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Lewis Acid Catalyzed Cyclizations of Epoxidized Baylis–Hillman Products: A Straightforward Synthesis of Octahydrobenzo[*e*]azulenes

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Tricyclic keto-diols have been synthesized from 2-cyclopenten-1-one in a three-step annulation procedure. The importance of aryl ring electronics and steric contributions and the choice of Lewis acid were investigated for the final cyclization step. An unexpected cyclization product was identified, suggesting multiple mechanisms for the cyclization process.

Introduction

Polycarbocyclic systems are present in many classes of natural products and their stereocontrolled synthesis is an active area of scientific interest.[1] A particularly challenging class are polyhydroxylated natural products with a central seven-membered ring, such as gnididin (**1**),[2] resinferatoxin (**2**)[3] and phorbol (**3**)[4] (Figure 1).

The construction of a 5–7–6 carbon skeleton has been demonstrated, for example, during the synthesis of (–)-presphaerene[5] and homosteroids[6] which employed a Tiffeneau–Demanjov ring enlargement to furnish the central seven-membered ring.

Previously a 3-step convergent route to hydroxylated tricyclic systems having a 6–6–6 and 6–7–6 carbon skeleton was developed based on the annulation of 2-cyclohexen-1-one (Scheme 1).[7,8] The synthesis involves a modified Baylis–Hillman[9] reaction with diethylaluminium iodide. Reaction of 2-cyclohexen-1-one with phenylacetaldehyde affords compounds with a central six-membered ring while homologous hydrocinnamaldehyde furnishes tricyclic compounds with a central seven-membered ring. Subsequent stereoselective Sharpless epoxidation[10] affords the *syn*-2,3-epoxy alcohol which, under Lewis acid catalysis cyclizes to the desired tricyclic systems. The final cyclization step involves a 7-*endo-tet* ring closure[11] with an unactivated benzene ring as π-nucleophile.

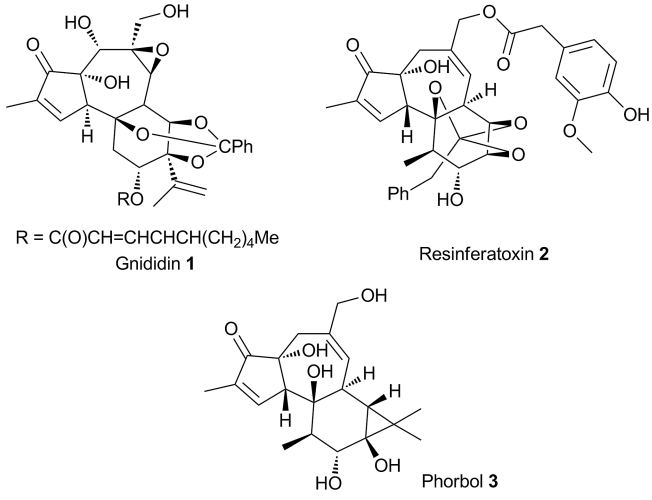

Figure 1. Polyhydroxylated natural products.

While the modified Baylis–Hillman reaction with diethylaluminium iodide proceeded in good yield with 2-cyclohexen-1-one, when used in conjunction with 2-cyclopenten-1-one to secure the 5–7–6 system, results were less promising.[12] Previously Itoh[13] had elegantly resolved this using dimethylaluminium thiophenol, which was generated in situ from *n*-butyllithium, trimethylaluminium and thiophenol, while developing aldol chemistry with α,β-unsaturated carbonyl compounds. More recent studies by Ikegami[14] have identified the milder cooperative catalysts of tributylphosphane with 2-naphthol which affords the smooth coupling of 2-cyclopenten-one with aldehydes.

During cyclization, attack is only possible at the two carbon atoms *ortho* to the alkyl substituent. In the example described in Scheme 1 with an unsubstituted aryl ring the two carbon atoms *ortho* to the alkyl substituent are identical. To determine the effect on both the regiochemistry and efficiency of the cyclization step, we planned to investi-

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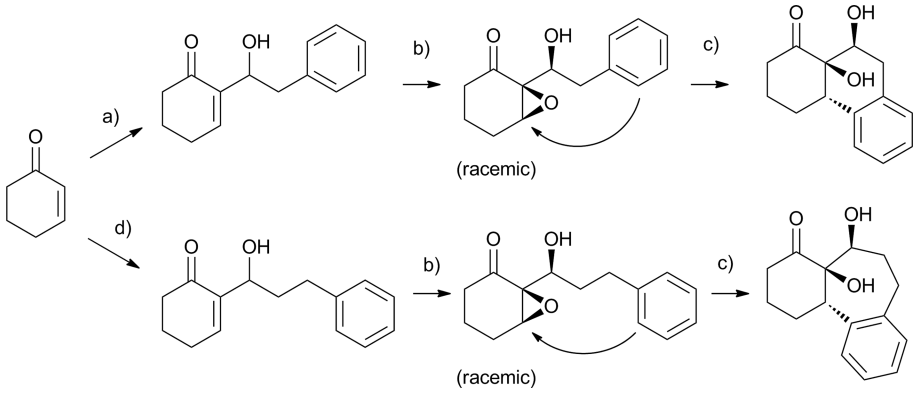


Scheme 1. 3-Step annulation of tricyclic keto diols from 2-cyclohexen-1-one; a) phenylacetaldehyde, b) epoxidation, c) cyclization: d) hydrocinnamaldehyde.

gate substituted phenyl rings. This would also facilitate additional functionalization of the aryl ring in the final tricyclic compound. In addition, the scope of Lewis acid catalysis would be investigated.

Herein we report the expansion of this annulation strategy and describe the synthesis of several hydroxylated 1,3a,4,5,6,10b-hexahydrobenzo[*e*]azulen-3(2*H*)-ones. In addition we discuss the factors that affect selectivity during the final cyclization step including the mechanism of an unusual rearrangement.

Results and Discussion

To interrogate both steric and electronic effects on the cyclization, three *meta*-substituted 2-phenylpropionaldehydes were selected: methoxy, chloro and methyl. These reagents were efficiently prepared from the starting carboxylic acids in two steps. Treatment of the carboxylic acids **4b** (R = OMe), **4c** (R = Cl), and **4d** (R = Me), with lithium aluminium hydride[15] afforded the corresponding alcohols **5b**, **5c** and **5d** in good yields. Subsequent oxidation of the alcohol using a stabilized form of 2-iodoxybenzoic acid (sIBX), which is composed of *o*-iodoxybenzoic acid (49%), benzoic acid (22%) and isophthalic acid (29%),[16] gave the desired aldehydes[17] **6b**, **6c** and **6d** in good overall yield.

While the use of diethylaluminium iodide proved successful for the addition of 3-phenylpropionaldehyde to 2-cyclohexenone, previous studies[12] had identified the use of *n*-butyllithium, trimethylaluminium and thiophenol[13] as the reagents of choice for coupling 3-phenylpropionaldehyde to 2-cyclopentenone. However, since these studies were conducted, the milder cooperative catalysts of tributylphosphane with 2-naphthol have been developed by Ikegami[14] for this coupling.

Using the Ikegami conditions, coupling of 2-cyclopentenone (**7**) with 3-phenylpropionaldehyde (**6a**) proceeded smoothly and afforded hydroxy ketone **8a** in very good yield (84%). This compared to 60% that was achieved using the *n*-butyllithium, trimethylaluminium and thiophenol conditions. The *meta*-substituted hydroxy ketones **8b**, **8c** and **8d** were similarly obtained in moderate to good yields.

The use of Sharpless epoxidation conditions [*t*BHP and $VO(acac)_2$ in refluxing benzene for 5 h] with hydroxy ketone **8a** had been shown to stereoselectively afford only *syn*-2,3-epoxy alcohol **9a** in 76% yield.[12] Subjecting the hydroxy ketones **8b**, **8c** and **8d** to these epoxidation conditions afforded the desired racemic *syn*-2,3-epoxy alcohols **9b**, **9c** and **9d** in yields ranging from 62–74%.

Upon standing at room temperature the methoxy substituted *syn*-2,3-epoxy alcohol **9b** crystallized and X-ray quality crystals were subsequently grown from diethyl ether. Compound **9b** crystallized in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit (Figure 2). The relative configurations of the hydroxyl group and epoxide are confirmed by the structure.

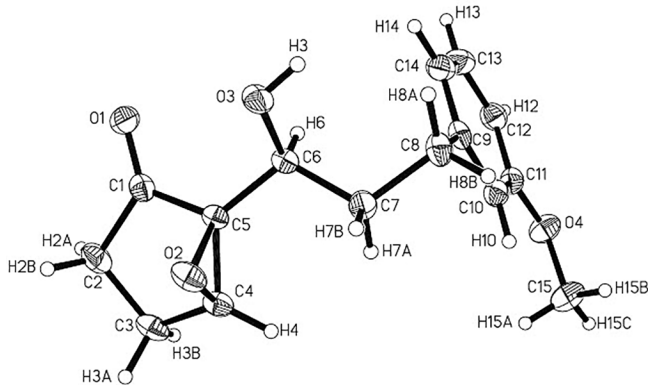


Figure 2. Thermal ellipsoid plot of the molecular unit of **20** showing 50% probability ellipsoids; H atoms are shown as spheres of arbitrary size.

