁺): *m/z* 282.1467, found 282.1463.

4.1.4. 6-Isopropyl-4,5,7-trimethoxy-1-indanone (**21**)—To a flask containing **20** (1.43

g, 5.06 mmol) in CH₂Cl₂ (16 mL) under N₂ at 0 °C was added oxalyl chloride (0.44 mL, 5.06 mmol), followed by DMF (3 drops) after 20 min. After stirring at 0 °C for 2 h, the resulting solution was warmed to rt. The resulting solution was then added to a suspension of AlCl₃ (1.35 g) in CH₂Cl₂ (8 mL) at 0 °C slowly via syringe. After stirring for 1 h, the mixture was poured into ice-water in a separatory funnel and diluted with 1 N HCl (25 mL) and CH₂Cl₂ (25 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2×25 mL). The combined organic layers were washed with 1 N NaOH (25 mL), dried over MgSO₄, and concentrated to give 1.18 g (4.46 mmol, 88%) of **21** as a thick light

yellow syrup, which was used without further purification. R_f 0.51 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, CDCl_3) 3.94 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.52 (m, 1H), 3.06–2.99 (m, 2H), 2.68–2.60 (m, 2H), 1.31 (d, $J=7.1$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) 203.5, 158.4, 153.7, 147.9, 146.1, 134.9, 125.5, 62.8, 61.1, 60.4, 37.3, 25.7, 22.5, 22.1; IR (film) ν_{max} 2936, 1708, 1583, 1470, 1418, 1320, 1274, 1136, 1060, 1035 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{21}\text{O}_4$ ($[\text{M}]^+$): m/z 264.1366, found 264.1362.

4.1.5. 2-(Carbomethoxy)-2-(4',4'-dimethyl-5'-hexynyl)-6-isopropyl-4,5,7-trimethoxy-1-indanone (24)—To a flask containing sodium bis(trimethylsilyl)amide (1.0 M in THF, 6.06 mL, 6.06 mmol) in THF (12 mL) under N_2 at -78°C was added a solution of **21** (641 mg, 2.43 mmol) in THF (8 mL) over 2 min. After 45 min at -78°C , the resulting bright orange solution was treated with methyl cyanofomate (0.21 mL, 2.67 mmol). The mixture was stirred at -78°C for 15 min, then poured into water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO_4 , and concentrated to give a dark yellow oil, which was used immediately without further purification. To a solution of the crude α -ketoester (**22**, 783 mg, 2.43 mmol) in acetone (10 mL) in a Schlenk flask was added K_2CO_3 (1.01 g, 7.28 mmol), and the resulting suspension was stirred at rt for 15 min. A solution of **23**^{11a} (573 mg, 2.43 mmol) in acetone (6 mL) was added, and the flask was evacuated and backfilled with N_2 ($3\times$). The flask was sealed and heated to 65°C for 40 h. After cooling to rt, the mixture was diluted with water (30 mL) and extracted with Et_2O (3×30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over MgSO_4 , and concentrated. Flash chromatography (9:1 to 4:1 hexanes/EtOAc) gave 689 mg (1.60 mmol, 66% over two steps) of **24** as a viscous pale yellow syrup. R_f 0.59 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, CDCl_3) 3.93 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H), 3.60 (d, $J=17.5$ Hz, 1H), 3.48 (septet, $J=7.1$ Hz, 1H), 2.95 (d, $J=17.5$ Hz, 1H), 2.15–2.06 (m, 1H), 2.00 (s, 1H), 1.83–1.73 (m, 1H), 1.48–1.32 (m, 4H), 1.28 (d, $J=7.1$ Hz, 6H), 1.14 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) 198.3, 171.6, 158.6, 154.0, 145.3, 145.0, 134.8, 122.9, 91.4, 67.8, 62.3, 61.1, 60.6, 60.1, 52.6, 43.1, 35.2, 32.7, 30.9, 29.1, 29.0, 25.3, 21.6, 20.6; IR (film) ν_{max} 3290, 2963, 2872, 1746, 1709, 1582, 1471, 1420, 1323, 1275, 1200, 1172, 1136, 1039 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{34}\text{O}_5$ ($[\text{M}]^+$): m/z 430.2355, found 430.2351.

4.1.6. 2-(4',4'-Dimethyl-5'-hexynyl)-6-isopropyl-4,5,7-trimethoxyindene (16)—To a solution of **24** (1.88 g, 4.37 mmol) in 3:1 THF/water (20 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (916 mg, 21.8 mmol). The resulting mixture was heated at 65°C for 16 h in a sealed tube under N_2 . After cooling to rt, the reaction mixture was acidified with 1 N HCl (40 mL) and extracted with Et_2O (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO_4 , and concentrated to give **25** as a light yellow oil, which was used without further purification, R_f 0.64 (2:1 hexanes/EtOAc). To a solution of the **25** (1.63 g, 4.37 mmol) in CH_2Cl_2 (35 mL) under N_2 at 0°C was added diisobutylaluminum hydride (1.0 M in toluene, 5.28 mL, 5.28 mmol) dropwise over 5 min. The resulting solution was stirred at 0°C for 30 min and then quenched by the addition of an aq solution of Rochelle's salt (4.47 g in 40 mL water). The resulting biphasic mixture was allowed to warm to rt and stirred vigorously for 1 h before it was diluted with water (40 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO_4 , and concentrated to give a pale yellow oil, which was used immediately without further purification, R_f 0.40 (4:1 hexanes/EtOAc). To a solution of the crude indanol (1.63 g, 4.37 mmol) and Et_3N (1.84 mL, 13.2 mmol) in benzene (30 mL) was added methanesulfonic anhydride (1.53 g, 8.81 mmol). The resulting mixture was stirred at rt for 35 min before it was poured onto water (40 mL) and extracted with Et_2O (3×40 mL). The combined organic layers were washed with saturated aq NaHCO_3 (40 mL), and brine (40

mL), dried over MgSO₄, and concentrated. Flash chromatography (20:1 hexanes/EtOAc) to give 1.23 g (3.45 mmol, 79% over three steps) of **16** as a viscous pale yellow oil. *R*_f 0.57 (4:1 hexanes/EtOAc); ¹H NMR (400 MHz, CDCl₃) 6.61 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.50 (septet, *J* = 7.1 Hz, 1H), 3.35 (s, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.11 (s, 1H), 1.86–1.73 (m, 2H), 1.51–1.43 (m, 2H), 1.37 (d, *J* = 7.1 Hz, 6H), 1.24 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) 148.5, 148.4, 146.9, 145.5, 133.9, 133.1, 133.0, 122.8, 91.7, 67.9, 61.8, 60.9, 59.6, 42.6, 38.7, 31.3, 30.9, 29.1, 25.7, 24.6, 22.1; IR (film) _{max} 3288, 2963, 2937, 2870, 2831, 2107, 1467, 1419, 1338, 1278, 1213, 1121, 1058, 1042, 999, 980, 918, 834 cm⁻¹; HRMS (EI) calcd for C₂₃H₃₂O₃ ([M]⁺): *m/z* 356.2351, found 356.2350.