Having secured the desired *syn*-2,3-epoxy alcohols, it was now possible to study the impact on the cyclization step of both the *meta*-aryl substituents and the Lewis acid.[18] Epoxide **9a**, with the unsubstituted aryl ring, was used as the control compound for this study with $AlCl_3$, $SnCl_4$, $TiCl_4$ and BF_3OEt_2 selected as the panel of Lewis acids.

Treatment of epoxy alcohol **9a** with $AlCl_3$ (5 equiv.) at room temperature for 24 h gave two isolated products, the desired tricycle **10a** in 23% yield and undesired chlorohydrin **13a** a by-product resulting from chloride ion ring

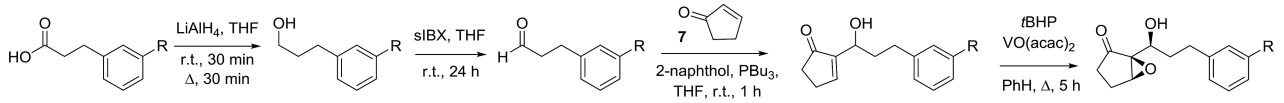
opening of the epoxide as the major product in 47% yield. Both the stereo- and regiochemical assignments for the epoxide opening to afford chlorohydrin **13a** was based on earlier X-ray structures in the group.[7] Subsequently epoxy alcohol **9a** was treated with both $SnCl_4$ (5 equiv.) and $TiCl_4$ (5 equiv.) at room temperature for 24 h. For these reactions, the compounds were not isolated; instead the spectroscopic data from the $AlCl_3$ reaction were used to establish the ratio of **10a** and **13a**. In the case of treatment with $SnCl_4$ tricycle **10a** and chlorohydrin **13a** were obtained in 91% yield in a ratio of 6:1. After treatment with $TiCl_4$, tricycle **10a** was the only isolated product in 92% yield.

Treatment of epoxy alcohol **9a** with BF_3OEt_2 (5 equiv.) at 20 °C for 3 h afforded compound **14b** as white needles. Surprisingly, analysis by ^{13}C NMR showed the absence of the carbonyl of the expected cyclization product. Consideration of both ^1H and ^{13}C NMR spectra together with the IR spectrum allowed the structure depicted in Scheme 2 to be proposed for **14b**. It is likely that coordination of the boron increases the electrophilic character of the carbonyl group offering an alternative, and more favoured, pathway to cyclization at the 1-position of the cyclopentenone ring. Structures similar to epoxy diol **14b** have been proposed as intermediates in very different cyclizations.[19]

To avoid an unwanted cyclization process competing with the desired route during studies on the directing effects of the *meta*-substituents on epoxy alcohols **9b**, **9c** and **9d** $BF_3{\cdot}OEt_2$ was not included in further studies. Instead $SnCl_4$, $TiCl_4$, and $AlCl_3$ were selected for their precedence in mediating similar cyclization reactions.[20]

Introduction of the electron-donating methoxy group was expected to enhance cyclization and favour the carbon *para* to the methoxy due to steric considerations. Treatment of epoxide **9b** with $SnCl_4$ at room temperature for 24 h afforded three products. Tricycle **10b**, in which cyclization occurs *para* to the methoxy in 33% yield and tricycle **11b**, which is derived from **9b** by a cyclization *ortho* to the methoxy, in 11% yield by LCMS. Chlorohydrin **13b** was detected only in trace quantities and was characterized by analysis of the reaction mixture and comparison with the spectroscopic data of chlorohydrin **13a**.

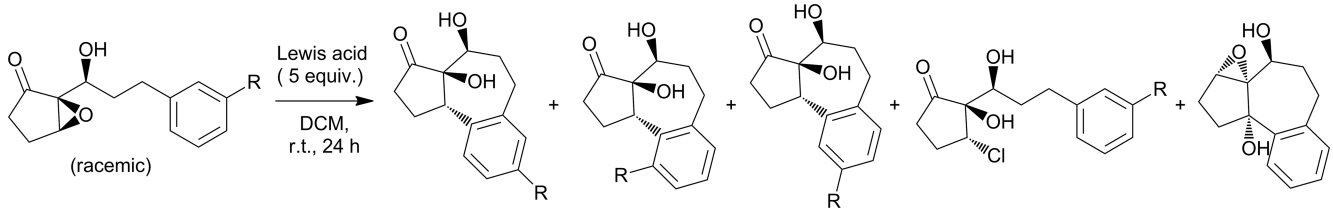
When epoxy alcohol **9b** was treated with $TiCl_4$ only the 2 products of cyclization **10b** and **11b** were detected in a 10:1 ratio in 95% overall yield based on LCMS. Subsequent treatment of epoxide **9b** with $AlCl_3$ gave the same 3 products observed in the $SnCl_4$ reaction. Compounds **10b**, **11b** and **13b** were obtained in a 7:1:4 ratio in 95% overall yield based on LCMS. For the reactions with $AlCl_3$ and $TiCl_4$



R	Acid	Alcohol (yield [%])	Aldehyde (yield [%])	Hydroxy ketone (yield [%])	Epoxy alcohol (yield [%])
H			**6a**	**8a** (84)	**9a** (76)
OMe	**4b**	**5b** (82)	**6b** (69)	**8b** (57)	**9b** (74)
Cl	**4c**	**5c** (67)	**6c** (76)	**8c** (72)	**9c** (67)
Me	**4d**	**5d** (71)	**6d** (89)	**8d** (79)	**9d** (62)

Scheme 2. Synthesis of *syn*-2,3-epoxy alcohols **9a**, **9b**, **9c** and **9d**.

Table 1. Study of the Lewis acid catalyzed treatment of *syn*-2,3-epoxy alcohols **9a**, **9b**, **9c** and **9d**.



Epoxide	R	Lewis acid	Product (yield [%])	Product (yield [%])	Product (yield [%])	Product (yield [%])	Product (yield [%])
9a	H	$SnCl_4$	**10a** (78)[a]			**13a** (13)[a]	
9a	H	$TiCl_4$	**10a** (92)[a]			**13a** (0)[a]	
9a	H	$AlCl_3$	**10a** (23)[b]			**13a** (47)[b]	
9a	H	BF_3OEt_2					**14b** (32)[b]
9b	OMe	$SnCl_4$	**10b** (33)[a]	**11b** (11)[a]		**13b** (trace)[a]	
9b	OMe	$TiCl_4$	**10b** (86)[a]	**11b** (9)[a]		**13b** (0)[a]	
9b	OMe	$AlCl_3$	**10b** (55)[c]	**11b** (8)[a]		**13b** (32)[a]	
9c	Cl	$SnCl_4$	**10c**[c] (49)[a]			**13c** (40)[a]	
9c	Cl	$TiCl_4$	**10c**[c] (51)[a]			**13c** (37)[a]	
9c	Cl	$AlCl_3$	**10c**[c] (10)[a]			**13c** (30)[b]	
9d	Me	$SnCl_4$	**10d** (14)[a]		**12d** (34)[a]	**13d** (10)[a]	
9d	Me	$TiCl_4$	**10d** (55)[c]		**12d** (35)[c]	**13d** (5)[c]	
9d	Me	$AlCl_3$	**10d** (51)[a]		**12d** (37)[a]	**13d** (7)[a]	

[a] Yield based on LCMS. [b] Isolated yield. [c] Individual products of cyclization not isolated; structures of **9a**, **10b**, **11b**, **10d** and **12d** confirmed by X-ray crystallography.

the individual components were not isolated, but rather the crude reaction mixtures were analyzed. The spectroscopic data for **10b** and **11b** from the $SnCl_4$ cyclization of epoxy alcohol **9b**, as well as the spectroscopic data characterizing chlorohydrin **13a** were used to characterize the product ratios and to determine whether any of the chlorohydrin **13b** had formed in either the $AlCl_3$ or $TiCl_4$ cyclizations. Although chlorohydrin **13b** was not isolated, peaks in the crude ^{1}H NMR spectra correlated with the R_2CH-Cl and R_2CH-OH peaks of **13a**. To calculate the product ratios, the representative peaks of **10b**, **11b** and **13b** were integrated individually and their values compared (Table 1).

The hypothesis that the methoxy substituent would favour cyclization was confirmed when the $AlCl_3$ catalyzed cyclizations were compared. In the reaction with epoxy alcohol **9a** with the unsubstituted aryl ring, the chlorohydrin is favoured over the cyclized product in a ratio of 3:1. For epoxy alcohol **9b** with the methoxy substituted aryl ring, the reaction favoured cyclized products (**10b** and **11b**) in a 2:1 ratio over chlorohydrin **13b**, showing that epoxy alcohol **20** undergoes a more facile cyclization.