4.1.7. 8-Isopropyl-6,7,9-trimethoxy-1,1-dimethyl-2,3,4,5-tetrahydro-1H-

dibenzo[a,d][7]annulene (15)—In an N₂ dry box, a Schlenk flask was charged with GaCl₃ (122 mg, 0.69 mmol) and powdered 4 Å molecular sieves (244 mg). The flask was removed from the dry box and a solution of **16** (1.23 g, 3.45 mmol) in freshly distilled benzene (85 mL) was added via syringe under N₂ to give a dark red solution. The flask was sealed and placed in an oil bath that was preheated to 40 °C. After being stirred at 40 °C for 24 h, the mixture was allowed to cool to rt and the sieves were removed by filtration through a plug of glass wool. The filtrate was poured onto a solution of saturated aq NaHCO₃ (50 mL) and extracted with Et₂O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, and concentrated to give a viscous dark yellow syrup. Flash chromatography (30:1 hexanes/EtOAc) gave 1.07 g (3.00 mmol, 87%) of **15** as a viscous pale yellow oil, which crystallized to a white solid on standing at rt. *R*_f 0.66 (4:1 hexanes/EtOAc); mp 101.1–102.0 °C; ¹H NMR (500 MHz, CDCl₃) 7.12 (d, *J* = 12.0 Hz, 1H), 6.66 (d, *J* = 12.0 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.69 (s, 3H), 3.49 (septet, *J* = 7.0 Hz, 1H), 2.97 (br s, 2H), 2.36 (t, *J* = 5.9 Hz, 2H), 1.69–1.59 (m, 2H), 1.51–1.42 (m, 2H), 1.37 (d, *J* = 7.1 Hz, 6H), 1.08 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 152.4, 151.2, 145.4, 136.5, 132.5, 132.3, 131.5, 129.6, 126.6, 125.4, 61.6, 60.7, 60.3, 38.9, 33.4, 32.27, 32.26, 29.1, 25.6, 22.2, 19.6; IR (film) _{max} 2933, 2868, 2827, 1580, 1454, 1400, 1341, 1315, 1120, 1101, 1061, 1047, 996, 969, 740 cm⁻¹; HRMS (EI) calcd for C₂₃H₃₂O₃ ([M]⁺): *m/z* 356.2351, found 356.2351.

4.1.8. 8-Isopropyl-6,7,9-trimethoxy-1,1-

dimethyl-1,2,3,4,5,10,11,11a-octahydro-4a,10-epoxydibenzo[a,d][7]annulene-11-ol (26)—A mixture of cycloheptadiene **15** (229 mg, 0.64 mmol) and NaHCO₃ (108 mg, 1.28 mmol) in CH₂Cl₂ (6.4 mL) at 0 °C was treated with *m*-chloroperbenzoic acid (77%, 173 mg, 0.77 mmol). The resulting mixture was stirred at 0 °C for 1 h before it was quenched by the addition of saturated aq. NaHSO₃ (7 mL). The mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with saturated aq. NaHCO₃ (2 × 15 mL), and brine (15 mL), dried over MgSO₄, and concentrated. Flash chromatography (20:1 hexanes/EtOAc) gave 174 mg (0.47 mmol, 73%) of the dihydrofuran as a viscous colorless oil. *R*_f 0.50 (4:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) 6.06 (d, *J* = 1.5 Hz, 1H), 5.47 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.33 (septet, *J* = 7.1 Hz, 1H), 2.94 (d, *J* = 17.3 Hz, 1H), 2.66 (d, *J* = 17.3 Hz, 1H), 2.16–2.07 (m, 1H), 1.83–1.69 (m, 3H), 1.55–1.49 (m, 1H), 1.40–1.34 (m, 1H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 151.3, 150.3, 148.6, 148.5, 131.5, 127.82, 127.78, 125.8, 83.3, 74.8, 62.6, 60.2, 59.4, 40.0, 38.6, 33.8, 30.5, 29.8, 27.5, 25.6, 22.2, 22.0, 19.0; IR (film) _{max} 2936, 2868, 1454, 1411, 1341, 1285, 1244, 1166, 1121, 1092, 1058, 1040, 1018, 1001, 965, 738 cm⁻¹; HRMS (EI) calcd for C₂₃H₃₂O₄ ([M]⁺): *m/z* 372.2301, found 372.2299. To a solution of dihydrofuran (72 mg, 0.19 mmol) in THF (1.5 mL) under N₂ was added a solution of BH₃•THF (1.0 M in THF, 1.54 mL, 1.54 mmol). The resulting solution was stirred at rt for 11 h. After cooling the solution to 0 °C, the excess borane was carefully quenched by slow, dropwise addition of

EtOH (0.54 mL). The resulting mixture was then treated with a solution of NaOH (125 mg, 3.12 mmol) in water (2.19 mL), followed by a solution of H₂O₂ (30% in water, 1.15 mL, 10.2 mmol). After addition was complete, the mixture was allowed to warm to rt and was stirred for 4 h. The reaction mixture was poured onto a 1:1 mixture of NH₄Cl:water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO₄, and concentrated to give 77 mg (0.19 mmol, 100%) of crude alcohol **26** as a colorless oil, which was used without further purification. *R*_f 0.16 (4:1 hexanes/EtOAc); ¹H NMR (600 MHz, CDCl₃) 5.04 (s, 1H), 3.99 (d, *J*=7.3 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.37 (dd, *J*=14.2, 7.1 Hz, 1H), 3.20 (d, *J*=18.3 Hz, 1H), 2.66 (d, *J*=18.3 Hz, 1H), 2.03 (m, 1H), 1.81–1.74 (m, 2H), 1.74–1.70 (m, 2H), 1.70–1.65 (m, 2H), 1.56 (m, 1H), 1.33 (d, *J*=7.1 Hz, 3H), 1.31 (d, *J*=7.1 Hz, 3H), 1.07 (s, 3H), 0.94 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) 151.2, 148.2, 147.3, 132.5, 128.2, 124.7, 82.1, 80.5, 79.3, 68.8, 62.7, 60.2, 59.5, 41.1, 40.8, 33.3, 33.1, 31.1, 25.7, 22.2, 22.0, 21.1, 20.2; IR (film) ν_{max} 3422, 2938, 2870, 1646, 1456, 1415, 1360, 1341, 1284, 1173, 1123, 1071, 1042, 1013 cm⁻¹; HRMS (EI) calcd for C₂₃H₃₄O₅ ([M]⁺): *m/z* 390.2406, found 390.2411.

4.1.9. 8-Isopropyl-6,7,9-trimethoxy-1,1-dimethyl-1,3,4,5,10,11a-hexahydro-4a,10-epoxydibenzo[a,d][7]annulen-11(2H)-one (27)—To a solution of the alcohol **26** (82 mg, 0.21 mmol) in CH₂Cl₂ (4.2 mL) were added NaHCO₃ (53 mg, 0.63 mmol) and Dess–Martin periodinane (106 mg, 0.25 mmol) at rt. After 1 h, the mixture was poured onto saturated aq Na₂SO₃ (8 mL) and extracted with EtOAc (3×16 mL). The combined organic layers were washed with saturated aq NaHCO₃ (2×16 mL) and brine (16 mL), dried over MgSO₄, and concentrated to give 62 mg (0.16 mmol, 76%) of a yellow oil. To a solution of the crude *cis*-fused ketone (62 mg, 0.16 mmol) in 3:1 MeOH/CH₂Cl₂ (2.0 mL) was added sodium methoxide (9.6 mg, 0.18 mmol). The resulting pale yellow solution was stirred at rt for 21 h before it was poured onto a 1:1 mixture of water/saturated aq NH₄Cl (20 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO₄, and concentrated to give a colorless oil. Flash chromatography (20:1 hexanes/EtOAc) gave 53 mg (0.14 mmol, 88%) of ketone **27** as a colorless oil. *R*_f 0.64 (2:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) 5.16 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.36 (m, 1H), 2.90 (d, *J*=18.1 Hz, 1H), 2.43 (d, *J*=18.0 Hz, 1H), 2.13–2.06 (m, 1H), 1.91–1.81 (m, 1H), 1.88 (s, 1H), 1.69–1.60 (m, 1H), 1.59–1.48 (m, 2H), 1.32 (d, *J*=7.1 Hz, 3H), 1.29 (d, *J*=7.1 Hz, 3H), 1.29–1.23 (m, 1H), 1.16 (s, 3H), 1.06 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 213.2, 152.5, 149.9, 147.5, 133.7, 125.5, 123.2, 79.7, 75.2, 63.5, 60.1, 59.4, 59.0, 40.0, 37.5, 35.1, 32.8, 31.8, 25.8, 22.8, 22.0, 21.9, 17.4; IR (film) ν_{max} 2952, 2872, 2838, 1749, 1459, 1414, 1345, 1271, 1250, 1174, 1121, 1067, 1040, 961, 836, 795, 737 cm⁻¹; HRMS (EI) calcd for C₂₃H₃₂O₅ ([M]⁺): *m/z* 388.2250, found 388.2246.

4.1.10. Methyl 2-cyano-5-(triisopropylsilyloxy)pentanoate (35)—To a solution of 3-bromo-1-propanol (**34**, 20.0 mL, 230 mmol) in CH₂Cl₂ (575 mL) were added imidazole (39.0 g, 575 mmol) and triisopropylsilyl chloride (59.0 mL, 276 mmol). The cloudy reaction mixture was stirred at rt for 12 h. The solution was poured into water (500 mL) and extracted with CH₂Cl₂ (2×500 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO₄, and concentrated to give of a colorless oil that was used without purification. To a solution of (3-bromopropoxy)triisopropylsilane (67.5 g, 230 mmol) in DMF (460 mL) were added K₂CO₃ (95.0 g, 690 mmol) and methyl cyanoacetate (40 mL, 3460 mmol) at rt. The flask was fitted with a reflux condenser, then heated to 65 °C for 1 h. After cooling to rt, the mixture was diluted with water (500 mL) and extracted with Et₂O (3×100 mL). The combined organic layers were washed with brine (1500 mL), dried over MgSO₄, and concentrated to give a thick yellow oil. Flash chromatography (9:1 hexanes/EtOAc) gave 64.8 g (207 mmol, 90% over two steps) of **35** as a clear oil. *R*_f 0.68 (2:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) 3.85 (s, 3H), 3.79 (m, 2H), 3.69 (dd,

$J=8.4, 5.9$ Hz, 1H), 2.12 (m, 2H), 1.81–1.72 (m, 2H), 1.08 (m, 21H); ^{13}C NMR (126 MHz, CDCl_3) 167.1, 116.9, 62.6, 37.6, 30.1, 18.4, 18.1, 12.7, 12.3; IR (film) max 2943, 2867, 1754, 1463, 1250, 1110, 1013 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{32}\text{NO}_3\text{Si}$ ($[\text{M}+\text{H}]^+$): m/z 314.2146, found 314.2143.

4.1.11. 2-(Hydroxymethyl)-2-methyl-5-(triisopropylsilyloxy)pentanenitrile (36)

—To a solution of **35** (64.8 g, 207 mmol) in DMF (400 mL) was added NaH (60% in mineral oil, 9.89 g, 248 mmol) portion-wise, followed by methyl iodide (25.7 mL, 414 mmol) at rt. The reaction mixture was stirred for 1 h, after which the reaction was quenched with water (500 mL) then extracted with Et_2O (3×500 mL). The combined organic layers were washed with water (500 mL) and brine (300 mL), dried over MgSO_4 , and concentrated to give 67.8 g (207 mmol, 100%) of a clear oil, which was used without further purification. R_f 0.54 (4:1 hexanes/ EtOAc); ^1H NMR (500 MHz, CDCl_3) 3.81 (s, 3H), 3.71 (t, $J=5.9$ Hz, 2H), 2.08–2.00 (m, 1H), 1.93–1.85 (m, 1H), 1.79–1.69 (m, 1H), 1.60 (s, 3H), 1.63–1.55 (m, 1H), 1.04 (m, 21H). To a solution of the ester (68.7 g, 207 mmol) in 14:1 THF/water (690 mL) was added NaBH_4 (39.0 g, 1.03 mol) at rt. After stirring for 3 h, saturated aq NH_4Cl (300 mL) was added slowly at 0 °C. The mixture was stirred until gas evolution ceased. The reaction mixture was extracted with Et_2O (3×500 mL) and the combined organic layers were washed with saturated aq NaHCO_3 (300 mL), and brine (300 mL), dried over MgSO_4 , and concentrated to give 62 g (207 mmol, 100%) of **36** as a colorless oil, which was used immediately without purification. R_f 0.47 (2:1 hexanes/ EtOAc); ^1H NMR (500 MHz, CDCl_3) 3.77 (t, $J=5.8$ Hz, 2H), 3.67 (m, 2H), 2.04 (t, $J=6.7$ Hz, 1H), 1.90–1.76 (m, 1H), 1.67–1.59 (m, 3H), 1.38 (s, 3H), 1.09 (m, 21H); ^{13}C NMR (151 MHz, CDCl_3) 123.2, 68.0, 62.8, 39.4, 32.0, 28.0, 21.0, 18.0, 11.9; IR (film) max 3454, 2943, 2866, 1463, 1383, 1106, 1069 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{13}\text{H}_{26}\text{NO}_2\text{Si}$ ($[\text{M}-\text{C}_3\text{H}_7]^+$): m/z 256.1733, found 256.1737.