For the cyclization of epoxy alcohol **9c** with the electron-withdrawing *meta*-chloro substituent, it was predicted that cyclization would be less favourable relative to epoxy alcohol **9a**. Treatment of epoxy alcohol **9c** with $AlCl_3$ at room temperature for 24 h afforded chlorohydrin **13c** in 30% isolated yield. Due to the low yield, it was not possible to isolate the individual products of cyclization. However, because of the distinctive peaks in the 5.0–3.0 ppm region of the ^{1}H NMR, it was possible to compare with the data obtained from the cyclization reactions of epoxy alcohols **9a** and **9b** and draw general conclusions about the cyclization of the chloro-substituted epoxy alcohol **9c**. This data, along with the spectroscopic data of chlorohydrin **13c**, were used to determine a reaction product ratio of cyclised material **10c**: chlorohydrin **13c** of 1:4.

Subsequent treatment of epoxy alcohol **9c** with both $SnCl_4$ and $TiCl_4$ gave nearly 1:1 mixtures of products of cyclization **10c**: chlorohydrin **13c**. In both cyclizations the individual components were not isolated, but rather the crude reaction mixtures analyzed. To calculate the product ratios, the representative peaks of **13c** in the ^{1}H NMR spectra were integrated and the values compared to the total integration of all peaks representative of products of cyclization as identified from previous cyclizations.

For epoxy alcohol **9d**, with the *meta*-methyl-substituted aryl ring, a scenario between the results observed for the methoxy and unsubstituted aryl ring analogues was expected with the cyclization again most favoured at the carbon *para* to the methyl group. Treatment of epoxy alcohol **9d** with $SnCl_4$ at room temperature for 24 h again afforded three products. Tricycle **10d**, in which cyclization occurs *para* to the methyl, was isolated in 14% yield. Surprisingly material consistent with cyclization ortho to the methyl was not detected. Instead tricycle **12d** was afforded in 34% yield. As observed in earlier cyclizations chlorohydrin **13d** was detected only in trace quantities and characterized by analysis of the reaction mixture and comparison with the spectroscopic data of chlorohydrin **13a**. When epoxy alcohol **9d** was treated with $TiCl_4$ the two products of cyclization **10d** and **12d** and chlorohydrin **13d** were detected in a ratio of 11:7:1 in 95% overall yield based on ^{1}H NMR spectroscopy. Surprisingly, treatment of epoxy alcohol **9d** with $AlCl_3$ gave a similar ratio of the three products with **10d**, **12d** and **13d** being produced in a ratio of 7:5:1.

Compound **10b** crystallized in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit (Figure 3, a) and the molecule adopting a somewhat twisted conformation.

Compound **11b** crystallized in the orthorhombic space group *Pbcn* with two molecules in the asymmetric unit (Figure 3, b and c) with the cyclopentanone ring again adopting a twisted conformation.

Compound **10d** crystallized in the monoclinic space group $P2_1/c$ and, like **11b**, there are two molecules in the asymmetric unit (Figure 3, d and e). As is the case for all of the products of cyclization, both of the hydroxyl groups are on the same face of the molecule and are staggered, but significantly less than was seen in **11b** and the cyclopentanone ring adopts the now-familiar twisted conformation.

Compound **12d** also crystalizes in the monoclinic space group $P2_1/c$ but with a single molecule in the asymmetric unit (Figure 3, f). The most striking aspect of the structure is the position of the methyl group on C12 rather than C11 or C13 as expected.

Although we find no examples of crystal structures of the carbocyclic 5–7–6 ring system prepared in this study, a number of related compounds containing additional fused or bridged ring have been reported. Halogenated analogues with an additional fused cyclopropyl ring,[21] or bridged polycyclic system are also known.[22] None however, contain the cyclopentanone functionality. Two related compounds with dioxane rings fused to the central cycloheptane ring are also known,[23] as well as two systems where the cycloheptane ring is bridged in bicyclic fashion by an addition ether functional group.[24]

The electronic effects of the phenyl ring substituents can explain why the methoxy-substituted material cyclizes more predictably than the methyl-substituted material. The methoxy group donates electron-density to the phenyl ring by resonance and withdraws electron density inductively, whereas the methyl group can both donate inductively and stabilize by hyperconjugation. This makes the ring more active in the case of R = OMe, therefore making it a better nucleophile and more likely to undergo the epoxide-opening/ring-closing reaction. This does not, however, explain the formation of the unexpected product in the case of **12d** (R = Me).

The crystal structures of the major products **10b** and **10d**, the expected minor product **11b**, and the unexpected minor product **12d** suggest that steric interactions were the largest contributing factor for the formation of the unexpected minor product. In the minor product of the methoxy-substituted cyclization, the conformation of the methoxy group is such that the CH_3 group is positioned away from the

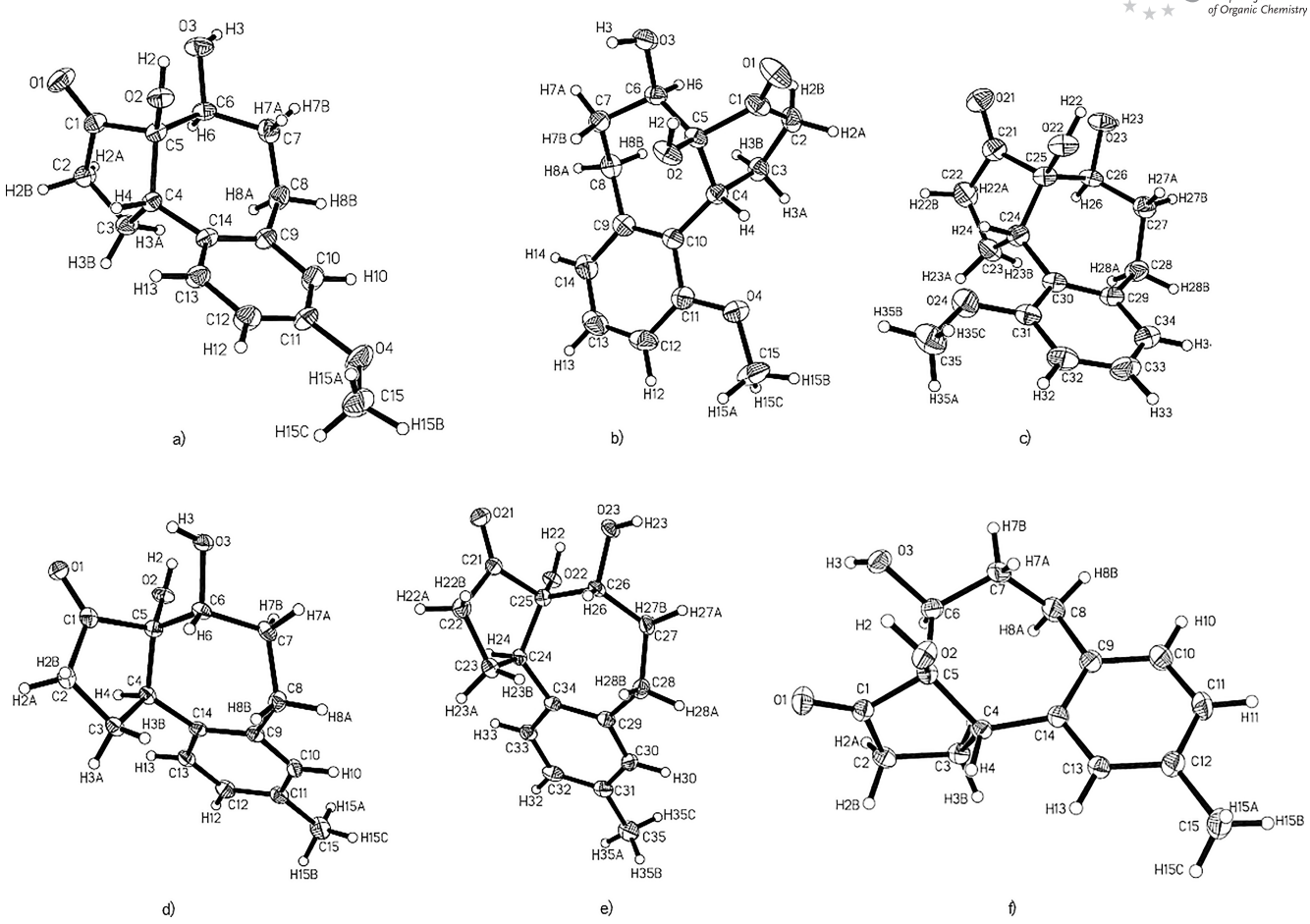
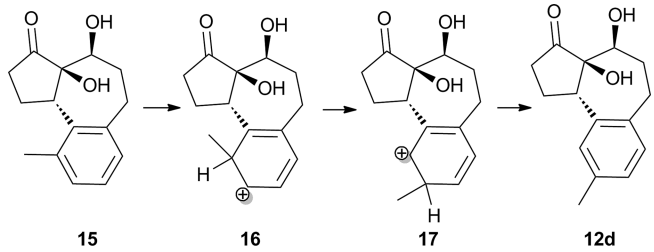


Figure 3. (a) Thermal ellipsoid plot of the molecular unit of **10b** showing 50% probability ellipsoids. Hydrogen atoms are shown as spheres of arbitrary size. Thermal ellipsoid plots of the individual molecules (b) and (c) in the asymmetric unit of **11b** showing 50% probability ellipsoids. Thermal ellipsoid plots of the individual molecules (d) and (e) in the asymmetric unit of **10d** showing 50% probability ellipsoids. (f) Thermal ellipsoid plot of the asymmetric unit of **12d** showing 50% probability ellipsoids. Hydrogen atoms are drawn as spheres of arbitrary size.

cyclopentyl ring. The oxygen linker provides the methyl group with enough space to reduce steric interactions with the cyclopentyl ring. However, if the methyl-substituted material cyclized in the same position as the minor product of the methoxy-substituted material, the methyl group would be forced into a position where it would interact unfavourably with the nearby cyclopentyl ring. To avoid this steric interaction, some sort of rearrangement or alternate mechanism must occur to avoid the interaction between the methyl group and the ring.