4.1.12. 2-Ethynyl-2-methyl-5-(triisopropylsilyloxy)pentanenitrile (37)—To a solution of anhydrous DMSO (31.0 mL, 436 mmol) in CH_2Cl_2 (500 mL) was added oxalyl chloride (18.3 mL, 218 mmol) under N_2 at -78 °C. After stirring for 120 min, a solution of **36** (32.5 g, 109 mmol) in CH_2Cl_2 (100 mL) was added at -78 °C via cannula. After an additional 4 h, Et_3N (121 mL, 872 mmol) was added at -78 °C. The resulting mixture was allowed to warm to rt and stirred for 12 h and then poured into a mixture of saturated aq NH_4Cl (300 mL) and water (300 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×500 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO_4 , and concentrated to give a yellow oil, which was taken on immediately without further purification. To a solution of the crude aldehyde (32.4 g, 109 mmol) in MeOH (600 mL) were added K_2CO_3 (30.1 g, 218 mmol) and the Ohira–Bestmann reagent (23.0 g, 120 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was poured into a mixture of saturated aq NaHCO_3 (150 mL) and water (150 mL), and extracted with Et_2O (3×500 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO_4 , and concentrated to give a yellow oil. Flash chromatography (9:1 hexanes/ EtOAc) gave 27.4 g (93 mmol, 85% over two steps) of **37** as a light yellow oil. R_f 0.67 (EtOAc); ^1H NMR (500 MHz, CDCl_3) 3.79 (t, $J=5.5$ Hz, 2H), 2.40 (s, 1H), 1.99–1.81 (m, 4H), 1.68 (s, 3H), 1.08 (m, 21H); ^{13}C NMR (126 MHz, CDCl_3) 120.8, 81.4, 72.4, 62.8, 38.2, 31.5, 29.4, 27.6, 18.4, 12.3; IR (film) max 3312, 2943, 2866, 1463, 1382, 1367, 1240, 1107, 1070, 1014 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{31}\text{NOSi}$ ($[\text{M}+\text{H}]^+$): m/z 294.2248, found 294.2259.

4.1.13. 2-Ethynyl-5-iodo-2-methylpentanenitrile (33)—To a solution of **37** (27.4 g, 93 mmol) in THF (370 mL) was added *tert*-butylammonium fluoride (1.0 M in THF, 112 mL) at rt. After stirring for 12 h, the reaction mixture was poured into saturated aq NaHCO_3

(300 mL) and extracted with Et₂O (3×300 mL), the combined organic layers were washed with brine (200 mL), dried over MgSO₄, and concentrated to give a crude colorless oil. Flash chromatography (2:1 hexanes/EtOAc) gave 9.79 g (71 mmol, 76%) of the alcohol as a colorless oil. To a solution of resulting alcohol (9.79 g, 71 mmol) in CH₂Cl₂ (280 mL) was added methanesulfonyl chloride (6.0 mL, 78 mmol) and Et₃N (14.8 mL, 107 mmol) under N₂ at 0 °C. The resulting mixture was allowed to warm to rt. After stirring for 2 h, the reaction mixture was washed with 1 N HCl (150 mL), saturated aq NaHCO₃ (150 mL), and brine (150 mL), dried over MgSO₄, and concentrated to give a light yellow oil that was immediately used without further purification. The resulting mesylate (15.2 g, 71 mmol) was added to a Schlenk flask with acetone (280 mL). NaI (16.0 g, 107 mmol) was added and the flask was sealed and placed in an oil bath preheated to 65 °C. After stirring at 65 °C for 15 h, the mixture was allowed to cool to rt and quenched with water (280 mL). The reaction mixture was extracted with pentane (3×300 mL) and the combined organic layers were washed with brine (200 mL), dried over MgSO₄, and concentrated to give 14.0 g (57 mmol, 80% over two steps) of **27** as a light yellow oil. *R*_f 0.62 (2:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) 3.26 (m, 2H), 2.45 (s, 1H), 2.17 (m, 2H), 1.99–1.86 (m, 2H), 1.69 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) 120.4, 80.8, 73.1, 42.1, 31.0, 29.7, 27.6, 5.0; IR (film) _{max} 3290, 2939, 1451, 1382, 1294, 1253, 1185, 1148 cm⁻¹; HRMS (EI) calcd for C₈H₁₈NI ([M]⁺): *m/z* 246.9858, found 246.9858.

4.1.14. Ethyl 2-(4-cyano-4-methylhex-5-yn-1-yl)-6-isopropyl-4,5,7-trimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (38)—To a flask containing KO^tBu (850 mg, 7.57 mmol) under N₂ were added **21** (1.00 g, 3.78 mmol) and diethyl carbonate (0.97 mL, 7.57 mmol) in THF (19 mL) at rt. The resulting mixture was heated to 70 °C in a flask fitted with a reflux condenser for 30 min. After cooling to rt over 1 h, the mixture was diluted with EtOAc (40 mL) and saturated aq NaHCO₃ (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO₄, and concentrated to give **32** as a thick orange oil that was used without further purification. *R*_f 0.43 (2:1 hexanes/EtOAc). To a solution of the **32** (1.23 g, 3.78 mmol) in acetone (20 mL) were added K₂CO₃ (1.56 g, 11.3 mmol) and **33** (933 mg, 3.78 mmol) in a Schlenk flask at rt. The flask was evacuated and backfilled with N₂ (3×), then sealed and heated at 65 °C for 48 h. After cooling to rt, the mixture was diluted with water (40 mL) and extracted with Et₂O (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO₄, and concentrated. Flash chromatography (9:1 to 4:1 hexanes/EtOAc) gave 1.48 g (3.25 mmol, 86% over two steps) of **38** as a viscous dark orange syrup. *R*_f 0.48 (2:1 hexanes/EtOAc); Mixture of diastereomers (1:1) ¹H NMR (600 MHz, CDCl₃) 4.20–4.07 (m, 4H), 3.93 (s, 6H), 3.84 (s, 6H), 3.84 (s, 6H), 3.60 (d, *J*=17.4 Hz, 1H), 3.58 (d, *J*=17.4 Hz, 1H), 3.52–3.45 (m, 2H), 2.93 (d, *J*=17.4 Hz, 2H), 2.36 (s, 1H), 2.32 (s, 1H), 2.21–2.10 (m, 2H), 1.87–1.67 (m, 6H), 1.55 (m, 4H), 1.59 (s, 6H), 1.28 (d, *J*=3.8 Hz, 12H), 1.20 (t, *J*=7.1 Hz, 6H). ¹³C NMR (151 MHz, CDCl₃) 198.1, 198.0, 170.9, 170.8, 158.8, 154.1, 145.36, 145.35, 144.9, 135.0, 134.9, 122.9, 122.7, 120.1, 120.0, 80.7, 80.6, 72.24, 72.19, 62.3, 62.2, 61.61, 61.57, 60.9, 60.8, 60.6, 60.14, 60.12, 41.0, 34.0, 33.9, 32.7, 31.14, 31.13, 27.13, 27.09, 25.3, 21.6, 21.1, 21.0, 14.0; IR (film) _{max} 3262, 2939, 2873, 1740, 1705, 1582, 1472, 1420, 1322, 1275, 1198, 1136, 1037 cm⁻¹; HRMS (ESI) calcd for C₂₆H₃₃NO₆ ([M+H]⁺): *m/z* 456.2381, found 456.2396.

4.1.15. 2-Ethynyl-5-(6-isopropyl-4,5,7-trimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-methylpentanenitrile (39)—To a solution of **38** (1.04 g, 2.35 mmol) in 3:1 THF/water (12 mL) was added LiOH·H₂O (246 mg, 5.88 mmol). The resulting mixture was heated at 65 °C for 12 h in a sealed flask. After cooling to rt, the reaction mixture was acidified with 1 N HCl (12 mL) and extracted with EtOAc (3×12 mL). The combined

organic layers were washed with brine (12 mL), dried over MgSO_4 , and concentrated to give 774 mg (2.01 mmol, 86%) of crude indanone **39** as a yellow oil, which was used without further purification. R_f 0.48 (2:1 hexanes/EtOAc); Mixture of diastereomers (1:1) ^1H NMR (600 MHz, CDCl_3) 3.95 (s, 6H), 3.92 (s, 6H), 3.88 (s, 6H), 3.57–3.49 (m, 2H), 3.31 (d, $J=8.0$ Hz, 1H), 3.28 (d, $J=8.0$ Hz, 1H), 2.73 (m, 1H), 2.70 (m, 1H), 2.68–2.58 (m, 2H), 2.43 (s, 1H), 2.41 (s, 1H), 2.08–1.97 (m, 2H), 1.91–1.78 (m, 8H), 1.68 (s, 6H), 1.58–1.45 (m, 2H), 1.34 (d, $J=7.1$ Hz, 12H); ^{13}C NMR (151 MHz, CDCl_3) 204.3, 158.2, 153.4, 145.7, 134.7, 124.6, 124.5, 120.3, 80.9, 72.2, 62.41, 62.39, 60.7, 60.1, 47.7, 47.5, 41.0, 40.9, 31.29, 31.26, 31.1, 31.0, 29.1, 29.0, 27.22, 27.18, 25.3, 23.8, 23.5, 21.6; IR (film) $\max$ 3260, 2939, 2871, 1704, 1583, 1470, 1419, 1322, 1273, 1201, 1172, 1138, 1058, 1037 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_4$ ($[\text{M}+\text{H}]^+$): m/z 384.2169, found 384.2188.

4.1.16. 2-Ethynyl-5-(5-isopropyl-4,6,7-trimethoxy-1H-inden-2-yl)-2-methylpentanenitrile (31)—To a solution of indanone **39** (748 mg, 1.95 mmol) in EtOH (10 mL) was added NaBH_4 (74.0 mg, 1.95 mmol) at rt in a water bath to maintain temperature. After 3 h, saturated aq NH_4Cl (30 mL) was added slowly at 0 °C, along with Et_2O (30 mL). The reaction mixture was stirred until bubbling was no longer observed. The layers were separated and the aqueous layer was extracted with Et_2O (2×30 mL). The combined organic layers were washed with saturated aq NaHCO_3 (30 mL) and brine (30 mL), dried over MgSO_4 , and concentrated to give 563 mg (1.45 mmol) of a clear oil, which was used immediately without purification. To a solution of the crude indanol (543 mg, 1.45 mmol) in toluene (7 mL) was added KHSO_4 (191 mg, 1.45 mmol) in a sealed vial. The reaction mixture was heated to 120 °C and stirred for 4 h. After cooling to rt, the reaction mixture was passed through a silica plug with 2:1 hexanes/EtOAc to give 456 mg (1.24 mmol, 63% over two steps) of **31** as a light yellow oil. R_f 0.63 (2:1 hexanes/EtOAc); ^1H NMR (600 MHz, CDCl_3) 6.64 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.51 (m, 1H), 3.37 (s, 2H), 2.59 (t, $J=7.2$ Hz, 2H), 2.43 (s, 1H), 2.05–1.93 (m, 2H), 1.91–1.79 (m, 2H), 1.68 (s, 3H), 1.37 (d, $J=7.1$ Hz, 6H); ^{13}C NMR (151 MHz, CDCl_3) 148.8, 147.1, 147.0, 145.6, 133.6, 133.2, 133.0, 123.6, 120.3, 80.9, 72.2, 62.0, 61.0, 59.8, 40.7, 38.7, 31.3, 30.5, 27.2, 25.7, 24.9, 22.2; IR (film) $\max$ 3275, 2937, 2832, 1460, 1418, 1337, 1278, 1218, 1121, 1057 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_3$ ($[\text{M}+\text{H}]^+$): m/z 368.2220, found 368.2229.

4.1.17. 8-Isopropyl-6,7,9-trimethoxy-1-methyl-2,3,4,5-tetrahydro-1H-dibenzo[a,d][7]annulene-1-carbonitrile (30)—In a N_2 dry box, a Schlenk flask was charged with GaCl_3 (9 mg, 0.05 mmol) and powdered 4 Å molecular sieves (18 mg). The flask was removed from the dry box and a solution of **31** (78 mg, 0.21 mmol) in freshly distilled toluene (2.1 mL) was added via syringe under N_2 to give a dark brown solution. The flask was sealed and placed in an oil bath that was preheated to 100 °C. After stirring at 100 °C for 48 h, the mixture was allowed to cool to rt and the reaction mixture was passed through a silica column with 4:1 hexanes/EtOAc to give 71 mg (0.19 mmol, 91%) of **30** as a viscous yellow oil. R_f 0.48 (4:1 hexanes/EtOAc); ^1H NMR (600 MHz, CDCl_3) 7.27 (d, $J=11.9$ Hz, 1H), 6.66 (d, $J=11.9$ Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H), 3.53–3.41 (m, 1H), 3.10 (s, 1H), 3.00 (s, 1H), 2.50–2.37 (m, 2H), 2.16–2.10 (m, 1H), 1.85–1.78 (m, 1H), 1.74 (m, 2H), 1.49 (s, 3H), 1.39 (d, $J=3.4$ Hz, 3H), 1.38 (d, $J=3.4$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) 153.3, 151.5, 145.7, 136.6, 132.4, 131.2, 129.0, 127.8, 127.3, 125.1, 124.6, 61.9, 60.8, 60.4, 35.6, 35.3, 32.1, 31.1, 26.3, 25.7, 22.09, 22.08, 19.1; IR (film) $\max$ 2937, 2870, 1453, 1417, 1400, 1342, 1316, 1260, 1121, 1060, 1043 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_3$ ($[\text{M}]^+$): m/z 367.2147, found 367.2149.