We propose the mechanism for the formation of the minor methyl-substituted product of cyclization **12d** via a rearrangement mediated by an ipso substitution at the methyl-substituted carbon (Scheme 3). Protonation of **15** forms a carbocation at the neighbouring carbon affording **16**. The methyl group then undergoes a Wagner–Meerwein rearrangement afford intermediate **17**. As methoxy groups cannot under such rearrangements a similar situation is not possible during Lewis acid treatment of epoxy alcohol **9b**. Finally aromatization affords tricycle **12d**. It should be noted that **17** could form directly and not via **16**. Such a mechanism would involve a [1,2]-proton shift of the Wheland intermediate formed by the initial protonation of **15**.



Scheme 3. Proposed mechanism for formation of **12d** via a rearrangement mediated by an ipso substitution at the methyl-substituted carbon.

Conclusions

The synthesis of hydroxylated 1,3a,4,5,6,10b-hexahydrobenzo[*e*]azulen-3(2*H*)-ones has been established via a linear 3-step route: i) annulation with 2-cyclopentenone, ii) stereo-

selective epoxidation, iii) Lewis acid catalyzed cyclization. $TiCl_4$ and $SnCl_4$ were identified as the preferred Lewis acids for catalyzing the final cyclization step and afforded primarily the desired tricyclic compounds while $AlCl_3$ favoured production of an undesired chlorohydrin product. Electron-rich aromatic rings were shown to enhance the rate of cyclization while for electron-deficient aromatic rings their reduced rate of cyclization resulted in increased chlorohydrin formation via a competing undesired route. Cyclization was also shown to occur preferentially at the sterically least hindered carbon of the aryl ring. In the case of the 3-methyl-substituted phenyl ring an unexpected cyclization product was observed which was likely formed by one of two proposed mechanisms. In addition $BF_3{\cdot}OEt_2$ was shown to promote an alternative cyclization pathway via nucleophilic attack of the 2-cyclopentenone carbonyl.

Experimental Section

General Details: All solvents and reagents were used as received without purification. All melting points were determined with a Stanford Research Systems OptiMelt. NMR spectra were run in $CDCl_3$ unless noted. Chemical shifts are quoted in ppm downfield from internal TMS standard, and the line separations (J) are expressed in Hertz. The following abbreviations are used to describe NMR signals: s singlet, d doublet, dd double doublet, t triplet, dt double triplet, q quartet, m multiplet, br. broad. ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker AM-250 or a Varian Mercury actively shielded 400 MHz at 26 °C. ^{1}H NMR were collected at 250 or 400 MHz. ^{13}C NMR spectra were collected at 69 or 101 MHz. Elemental analyses were carried out by Robertson Microlit Laboratories, Madison, NJ. Infrared spectra were obtained from neat samples on a Perkin–Elmer 684 or a Thermo Nicolet NEXUS 470 FT-IR ESP spectrometer with a Thermo Nicolet Smart DuraSamplIR accessory, yields are judged to be homogeneous by TLC and ^{1}H NMR spectroscopy. Thin-layer chromatography was performed on Merck HPTLC plates and visualized using ultra-violet light. Column chromatography was performed by using an AnaLogix Inteliflash 280 with Silicycle SiliaSep silica gel columns.

3-(3-Methoxyphenyl)propan-1-ol (5b): 3-Methoxycinnamic acid (10.0 g, 56.1 mmol) in 50 mL of THF was added dropwise to a solution of lithium aluminium hydride (4.3 g, 112.0 mmol) in THF (110 mL) at 0 °C. The resulting suspension was warmed to room temperature, stirred at room temperature for 30 min then heated at reflux for 30 min. The suspension was cooled and poured onto a saturated solution of tartaric acid in ethanol at 0 °C. 150 g of a 1:1 mixture of sodium sulfate dodecahydrate and Celite was added and the mixture was stirred for 10 min. Material was filtered through a pad of Celite and washed with diethyl ether. The filtrate was dried further over $MgSO_4$, filtered, and concentrated. This yielded **5b** (7.6 g, 82%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.44. IR (film): $\tilde{\nu}$ = 3350, 2937, 1599, 1584, 1487, 1452, 1434, 1257, 1151, 1037, 776, 694 cm^{-1}. $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found C 71.91, H 8.22. ^{1}H NMR (400 MHz) 7.19 (dd, J = 11.7, 4.1, 1 H), 6.80–6.70 (m, 3 H), 3.80–3.74 (m, 4 H), 3.65 (t, J = 6.4, 2 H), 2.70–2.63 (m, 2 H), 2.11 (s, 1 H), 1.92–1.83 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 159.6, 143.4, 129.4, 129.3, 129.3, 120.8, 120.7, 114.2, 111.1, 111.1, 111.1, 62.2, 55.1, 34.0, 32.1 ppm.

3-(3-Chlorophenyl)propan-1-ol (5c): Lithium aluminium hydride (2.1 g, 54.2 mmol) was added portion wise to a solution of 3-(3-chlorophenyl)propionic acid (5.0 g, 27.1 mmol) in THF (50 mL) at 0 °C. The resulting suspension was warmed to room temperature and stirred at room temperature for 30 min then heated at reflux for 30 min. The suspension was cooled and poured onto a saturated solution of tartaric acid in ethanol at 0 °C. 100 g of a 1:1 mixture of sodium sulfate dodecahydrate and Celite was added and the mixture was stirred for 10 min. Material was filtered through a pad of Celite and washed with diethyl ether, concentrated, and subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–1:1) as eluent. This yielded **5c** (3.1 g, 67%) as a colourless oil, R_f [heptane/ethyl acetate (1:1)] = 0.49. IR (film): $\tilde{\nu}$ = 3113, 2938, 2868, 1596, 1572, 1474, 1427, 1206, 1162, 1054, 920, 883, 847, 779, 694, 682 cm^{-1}. $C_9H_{11}ClO$ (170.64): calcd. C 63.35, H 6.50, Cl 20.78; found C 62.99, H 6.63, Cl 20.60. ^{1}H NMR (400 MHz): δ = 7.24–7.13 (m, 3 H), 7.12–7.04 (m, 1 H), 3.71–3.63 (m, 2 H), 2.74–2.64 (m, 2 H), 1.93–1.83 (m, 2 H), 1.47 (s, 1 H) ppm. ^{13}C NMR (101 MHz): δ = 143.8, 134.05, 129.6, 128.5, 126.6, 126.0, 61.9, 33.8, 31.7 ppm.

3-(3-Methylphenyl)propan-1-ol (5d): A solution of 3-(3-methylphenyl)propionic acid (1.0 g, 6.1 mmol) in THF (6 mL) was added dropwise to a solution of lithium aluminium hydride (0.46 g, 12.2 mmol) at 0 °C. The resulting suspension was warmed to room temperature and stirred at room temperature for 30 min, then heated to reflux for 30 min. The suspension was cooled and HCl (1 M) was added, followed by diethyl ether (2× 20 mL). The resulting mixture was filtered and the organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. This yielded **5d** (0.84 g, 92%) as a colourless oil, R_f [heptane/ethyl acetate (1:1)] = 0.49. IR (film): $\tilde{\nu}$ = 3306, 2935, 2862, 1607, 1485, 1449, 1377, 1043, 912, 779, 697 cm^{-1}. $C_{10}H_{14}O$ (150.22): calcd. C 79.37, H 8.88; found C 79.62, H 9.39. ^{1}H NMR (400 MHz): δ = 7.17 (t, J = 7.5 Hz, 1 H), 7.05–6.92 (m, 3 H), 3.65 (t, J = 6.5 Hz, 2 H), 2.71–2.60 (m, 2 H), 2.32 (s, 3 H), 1.93–1.82 (m, 2 H), 1.67 (s, 1 H) ppm. ^{13}C NMR (101 MHz): δ = 142.0, 138.2, 129.5, 128.5, 126.9, 125.7, 62.6, 34.5, 32.3, 21.6 ppm.