4.1.18. 8-Isopropyl-6,7,9-trimethoxy-1-methyl-2,3,4,5-tetrahydro-1H-dibenzo[a,d][7]annulene-1-carboxamide (29)—To a solution of cycloheptadiene **30**

(285 mg, 0.780 mmol) in 2:1 EtOH/water (4 mL) was added Pt catalyst **40**¹⁷ (11 mg, 0.03 mmol) in a vial at rt. The vial was sealed and the reaction mixture was heated to 80 °C. After stirring for 4 days, the solvent was removed and CH₂Cl₂ (1 mL) was added. The solution was filtered through a pad of Celite and concentrated to give 260 mg (0.67 mmol, 87%) of **29** as a light yellow oil that was used without further purification. *R*_f 0.25 (2:1 hexanes/EtOAc); ¹H NMR (600 MHz, CDCl₃) 7.18 (d, *J*=11.9 Hz, 1H), 6.54 (d, *J*=11.9 Hz, 1H), 5.36 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.64 (s, 3H), 3.45 (m, 1H), 3.13 (s, 1H), 2.94 (s, 1H), 2.44 (t, *J*=5.9 Hz, 2H), 2.07–1.99 (m, 1H), 1.66 (m, 1H), 1.58–1.52 (m, 2H), 1.35 (s, 3H), 1.33 (d, *J*=7.1 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃) 179.9, 153.2, 151.5, 145.6, 137.1, 132.3, 131.6, 131.1, 129.0, 128.1, 124.8, 61.9, 60.8, 60.3, 46.2, 36.3, 32.2, 31.8, 25.7, 24.2, 22.1, 22.0, 19.6; IR (film) _{max} 3468, 3179, 2935, 2870, 1676, 1581, 1453, 1400, 1378, 1341, 1316, 1260, 1120, 1059, 1042 cm⁻¹; HRMS (ESI) calcd for C₂₃H₃₂NO₄ ([M+H]⁺): *m/z* 386.2326, found 386.2336.

4.1.19. 8-Isopropyl-6,7,9-trimethoxy-1-methyl-2,3,4,5-tetrahydro-1H-4a,11a-epoxydibenzo[a,d][7]annulene-1-carboxamide (41)—A mixture of **29** (260 mg, 0.670 mmol) and NaHCO₃ (113 mg, 0.81 mmol) in CH₂Cl₂ (7 mL) at 0 °C was treated with *m*-chloroperbenzoic acid (70%, 185 mg, 0.810 mmol). The resulting mixture was stirred at 0 °C for 15 min, and then warmed to rt. After stirring for 3 h, the reaction mixture was quenched with saturated aq NaHSO₃ (5 mL). The solution was stirred for 1 h and then extracted with Et₂O (2×10 mL). The combined organic layers were washed with saturated aq NaHCO₃, (3×10 mL), and brine (10 mL), dried over MgSO₄, and concentrated to give 208 mg (0.52 mmol, 78%) of **41** as a clear oil. *R*_f 0.25 (2:1 hexanes/EtOAc); ¹H NMR (400 MHz, CDCl₃) 6.82 (d, *J*=11.6 Hz, 1H), 6.71 (s, 1H), 6.19 (d, *J*=11.6 Hz, 1H), 5.38 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H), 3.56 (d, *J*=13.2 Hz, 1H), 3.47 (m, 1H), 2.32 (d, *J*=13.0 Hz, 1H), 2.15 (m, 2H), 2.06–1.98 (m, 2H), 1.84 (m, 2H), 1.40 (d, *J*=7.1 Hz, 3H), 1.35 (d, *J*=7.1 Hz, 3H), 1.09 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) 178.7, 153.2, 152.2, 147.1, 133.6, 129.1, 128.5, 127.0, 125.5, 64.8, 62.4, 60.5, 60.4, 53.5, 45.2, 35.7, 32.5, 26.4, 25.7, 22.0, 19.9, 16.2; IR (film) _{max} 3461, 2936, 1680, 1454, 1416, 1395, 1340, 1257, 1121, 1044 cm⁻¹; HRMS (ESI) calcd for C₂₃H₃₂O₅ ([M+H]⁺): *m/z* 402.2275, found 402.2281.

4.1.20. 11a-Hydroxy-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4, 5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulene-13-one (42)—To a solution of **41** (190 mg, 0.470 mmol) in CH₂Cl₂ (18 mL) was added camphorsulfonic acid (109 mg, 0.470 mmol) at rt. After 2 h, the reaction mixture was quenched with saturated aq NaHCO₃ (20 mL) and extracted with Et₂O (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated to give 163 mg (0.40 mmol, 86%) of **42** as a white foam that was used without further purification. *R*_f 0.33 (2:1 hexanes/EtOAc); ¹H NMR (600 MHz, CDCl₃) 7.15 (d, *J*=12.6 Hz, 1H), 5.88 (d, *J*=12.6 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.69 (d, *J*=17.0 Hz, 1H), 3.65 (s, 3H), 3.45 (d, *J*=17.0 Hz, 1H), 3.43 (m, 1H), 1.83–1.76 (m, 2H), 1.71–1.65 (m, 3H), 1.65–1.58 (m, 2H), 1.34 (d, *J*=6.7 Hz, 3H), 1.32 (d, *J*=6.7 Hz, 3H), 1.30 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) 179.0, 154.1, 154.0, 148.7, 133.6, 128.1, 127.7, 123.03, 122.96, 85.6, 80.1, 62.8, 60.4, 59.6, 51.9, 31.5, 30.8, 30.6, 26.1, 21.9, 21.8, 18.2, 14.0; IR (film) _{max} 3466, 2932, 2874, 1781, 1653, 1570, 1558, 1507, 1455, 1416, 1397, 1341, 1256, 1123, 1092, 1035 cm⁻¹; HRMS (ESI) calcd for C₂₃H₃₁O₆ ([M+H]⁺): *m/z* 403.2115, found 403.2118.

4.1.21. 8-Isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4,5,10-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulene-13-one (43)—A mixture of **42** (100 mg, 0.25 mmol) and 10% Pd/C (40 mg) in EtOH (1.2 mL) was placed under an atmosphere of H₂ (balloon) and stirred rapidly at rt for 12 h. The mixture was then filtered through Celite and concentrated to give 77 mg (0.19 mmol) of a yellow foam, which was used without

further purification. To a solution of the resulting alcohol (77 mg, 0.19 mmol) in dry pyridine (1.6 mL) was added thionyl chloride (82 μ L, 1.14 mmol) at rt. The solution instantly turned yellow. After 90 min, the reaction mixture was quenched with 1 N HCl (3 mL) and extracted with Et₂O (3 $\times$ 3 mL). The combined organic layers were washed with brine (3 mL), dried MgSO₄, and concentrated to give 45 mg (0.12 mmol, 47% over two steps) of **43** as a yellow oil that was used without further purification. *R*_f 0.53 (2:1 hexanes/EtOAc); ¹H NMR (600 MHz, CDCl₃) 5.50 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.62 (s, 3H), 3.41 (m, 2H), 3.35 (m, 1H), 3.26 (m, 1H), 1.94 (m, 1H), 1.81–1.74 (m, 3H), 1.48–1.39 (m, 3H), 1.34 (d, *J*=4.4 Hz, 3H), 1.33 (d, *J*=4.4 Hz, 3H), 1.19 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) 177.8, 151.3, 150.8, 148.5, 146.7, 133.5, 127.5, 113.3, 84.5, 62.3, 60.3, 60.2, 49.0, 37.0, 30.3, 32.5, 26.0, 24.1, 24.2, 22.2, 22.1, 19.3, 16.3; IR (film) _{max} 2936, 2873, 1779, 1454, 1414, 1381, 1341, 1253, 1122, 1094, 1043, 1033; HRMS (ESI) calcd for C₂₃H₃₀O₅ ([M+H]⁺): *m/z* 387.2166, found 387.2167.

4.1.22. 8-Isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulen-13-one (44+45, from 43)—To a solution of **43** (60 mg, 0.15 mmol) in EtOAc (1.5 mL) were added *tert*-butyl hydrogen peroxide (0.15 mL) and 3 Å molecular sieves (150 mg) at rt. After 30 min, Mn(OAc)₃·H₂O (5 mg, 0.02 mmol) was added at rt and kept in the dark for 18 h. The reaction mixture was filtered through Celite to give 73 mg (0.15 mmol) as a yellow oil that was used without further purification. To a solution of the resulting peroxide (73 mg, 0.15 mmol) in Et₂O (1.5 mL) was added a freshly prepared amalgam from aluminum foil (150 mg) in 2% HgCl₂ solution that was washed with water (1 mL), ethanol (1 mL), and ether (1 mL). The reaction mixture was heated to 40 °C. After 2 h, the reaction mixture was filtered through Celite with Et₂O and concentrated to give 34 mg (0.085 mmol) of a clear oil that was used without further purification. To a solution of the crude alcohol (34.0 mg, 0.085 mmol) in 1,2 dichloroethane (8.5 mL) were added tosyl hydrazide (79 mg) and camphorsulfonic acid (9.8 mg, 0.085 mmol) at rt. The reaction mixture was sealed and heated to 80 °C for 12 h. The reaction mixture was cooled to rt and passed through a pad of Celite. Flash chromatography (4:1 hexanes/EtOAc) gave 10 mg (0.025 mmol, 17% over three steps) of a colorless oil. ¹H NMR analysis showed >10:1 dr with the intermediate leading to *epi*-icetexone (**44**) as the major diastereomer. *R*_f 0.55 (2:1 hexanes/EtOAc); ¹H NMR (600 MHz, CDCl₃) 6.97 (dd, *J*=12.2, 2.8 Hz, 1H), 5.68 (dd, *J*=12.2, 3.1 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.58 (d, *J*=16.4 Hz, 1H), 3.46–3.37 (m, 1H), 3.13 (d, *J*=16.4 Hz, 1H), 2.87 (s, 1H), 1.84–1.76 (m, 1H), 1.70–1.60 (m, 3H), 1.56–1.46 (m, 2H), 1.34 (d, *J*=2.6 Hz, 3H), 1.32 (d, *J*=2.6 Hz, 3H), 1.23 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) 180.1, 153.0, 148.6, 133.6, 127.0, 126.5, 124.7, 122.1, 85.3, 62.3, 60.4, 59.9, 55.4, 47.0, 37.3, 27.4, 27.0, 26.0, 22.0, 21.9, 19.3, 18.9; IR (film) _{max} 2935, 1778, 1451, 1396, 1340, 1254, 1121, 1034; HRMS (ESI) calcd for C₂₃H₃₁O₅ ([M+H]⁺): *m/z* 387.2166, found 387.2176.

4.1.23. 8-Isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulen-13-one (44+45, from 41)—To a solution of **41** (30 mg, 0.08 mmol) in benzene (1.5 mL) were added tosyl hydrazide (74.5 mg, 0.400 mmol) and camphorsulfonic acid (8.70 mg, 0.038 mmol) at rt. The reaction vessel was sealed and brought to 80 °C for 12 h. The reaction mixture was cooled to rt and passed through a pad of Celite. Basic alumina chromatography (4:1 hexanes/EtOAc) gave 12 mg (0.031 mmol, 42%) of **44** and **45** as a colorless oil. ¹H NMR analysis showed 2.5:1 dr with the intermediate leading to *epi*-icetexone (**44**) as the major diastereomer. *R*_f 0.53 (2:1 hexanes/EtOAc); Major diastereomer: ¹H NMR (500 MHz, CDCl₃) 6.97 (dd, *J*=12.2, 3.0 Hz, 1H), 5.68 (m, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.59 (d, *J*=16.4 Hz, 1H), 3.46–3.37 (m, 1H), 3.13 (d, *J*=16.4 Hz, 1H), 2.87 (s, 1H), 1.88–1.74 (m, 2H), 1.64 (m, 4H), 1.34 (d, *J*=2.9 Hz, 3H), 1.33 (d, *J*=2.8 Hz, 3H), 1.24 (s, 3H); Minor diastereomer: ¹H NMR

(500 MHz, CDCl₃) 6.79 (dd, *J*=11.0, 2.4 Hz, 1H), 6.09 (dd, *J*=11.0, 2.4 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 3.42 (m, 1H), 2.72 (m, 1H), 2.44–2.37 (m, 1H), 2.27 (s, 1H), 1.96–1.36 (m, 6H), 1.34 (d, *J*=2.9 Hz, 3H), 1.33 (d, *J*=2.8 Hz, 3H), 1.27 (s, 3H); IR (film) ν_{max} 2935, 1778, 1451, 1396, 1340, 1254, 1121, 1034 cm⁻¹; HRMS (ESI) calcd for C₂₃H₃₁O₅ ([M+H]⁺): *m/z* 387.2166, found 387.2176.

4.1.24. (R)-tert-Butyl 2-cyano-2-methyl-5-(triisopropylsilyloxy)pentanoate (53)

—A solution of *tert*-butyl 2-cyanopropanoate^{20d} (**49**, 2.33 g, 15.0 mmol) in benzene (47 mL) was evacuated and backfilled with N₂ (3×). Acrolein (**50**, 90%, 0.5 mL, 7.5 mmol) was added to the solution via syringe and the mixture was cooled to 0 °C. In a separate flask, Rh(acac)(CO)₂ (128 mg, 0.15 mmol) and (*S,S*)-(R,R)-PhTRAP^{20b} (**51**, 128 mg, 0.16 mmol) were dissolved in 3 mL of benzene, when the bubbling ceased the catalyst solution was added slowly to the reaction mixture via syringe. The resulting mixture was stirred at 0 °C for a 2 h and monitored by TLC. Once the reaction was completed, ethanol (99%, 10 mL) was added to the reaction mixture at 0 °C, NaBH₄ (283 mg, 7.5 mmol) was then slowly added. The reaction was warmed up to rt and stirred for ~3 h. The reaction was quenched with a saturated solution of NH₄Cl (50 mL) and extracted with EtOAc (4 × 30 mL). The combined organic layers were dried over MgSO₄, and concentrated. The crude product was used without further purification. *R_f* 0.40 (6:4 hexanes/EtOAc); ¹H NMR (300 MHz, CDCl₃) 3.68 (t, *J*=5.6 Hz, 2H), 2.07–1.96 (m, 1H), 1.87–1.73 (m, 2H), 1.73–1.61 (m, 1H), 1.56 (s, 3H), 1.50 (s, 9H), 1.22–1.13 (m, 1H). The crude alcohol (**52**) was dissolved in CH₂Cl₂ (50 mL). Imidazole (2.25 g, 33 mmol) and triisopropylsilyl chloride (3.5 mL, 16.5 mmol) were added to the flask and the reaction mixture was stirred at rt. When the reaction was complete by TLC (~4 h), saturated aq NH₄Cl (30 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated. The crude material was purified via flash chromatography (9:1 hexanes/EtOAc) to give 4.32 g (11.7 mmol, 78%) of **53** as a clear oil. The desired product was often isolated along with triisopropyl silanol and it was carried on as is in the following reaction. *R_f* 0.66 (4:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃): 3.71 (t, *J*=5.9 Hz, 2H), 1.99 (td, *J*=12.9, 4.4 Hz, 1H), 1.82 (td, *J*=13.0, 4.3 Hz, 1H), 1.78–1.69 (m, 1H), 1.64–1.57 (m, 1H), 1.54 (s, 3H), 1.48 (s, 9H), 1.09–1.02 (m, 21H); ¹³C NMR (126 MHz, CDCl₃): 168.4, 120.5, 83.7, 62.5, 44.6, 35.2, 28.9, 27.8, 23.3, 18.1, 12.0; IR (film) ν_{max} 2943, 2867, 1739 cm⁻¹; HRMS (ESI) calcd for C₂₀H₃₉O₃ NNaSi ([M+Na]⁺): *m/z* 392.2591, found 392.2594; [α]_D²¹ –33.32 (*c* 1.17, CHCl₃).