3-(3-Methoxyphenyl)propanal (6b): Stabilized 2-iodobenzoic acid (18.7 g, 30.0 mmol, 45% w/w) was added in one portion to **5b** (4.2 g, 25.0 mmol) in THF (200 mL). The resulting suspension was stirred vigorously at room temperature overnight, then heated to reflux for 3 h. The reaction mixture was cooled, filtered through a pad of Celite, and washed with diethyl ether (100 mL). The solution was then washed with satd. $NaHCO_3$ (4× 50 mL) and water (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. This yielded **6b** (2.9 g, 68.9%) as a colourless oil, R_f [heptane/ethyl acetate (1:1)] = 0.68. IR (film): $\tilde{\nu}$ = 2942, 2834, 2724, 1721, 1599, 1593, 1489, 1453, 1436, 1408, 1388, 1314, 1256, 1157, 1036, 994, 872, 779, 694, 570, 553 cm^{-1}. ^{1}H NMR (400 MHz): δ = 9.82 (t, J = 1.4 Hz, 1 H), 7.21 (ddd, J = 7.6, 6.7, 1.0 Hz, 1 H), 6.82–6.71 (m, 3 H), 3.79 (s, 3 H), 2.93 (t, J = 7.6 Hz, 2 H), 2.82–2.74 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 201.5, 159.7, 141.9, 129.5, 120.5, 114.1, 111.4, 55.1, 45.1, 28.1 ppm.

3-(3-Chlorophenyl)propanal (6c): Stabilized 2-iodobenzoic acid (6.4 g, 10.3 mmol, 45% w/w) was added in one portion to **5c** (1.5 g, 8.6 mmol) in ethyl acetate (60 mL). The resulting suspension was stirred vigorously at reflux for 3 h, cooled, and filtered through a pad of Celite. The filter cake was washed with ethyl acetate (3× 50 mL) and the filtrate was washed with satd. $NaHCO_3$ (4× 50 mL) and water (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. This yielded **6c** (1.1 g, 76%) as a colourless oil, R_f [heptane/ethyl acetate (1:1)] = 0.72. IR (film): $\tilde{\nu}$ = 2951, 2723, 1721, 1597, 1573, 1476, 1430, 1408, 1388, 1203, 1077, 1034, 997, 885, 780, 684 cm^{-1}. ^{1}H NMR (400 MHz): δ = 9.81 (dt,

J = 3.8, 1.3 Hz, 1 H), 7.24–7.15 (m, 3 H), 7.07 (dt, *J* = 7.1, 1.6 Hz, 1 H), 2.97–2.90 (m, 3 H), 2.82–2.74 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 200.8, 142.3, 134.3, 129.8, 128.4, 126.5, 126.5, 44.9, 27.6 ppm.

3-(3-Methylphenyl)propanal (6d): Stabilized 2-iodobenzoic acid (3.4 g, 6.2 mmol, 45% w/w) was added in one portion to **5d** (0.78 g, 5.2 mmol) in THF (33 mL). The resulting suspension was heated to reflux for 5 h. Reaction mixture was cooled, filtered through a pad of Celite, and washed with diethyl ether (100 mL). Solution was then washed with satd. $NaHCO_3$ (3× 50 mL) and water (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. This yielded **6d** (0.68 g, 89%) as a colourless oil, R_f [heptane/ethyl acetate (1:1)] = 0.72. IR (film): $\tilde{\nu}$ = 3021, 2920, 2722, 1721, 1608, 1589, 1488, 1447, 1407, 1387, 1171, 1094, 1055, 906, 883, 781, 697, 572, 534 cm^{-1}. ^{1}H NMR (400 MHz): δ = 9.81 (t, *J* = 1.5 Hz, 1 H), 7.18 (dd, *J* = 11.4, 4.1 Hz, 1 H), 7.05–6.96 (m, 3 H), 2.92 (dd, *J* = 9.8, 5.3 Hz, 2 H), 2.79–2.73 (m, 2 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (101 MHz): δ = 201.5, 201.6, 140.2, 138.2, 129.0, 128.5, 127.0, 125.2, 45.2, 28.0, 21.3 ppm.

2-(1-Hydroxy-3-phenylpropyl)cyclopent-2-en-1-one (8a): 2-Cyclopenten-1-one (**7**, 1.0 mL, 11.9 mmol), tributylphosphane (0.59 mL, 2.4 mmol), and 2-naphthol (0.34 g, 2.4 mmol) in THF (10 mL) were each added sequentially to a solution of **6a** (2.0 g, 15.2 mmol) in THF (30 mL) under nitrogen. The solution was stirred at room temperature overnight. THF was removed under reduced pressure and the crude mixture was subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–2:1) as eluent. This yielded **8a** (2.2 g, 84%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.31. IR (film): $\tilde{\nu}$ = 3408, 2920, 2858, 1682, 1629, 1495, 1452, 1438, 1339, 1252, 1070, 999, 919, 788, 747, 698 cm^{-1}. $C_{15}H_{18}O_3$ (246.31): calcd. C 77.75, H 7.46; found C 78.58, H 7.88. ^{1}H NMR (400 MHz): δ = 7.44 (td, *J* = 2.7 Hz, 1 H), 7.31–7.24 (m, 2 H), 7.19 (ddt, *J* = 8.5, 6.5, 1.5 Hz, 3 H), 4.47 (ddd, *J* = 6.9, 2.7 Hz, 1.3 1 H), 2.88–2.78 (m, 1 H), 2.70 (dt, *J* = 13.9, 8.0 Hz, 1 H), 2.62–2.56 (m, 2 H), 2.45–2.39 (m, 2 H), 2.06–1.95 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 210.1, 158.0, 147.4, 141.6, 128.4, 128.3, 125.8, 67.1, 37.1, 35.2, 31.6, 26.6 ppm.

2-[1-Hydroxy-3-(3-methoxyphenyl)propyl]cyclopent-2-en-1-one (8b): 2-Cyclopenten-1-one (**7**, 1.32 mL, 15.7 mmol), tri-*n*-butylphosphane (0.64 g, 3.1 mmol), and 2-naphthol (0.45 g, 3.1 mmol) in THF (10 mL) were each added sequentially to a solution of **6b** (3.2 g, 19.6 mmol) in THF (50 mL) under nitrogen. The solution was stirred at room temperature overnight. THF was removed under reduced pressure and the crude mixture was taken up in a minimal amount of dichloromethane and subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0_1:1) as eluent. This yielded **8b** (2.2 g, 57%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.21. IR (film): $\tilde{\nu}$ = 3424, 2919, 2835, 1685, 1629, 1599, 1488, 1453, 1436, 1401, 1256, 1193, 1151, 1041, 998, 992, 975, 785, 695, 555 cm^{-1}. $C_{15}H_{18}O_3$ (246.31): calcd. C 73.15, H 7.37; found C 72.88, H 7.48. ^{1}H NMR (400 MHz): δ = 7.43 (t, *J* = 2.7 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 6.83–6.69 (m, 3 H), 4.48 (td, *J* = 6.7 Hz, 1.3 1 H), 3.79 (s, 3 H), 2.85–2.64 (m, 2 H), 2.60 (ddd, *J* = 4.4, 3.6, 2.1 Hz, 2 H), 2.45–2.41 (m, 2 H), 2.00 (ddd, *J* = 8.7, 7.2, 3.5 Hz, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 210.0, 159.6, 157.9, 147.4, 143.2, 129.3, 120.8, 114.1, 111.2, 67.2, 55.1, 37.0, 35.2, 31.7, 26.6 ppm.

2-[1-Hydroxy-3-(3-methylphenyl)propyl]cyclopent-2-en-1-one (8c): 2-Cyclopenten-1-one (**7**, 1.66 mL, 19.8 mmol), tri-*n*-butylphosphane (0.98 mL, 4.0 mmol) and 2-naphthol (0.45 mL, 4.0 mmol) were each added sequentially to a solution of **6c** (3.67 g, 24.8 mmol) in THF (80 mL) under nitrogen. The solution was stirred at room temperature overnight. THF was removed under reduced pressure and the crude mixture was taken up in a minimal amount of dichloromethane and subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–2:1) as eluent. This yielded **8c** (3.59 g, 79%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.24. IR (film): $\tilde{\nu}$ = 3412, 2918, 2859, 1683, 1629, 1607, 1440, 1343, 1251, 1077, 999, 922, 785, 699 cm^{-1}. $C_{15}H_{18}O_2$ (230.31): calcd. C 78.23, H 7.88; found C 77.98, H 8.00. ^{1}H NMR (400 MHz): δ = 7.43 (t, *J* = 2.7 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.04–6.96 (m, 3 H), 4.52–4.42 (m, 1 H), 2.82–2.61 (m, 2 H), 2.61–2.57 (m, 2 H), 2.44–2.41 (m, 2 H), 2.32 (s, 3 H), 2.03–1.96 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 210, 157.9, 147.5, 141.5, 137.9, 129.2, 128.2, 126.6, 125.4, 67.2, 37.2, 35.2, 31. 5, 26.6, 21.3 ppm.

2-[1-Hydroxy-3-(3-chlorophenyl)propyl]cyclopent-2-en-1-one (8d): 2-Cyclopenten-1-one (**7**, 0.39 g, 4.7 mmol), tri-*n*-butylphosphane (0.19 g, 0.95 mmol), and 2-naphthol (0.14 g, 0.95 mmol) in THF (10 mL) were each added sequentially to a solution of **6d** (1.0 g, 5.9 mmol) in THF (10 mL) under nitrogen. The solution was stirred at room temperature for 1.5 h. THF was removed under reduced pressure and the crude mixture was taken up in a minimal amount of dichloromethane and subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–2:1) as eluent. This yielded **8d** (0.86 g, 72%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.31. IR (film): $\tilde{\nu}$ = 3409, 3059, 2920, 2860, 1681, 1629, 1596, 1572, 1476, 1433, 1341, 1253, 1197, 1076, 998, 919, 878, 783, 696, 682 cm^{-1}. $C_{14}H_{15d}lO_2$: calcd. C 67.07, H 6.03, Cl 14.14; found C 66.74, H 6.05; Cl, 13.74. ^{1}H NMR (400 MHz): δ = 7.44 (t, *J* = 2.7 Hz, 1 H), 7.24–7.13 (m, 3 H), 7.11–7.06 (m, 1 H), 4.48–4.43 (m, 1 H), 2.85–2.64 (m, 3 H), 2.64–2.57 (m, 2 H), 2.43 (ddd, *J* = 4.2, 2.7, 1.1 Hz, 2 H), 2.05–1.93 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 210.0, 157.9, 147.3, 143.7, 134.1, 129.6, 128.6, 126.7, 126.1, 67.0, 36.8, 35.2, 31.3, 26.6 ppm.

***syn*-2,3-Oxirano-2-(1-hydroxy-3-phenylpropyl)cyclopentan-1-one (9a):** To a stirred solution of 2-(1-Hydroxy-3-phenylpropyl)-cyclopent-2-en-1-one (**8a**, 1.23 g, 5.7 mmol) and vanadyl acetylacetonate (0.021 g, 0.8 mmol) in refluxing benzene (90 mL) in a Dean–Stark apparatus was added *tert*-butyl hydroperoxide (0.81 mL, 6.3 mmol, 70% in water) dropwise. The solution was heated at reflux for 5 h and then cooled. The solution was washed with saturated sodium bisulfate solution (2× 40 mL) and brine (45 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford a residue that was subjected to column chromatography on silica gel using dichloromethane as eluent. This yielded **9a** (0.98 g, 76%) as a colourless oil, R_f [dichloromethane] = 0.24. IR (film): $\tilde{\nu}$ = 3459, 3026, 2932, 2864, 1735, 1602, 1495, 1452, 1421, 1305, 1274, 1239, 1212, 1073, 1033, 988, 921, 867, 837, 747, 699, 570 cm^{-1}. $C_{15}H_{18}O_4$ (262.30): calcd. C 72.39, H 6.94; found C 72.66, H 7.03. $C_{14}H_{14}O_2$ (M^+ – 18): calcd. 214.0994, found 214.0995. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 2 H), 7.23–7.15 (m, 3 H), 4.26–4.16 (m, 1 H), 3.94–3.83 (m, 1 H), 2.92–2.83 (m, 1 H), 2.73 (dt, *J* = 13.9, 8.1 Hz, 1 H), 2.44–2.34 (m, 1 H), 2.31–2.23 (m, 1 H), 2.17–2.08 (m, 1 H), 1.94–1.83 (m, 3 H) ppm. ^{13}C NMR (101 MHz): δ = 210.5, 141.5, 128.5, 128.4, 125.9, 64.6, 62.0, 33.8, 32.3, 31.3, 22.1 ppm.

***syn*-2,3-Oxirano-2-[1-hydroxy-3-(3-methoxyphenyl)propyl]cyclopentan-1-one (9b):** *tert*-Butyl hydroperoxide (1.2 mL, 8.8 mmol, 70% in water) was added to a refluxing solution of **8b** (1.96 g, 8.0 mmol) and vanadyl acetylacetonate (0.04 g, 0.16 mmol) in benzene (200 mL) in a Dean–Stark apparatus. The solution was heated at reflux for 5 h. The solution was cooled, then washed with saturated sodium bisulfate solution (2× 50 mL), water (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated

under reduced pressure to afford a residue that was subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–1:1) as eluent. This yielded **9b** (1.55 g, 74%) as a white solid, R_f [heptane/ethyl acetate (1:1)] = 0.20, recrystallized from diethyl ether, m.p. 65–66 °C. IR (film): $\tilde{\nu}$ = 3491, 2949, 1727, 1599, 1467, 1452, 1292, 1257, 1164, 1036, 951, 897, 865, 781, 730, 697, 564 cm^{-1}. $C_{15}H_{18}O_4$ (262.30): calcd. C 68.68, H 6.92; found C 68.60, H 7.19. ^1H NMR (400 MHz): δ = 7.19 (t, J = 7.8 Hz, 1 H), 6.83–6.77 (m, 1 H), 6.77–6.69 (m, 2 H), 4.21 (t, J = 6.2 Hz, 1 H), 3.90 (d, J = 0.7 Hz, 1 H), 3.79 (s, 2 H), 2.85 (dd, J = 14.2, 7.1 Hz, 1 H), 2.72 (dd, J = 15.1, 7.0 Hz, 1 H), 2.44–2.34 (m, 1 H), 2.31–2.23 (m, 1 H), 2.12 (ddd, J = 18.3, 9.6, 1.5 Hz, 1 H), 1.97–1.81 (m, 3 H) ppm. ^{13}C NMR (101 MHz): δ = 210.5, 159. 7, 143.1, 129.4, 120.8, 114.1, 111.4, 64.6, 64.5, 62.0, 55.1, 33.6, 32.3, 31.3, 22.0 ppm.

***syn*-2,3-Oxirano-2-[1-hydroxy-3-(3-chlorophenyl)propyl]cyclopentan-1-one (9c):** *tert*-Butyl hydroperoxide (0.39 mL, 2.8 mmol, 70% in water) was added to a refluxing solution of **8c** (0.65 g, 2.6 mmol) and vanadyl acetylacetonate (0.014 g, 0.052 mmol) in benzene (50 mL) in a Dean–Stark apparatus. The solution was heated at reflux for 5 h. The solution was cooled, then washed with saturated sodium bisulfate solution (2× 25 mL), water (25 mL), and brine (25 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford a residue that was subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–2:1) as eluent. This yielded **9c** (0.46 g, 67%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.44. IR (film): $\tilde{\nu}$ = 3453, 2931, 1736, 1597, 1572, 1476, 1426, 1302, 1208, 1077, 1036, 988, 868, 783, 680, 571, 538 cm^{-1}. $C_{14}H_{15d}lO_3$: calcd. C 63.04, H 5.67, Cl 13.29; found C 63.25, H 5.81, Cl 13.14. ^1H NMR (400 MHz): δ = 7.32–7.13 (m, 3 H), 7.09 (dt, J = 5.1, 1.5 Hz, 1 H), 4.17 (m, 1 H), 3.91 (t, J = 2.1 Hz, 1 H), 2.91–2.81 (m, 1 H), 2.71 (dt, J = 14.0, 8.1 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.33–2.25 (m, 2 H), 2.19–2.09 (m, 1 H), 1.98–1.84 (m, 3 H) ppm.

***syn*-2,3-Oxirano-2-[1-hydroxy-3-(3-methylphenyl)propyl]cyclopentan-1-one (9d):** *tert*-Butyl hydroperoxide (1.97 mL, 14.3 mmol, 70% in water) was added to a refluxing solution of **8d** (3 g, 13.0 mmol) and vanadyl acetylacetonate (0.07 g, 0.26 mmol) in benzene (300 mL) in a Dean–Stark apparatus. The solution was heated at reflux for 5 h. The solution was cooled, then washed with saturated sodium bisulfate solution (2× 50 mL), water (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford a residue that was subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–1:1) as eluent. This yielded **9d** (1.98 g, 62%) as a pale yellow oil, R_f [heptane/ethyl acetate (1:1)] = 0.51. IR (film): $\tilde{\nu}$ = 3465, 2926, 2864, 1737, 1608, 1487, 1446, 1082, 1036, 866, 782, 699, 570 cm^{-1}. $C_{15}H_{18}O_3$ (246.31): calcd. C 73.15, H 7.37; found C 72.83, H 7.44. ^1H NMR (400 MHz): δ = 7.17 (t, J = 7.5 Hz, 1 H), 7.06–6.95 (m, 3 H), 4.26–4.16 (m, 1 H), 3.90 (d, J = 0.7 Hz, 1 H), 2.88–2.79 (m, 1 H), 2.69 (dt, J = 13.9, 8.1 Hz, 1 H), 2.44–2.23 (m, 2 H), 2.32 (s, 3 H), 2.11 (ddd, J = 18.3, 9.6, 1.5 Hz, 1 H), 1.94–1.80 (m, 3 H) ppm.