4.1.25. (R)-2-(Hydroxymethyl)-2-methyl-5-(triisopropylsilyloxy)pentanenitrile (36)

—To a solution of **53** (4.32 g, 11.7 mmol) in a mixture of ethanol(99%)/THF (4:1, 100 mL, 0.15 M) was added NaBH₄ (2.84 g, 75 mmol). The resulting mixture was stirred at ambient temperature for 18 h. The reaction mixture was cooled to 0 °C and then quenched slowly by addition of a saturated aq NH₄Cl (100 mL). The aqueous layer was extracted with EtOAc (4×30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated. The crude product was purified via flash chromatography (9:1 to 3:2 hexanes/EtOAc) to give 2.82 g (9.41 mmol, 80%) alcohol **36** as a clear oil. The alcohol **36** showed identical NMR data to the previously reported data for the racemic alcohol. *R_f* 0.27 (8:2 hexanes/EtOAc).

4.1.26. (S)-N-((8-Isopropyl-6,7,9-trimethoxy-1-methyl-2,3,4,5-tetra hydro-1H-dibenzo[a,d][7]annulen-1-yl)methyl)-4-bromobenzamide (54)

—To a flame dried Schlenk flask equipped with a stir bar and under N₂ atmosphere was added lithium aluminum hydride (38 mg, 1.0 mmol). Nitrile **30** (79 mg, 0.20 mmol) was added as a solution in anhydrous THF (4 mL). The Schlenk flask was sealed and the reaction was heated to 65 °C for 2 h. The reaction mixture was cooled to rt and slowly quenched by the

addition of powdered $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (~200 mg). The solution was stirred overnight open to air, filter through Celite, wash with EtOAc (50 mL), and concentrated to give 73 mg (0.20 mmol, 100%) of the amine that was used without further purification. The amine (25 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (1.4 mL) and to the solution was added triethylamine (20 μL , 0.14 mmol) followed by the 4-bromobenzoyl chloride (23 mg, 0.11 mmol). The reaction was stirred at ambient temperature and monitored by TLC. When the reaction was completed, the solution was concentrated and loaded directly onto a silica column. The product was purified by flash chromatography (4:1 hexanes/EtOAc) to yield 27 mg (0.05 mmol, 71%) of **54** as a white solid. Slow diffusion crystallization of hexanes into EtOAc provided X-ray quality crystals. R_f 0.60 (2:1 hexanes/EtOAc); mp 148–157 °C; ^1H NMR (600 MHz, CDCl_3) 7.34 (d, $J=8.0$ Hz, 2H), 7.22 (d, $J=11.9$ Hz, 1H), 6.98 (s, 2H), 6.67 (d, $J=11.9$ Hz, 1H), 5.45 (s, 1H), 3.97 (s, 3H), 3.83 (s, 3H), 3.60 (dd, $J=13.2, 8.7$ Hz, 1H), 3.52–3.31 (m, 5H), 3.08 (d, $J=12.7$ Hz, 1H), 2.69 (s, 1H), 2.38 (t, $J=6.1$ Hz, 2H), 1.70–1.60 (m, 2H), 1.47 (t, $J=5.2$ Hz, 2H), 1.29 (d, $J=7.1$ Hz, 3H), 1.28–1.24 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) 165.8, 153.4, 151.6, 145.8, 133.1, 132.7, 132.5, 132.0, 131.9, 128.9, 128.1, 128.0, 126.0, 124.8, 61.7, 61.1, 60.6, 49.4, 38.2, 34.1, 32.7, 32.5, 25.8, 24.1, 22.2, 22.2, 19.3; IR (film) max 3338, 3425, 2931, 2869, 1656, 1590, 1525 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{37}\text{O}_4\text{N}^{79}\text{Br}$ ($[\text{M}+\text{H}]^+$): m/z 554.1900, found 554.1900; $[\alpha]_{\text{D}}^{21} +72.0$ (c 0.65, CHCl_3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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21. Determined using a ChiralPak IC column. For details, see the Supplementary data.

Fig. 1.
Selected icetexone natural products.

A. Chatani and Murai **B. Our proposed variant**

Scheme 1.
Ga(III)-catalyzed cycloisomerization reaction.

Scheme 2.
Retrosynthetic analysis of icetexone (**1**).

Scheme 3.
Synthesis of indanone **21**.

Scheme 4.
Synthesis of adduct **24**.

Scheme 5.
Synthesis of cycloheptadiene **15**.

Scheme 6.
Remote functionalization attempts.

Scheme 7.
Second generation retrosynthesis.

Scheme 8.
Synthesis of alkyl iodide **33**.

Scheme 9.
Synthesis of cycloisomerization substrate **31**.

Scheme 10.
Lactone formation.

Scheme 11.
An initial formal synthesis of *epi*-icetexone.

Scheme 12.
Formal synthesis of icetexone and *epi*-icetexone.

Scheme 13.
Proposed mechanism.

Scheme 14.
 Synthesis of an enantioenriched common intermediate.

Table 1

Cycloisomerization optimization

Entry	Catalyst	Equiv	Temp (°C)	Time (d)	Result (SM/Product) ^a
1	GaCl ₃	0.2	40	2	1.36:1.0
2	GaBr ₃	0.2	40	2	1.29:1.0
3	GaI ₃	0.2	40	2	0.63:1.0
4	GaI ₃	0.5	65	4	Complete
5	GaI ₃	0.25	80	4	Complete
6	GaCl ₃	0.25	100 ^b	2	Complete

^aConversion of substrate based on ¹H NMR of crude product after aqueous workup.

^bReaction run in toluene.