***syn*-3a,4-Dihydroxy-1,2,3a,4,5,6-hexahydrobenzo[*e*]azulen-3(10b*H*)-one (10a), 3-Chloro-2-hydroxy-2-(1-hydroxy-3-phenylpropyl)cyclopentanone (24) and (2a*R*,3a*R*,4*R*)-2,2a,4,5,6,10b-Hexahydro-1*H*-benzo[4,5]azuleno[1,8a-*b*]oxirene-4,10b-diol (14b)**

(a) Using Aluminium(III) Chloride: Aluminium(III) chloride (0.574 g, 4.31 mmol) was added dropwise to a solution of **9a** (0.200 g, 0.862 mmol) in dichloromethane (16 mL) at 0 °C. Solution was stirred at room temperature for 24 h. Reaction mixture was poured onto 40 mL of ice water and extracted with dichloromethane (2× 20 mL). The combined organic layers were washed with HCl (20 mL, 1 M), water (20 mL), and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–1:1) as eluent. Individual fractions were concentrated and products recrystallized from diethyl ether to yield **10a** (0.046 g, 23%) as prisms, m.p. 140–142 °C, R_f [heptane/ethyl acetate (1:1)] = 0.60. IR (film): $\tilde{\nu}$ = 3527, 3376, 2954, 2931, 2852, 1756, 1728, 1451, 1403, 1296, 1273, 1153, 1088, 1064, 1047, 955, 752, 647, 564 cm^{-1}. $C_{14}H_{16}O_3$ (232.28): calcd. C 72.39, H 6.94; found C 72.06, H 7.01. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.10 (m, 4 H), 3.53 (m, 2 H), 3.44 (s, 1 H), 3.09 (s, 1 H), 2.98 (dt, J = 14.9, 8.2 Hz, 1 H), 2.82 (dt, J = 14.7, 5.9 Hz, 1 H), 2.69–2.50 (m, 2 H), 2.49–2.38 (m, 2 H), 2.01–1.87 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.9, 139.8, 135.9, 129.5, 127.6, 126.9, 126.8, 78.1, 70.5, 48.4, 34.5, 29.4, 26.7, 22.2 ppm, and **13a** (0.094 g, 47%) as needles, m.p. 59–60 °C, R_f [heptane/ethyl acetate (1:1)] = 0.31. IR (film): $\tilde{\nu}$ = 3381, 3025, 2948, 2923, 2862, 1737, 1406, 1305, 1085, 1039, 1011, 919, 893, 823, 755, 701, 631, 557 cm^{-1}. $C_{14}H_{17}ClO_3$ (268.74): calcd. C 62.57, H 6.38, Cl 13.19; found C 62.92, H 6.35, Cl 13.17. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.16 (m, 5 H), 4.25–4.19 (m, 1 H), 4.15 (dd, J = 10.5, 2.6 Hz, 1 H), 3.60 (s, 1 H), 3.34 (s, 1 H), 2.94 (ddd, J = 14.1, 9.6, 4.9 Hz, 1 H), 2.75–2.63 (m, 2 H), 2.54–2.48 (m, 2 H), 2.22 (dddd, J = 13.7, 6.2, 3.8, 1.2 Hz, 1 H), 1.95–1.77 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 217.1, 141.6, 128.5, 128.3, 125.9, 78.6, 70.2, 61.4, 32.3, 31.5, 30.7, 29.2 ppm.

(b) Using Tin(IV) Chloride: Tin(IV) chloride (2.15 mL, 2.15 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9a** (0.100 g, 0.431 mmol) in dichloromethane (8 mL) at 0 °C. Solution was stirred at room temperature for 24 h. Reaction mixture was poured onto 20 mL of ice water and extracted with dichloromethane (2× 10 mL). The combined organic layers were washed with HCl (10 mL, 1 M), water (10 mL), and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of **10a** and **13a** (0.091 g, 91%), in a ratio of 6:1 by ^1H NMR spectroscopy.

(c) Using Titanium(IV) Chloride: Titanium(IV) chloride (2.15 mL, 2.15 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9a** (0.100 g, 0.431 mmol) in dichloromethane (8 mL) at 0 °C. Solution was stirred at room temperature for 24 h. Reaction mixture was poured onto 20 mL of ice water and extracted with dichloromethane (2× 10 mL). The combined organic layers were washed with HCl (10 mL, 1 M), water (10 mL), and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give **10a** (0.092 g, 92%).

(d) Using Boron Trifluoride–Diethyl Ether: To a stirred solution of **9a** (0.59 g, 2.54 mmol) in dichloromethane (40 mL) at 0 °C under nitrogen was added boron trifluoride–diethyl ether (1.56 mL, 12.70 mmol). On completion of the addition the ice bath was removed and the mixture stirred at 20 °C for 3 h. The mixture was then poured onto ice and extracted with DCM (2× 30 mL). The combined organic extracted were washed with water (2× 30 mL) and saturated sodium chloride solution (30 mL), dried (Na_2SO_4), filtered and solvent removed to afford a residue that was subjected to purification by column chromatography on alumina, using chloroform as eluent. This gave **14b** (0.19 g, 32%) as white needles, R_f [$CHCl_3$] 0.70. IR (KBr disc): $\tilde{\nu}$ = 3459 (br), 3069, 3017, 2947, 2870 and 1492 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.23–7.05 (m, 4 H), 4.34 (dd, J = 11.5 and 5.5 Hz, 1 H), 3.59 (dd, J = 12.5 and 6.5 Hz, 1 H), 2.79–2.57 (m, 4 H), 2.33–1.79 (m, 2 H) and 1.61–1.46 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 141.4 (s), 136.4 (s), 131.3 (d), 129.5 (d), 127.1 (d), 126.7 (d), 112.5 (s), 87.9

(s), 75.0 (d), 50.0 (d), 32.6 (d), 31.0 (t), 29.4 (t) and 28.9 (t) ppm. MS: *m*/*z* (%) = 234 (16), 216 (19), 198 (17), 129 (87), 84 (85) and 49 (100).

***syn*-3a,4-Dihydroxy-8-methoxy-1,2,3a,4,5,6-hexahydrobenzo[*e*]azulen-3(10b*H*)-one (26), *syn*-3a,4-Dihydroxy-10-methoxy-1,2,3a,4,5,6-hexahydrobenzo[*e*]azulen-3(10b*H*)-one (11b), and 3-Chloro-2-hydroxy-2-[1-hydroxy-3-(3-methoxyphenyl)propyl]cyclopentanone (13b): (a) Using Tin(IV) Chloride:** Tin(IV) chloride (19.5 mL, 19.5 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9b** (1 g, 3.8 mmol) in dichloromethane (100 mL) at 0 °C. Solution was stirred at room temperature for 24 h. Reaction mixture was poured onto 200 mL of ice water and extracted with dichloromethane (2× 50 mL). The combined organic layers were washed with HCl (50 mL, 1 M), water (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material contained a mixture of **10b**, **11b** and **13b** in a ratio of 20/6:1 according to ^{1}H NMR spectrum. This material was taken up in a minimal amount of dichloromethane and subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–1:1) as eluent. Keto diol **10b** crystallized in eluent tubes and was recovered as needles. The remainder of the material was concentrated to give a mixture of **10b** and **11b** (0.433 g, 44%), in a ratio of 3:1 by ^{1}H NMR spectroscopy. 100 mg of the heterogeneous mixture was separated into its isomers using reverse-phase HPLC to give **10b** (0.060 g) as needles, m.p. 148–150 °C, R_f [heptane/ethyl acetate (1:1)] = 0.18. IR (film): $\tilde{\nu}$ = 3493, 3343, 2932, 2892, 2836, 1740, 1612, 1579, 1499, 1455, 1420, 1396, 1381, 1263, 1157, 1119, 1095, 1044, 1011, 969, 888, 803, 791, 706, 656, 599, 578, 560 cm^{-1}. $C_{15}H_{18}O_4$ (262.30): calcd. C 68.68, H 6.92; found C 68.82, H 6.99. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, J = 8.2 Hz, 1 H), 6.73 (m, 2 H), 3.78 (s, 3 H), 3.55 (dd, J = 10.6, 5.7 Hz, 1 H), 3.48–3.43 (m, 1 H), 3.42 (s, 1 H), 3.05 (s, 1 H), 2.97–2.90 (m, 1 H), 2.78 (dt, J = 14.7, 6.0 Hz, 1 H), 2.65–2.51 (m, 2 H), 2.40 (ddd, J = 14.0, 12.0, 5.6 Hz, 2 H), 1.98–1.88 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.9, 158.9, 141.2, 128.1, 127.9, 115.8, 111.2, 78.3, 70.6, 55.2, 47.9, 34.4, 29.8, 26.8, 22.5 ppm; and **11b** (0.025 g) as needles, m.p. 163–165 °C, R_f [heptane/ethyl acetate (1:1)] = 0.18. IR (film): $\tilde{\nu}$ = 3505, 3388, 2958, 1937, 2844, 1739, 1582, 1464, 1400, 1345, 1293, 1257, 1168, 1090, 1076, 1052, 1038, 978, 957, 896, 862, 841, 788, 747, 728, 704, 631, 578, 545 cm^{-1}. $C_{15}H_{18}O_4$ (262.30): calcd. C 68.68, H 6.92; found C 68.03, H 6.90. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.08 (m, 1 H), 6.77 (dd, J = 17.5, 7.8 Hz, 2 H), 4.22 (dd, J = 12.8, 8.0 Hz, 1 H), 3.98 (dd, J = 11.2, 3.5 Hz, 1 H), 3.80 (s, 3 H), 3.31 (s, 1 H), 2.96–2.81 (m, 2 H), 2.70 (ddd, J = 8.5, 7.3, 2.7 Hz, 1 H), 2.59–2.46 (m, 1 H), 2.41 (s, 1 H), 2.15–1.98 (m, 3 H), 1.90 (td, J = 11.1, 2.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 217.1, 158.3, 142.2, 127.7, 125.2, 122.6, 109.1, 80.2, 71.2, 55.8, 40.7, 33.4, 32.0, 29.6, 21.2 ppm. Compound **13b** was not isolated, but its ratio in the crude mixture was determined according to the characteristic peaks in the analogous compound **9a**.

(b) Using Titanium(IV) Chloride: Titanium(IV) chloride (0.95 mL, 0.95 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9b** (0.050 g, 0.19 mmol) in dichloromethane (4 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 10 mL of ice water and extracted with dichloromethane (2× 5 mL). The combined organic layers were washed with HCl (5 mL, 1 M), water (5 mL), and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of **10b** and **11b** (0.047 g, 95%), in a ratio of 10:1 by ^{1}H NMR spectroscopy.

(c) Using Aluminium(III) Chloride: Aluminium(III) chloride (19.5 mL, 19.5 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9b** (1 g, 3.8 mmol) in dichloromethane (100 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 200 mL of ice water and extracted with dichloromethane (2× 50 mL). The combined organic layers were washed with HCl (50 mL, 1 M), water (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of **10b**, **11b** and **13b** (0.047 g, 95%), in a ratio of 50:7:30 by ^{1}H NMR spectroscopy.

3-Chloro-2-[3-(3-chlorophenyl)-1-hydroxypropyl]-2-hydroxycyclopentanone (30)

(a) Using Aluminium(III) Chloride: Aluminium(III) chloride (0.375 g, 2.81 mmol) was added dropwise to a solution of **9c** (0.150 g, 0.562 mmol) in dichloromethane (10 mL) at 0 °C. Solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 20 mL of ice water and extracted with dichloromethane (3× 10 mL). The combined organic layers were washed with HCl (10 mL, 1 M), water (10 mL), and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material contained a mixture of products of cyclization **10c** and **13c** in a ratio of 1:4 according to ^{1}H NMR spectrum. The material was taken up in 2 mL of DMSO and purified by reverse-phase HPLC to give **13c** (0.051 g, 30%) as needles, m.p. 59–60 °C, R_f [heptane/ethyl acetate (1:1)] = 0.41. IR (film): $\tilde{\nu}$ = 3490, 3360, 2950, 2923, 1736, 1596, 1573, 1476, 1406, 1305, 1207, 1170, 1135, 1087, 1079, 1042, 1013, 956, 912, 903, 871, 822, 791, 763, 742, 701, 682, 639, 608, 558, 537 cm^{-1}. $C_{15}H_{18}O_4$ (262.30): calcd. C 55.46, H 5.32, Cl 23.39; found C 55.61, H 5.29, Cl 22.95. ^{1}H NMR (400 MHz): δ = 7.24–7.14 (m, 3 H), 7.10 (dt, J = 7.3, 1.5 Hz, 1 H), 4.24–4.20 (m, 1 H), 4.13 (dd, J = 10.6, 2.4 Hz, 1 H), 3.68 (s, 1 H), 3.41 (s, 1 H), 2.91 (ddd, J = 14.1, 9.5, 4.8 Hz, 1 H), 2.75–2.62 (m, 2 H), 2.55–2.49 (m, 2 H), 2.23 (dddd, J = 13.7, 6.2, 3.8, 1.1 Hz, 1 H), 1.94–1.75 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 217.1, 143.6, 134.1, 129.6, 128.6, 126.7, 126.1, 78.5, 70.0, 61.4, 32.3, 31.1, 30.4, 29.2 ppm. Under these purification conditions, it was not possible to isolate the products of cyclization.

(b) Using Tin(IV) Chloride: Tin(IV) chloride (2.81 mL, 2.81 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9c** (0.150 g, 0.562 mmol) in dichloromethane (10 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction combined organic layers were washed with HCl (10 mL, 1 M), water (10 mL), and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of products of cyclization **10c** and **13c** (0.048 g, 96% mass recovery), in a ratio of 14:13 by ^{1}H NMR spectroscopy.

(c) Using Titanium(IV) Chloride: Titanium(IV) chloride (0.93 g, 0.94 mmol) was added dropwise to a solution of **9c** (0.05 g, 0.19 mmol) in dichloromethane (3.5 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 10 mL of ice water and extracted with dichloromethane (2× 5 mL). The combined organic layers were washed with HCl (5 mL, 1 M), water (5 mL), and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of products of cyclization **10c** and **13c** (0.047 g, 95%), in a ratio of 6:5 by ^{1}H NMR spectroscopy.

***syn*-3a,4-Dihydroxy-8-methyl-1,2,3a,4,5,6-hexahydrobenzo[*e*]azulen-3(10bH)-one (10d), *syn*-3a,4-Dihydroxy-10-methyl-1,2,3a,4,5,6-hexahydrobenzo[*e*]azulen-3(10b*H*)-one (12d), and 3-Chloro-2-hydroxy-2-[1-hydroxy-3-(3-methylphenyl)propyl]cyclopentenone (13d)**

(a) Using Tin(IV) Chloride: Tin(IV) chloride (19.5 mL, 19.5 mmol, 1 M solution in dichloromethane) was added dropwise to a solution

of **9d** (1 g, 4.06 mmol) in dichloromethane (100 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 200 mL of ice water and extracted with dichloromethane (3× 50 mL). The combined organic layers were washed with HCl (50 mL, 1 M), water (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material contained a mixture of **10d**, **12d**, and **13d** in a ratio of 2:5:2 according to ^{1}H NMR spectrum. The crude material was taken up in a minimal amount of dichloromethane and subjected to column chromatography on silica gel using heptane/ethyl acetate (1:0–2:1) as eluent. This yielded one peak; the tubes were combined to yield **10d** and **12d** (0.48 g, 48%). 100 mg of the heterogeneous mixture was separated into its isomers using reverse-phase HPLC to give **10d** (0.06 g) as needles, m.p. 144–145 °C, R_f [heptane/ethyl acetate (1:1)] = 0.31. IR (film): $\tilde{\nu}$ = 3473, 3434, 3397, 2953, 2926, 2851, 1739, 1503, 1466, 1443, 1400, 1333, 1295, 1277, 1219, 1191, 1157, 1094, 1047, 1034, 964, 944, 902, 812, 787, 705, 662, 630, 590, 562, 542 cm^{-1}. $C_{15}H_{18}O_3$ (246.31): calcd. C 73.15, H 7.37; found C 72.78, H 7.34. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dd, J = 19.1, 7.6 Hz, 2 H), 6.94 (s, 1 H), 3.57 (dd, J = 10.6, 5.7 Hz, 1 H), 3.47 (t, J = 6.6 Hz, 1 H), 3.45 (s, 1 H), 3.03 (s, 1 H), 2.98–2.87 (m, 1 H), 2.79 (dt, J = 14.8, 6.0 Hz, 1 H), 2.61 (dt, J = 13.7, 10.0 Hz, 2 H), 2.40 (dd, J = 14.6, 7.5 Hz, 2 H), 2.31 (s, 3 H), 1.92 (ddt, J = 8.6, 7.0, 5.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.7, 136.7, 136.4, 135.7, 129.4, 128.2, 128.0, 78.4, 70.6, 48.7, 34.4, 29.1, 27.05, 22.22, 21.11 ppm; and **12d** (0.015 g) as needles, m.p. 147–149 °C, R_f [heptane/ethyl acetate (1:1)] = 0.31. IR (film): $\tilde{\nu}$ = 3464, 3436, 3396, 2953, 2928, 2895, 2885, 1743, 1502, 1445, 1396, 1349, 1330, 1296, 1274, 1215, 1157, 1089, 1045, 1013, 974, 959, 899, 810, 708, 647, 592, 562 cm^{-1}. $C_{15}H_{18}O_4$ (262.30): calcd. C 72.78, H 7.34; found C 72.77, H 7.33. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, J = 1.1 Hz, 2 H), 6.99 (s, 1 H), 3.54 (dd, J = 10.2, 6.2 Hz, 1 H), 3.48 (t, J = 6.3 Hz, 1 H), 3.45 (d, J = 3.9 Hz, 1 H), 3.07 (s, 1 H), 2.99–2.89 (m, 1 H), 2.78 (dt, J = 14.7, 6.0 Hz, 1 H), 2.68–2.50 (m, 2 H), 2.46–2.36 (m, 2 H), 2.31 (s, 3 H), 1.93 (m, 2 H) ppm. ^{13}C NMR (101 MHz): δ = 220.0, 139.6, 137.2, 132.7, 130.4, 127.4, 127.0, 78.2, 70.6, 48.1, 34.5, 29.4, 26.8, 22.3, 20.8 ppm. Compound **12d** was not isolated, but its ratio in the crude mixture was determined according to the characteristic peaks in the analogous compound **24**.

(b) Using Titanium(IV) Chloride: Titanium(IV) chloride (1.01 mL, 1.01 mmol, 1 M solution in dichloromethane) was added dropwise to a solution of **9d** (0.050 g, 0.203 mmol) in dichloromethane (4 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 200 mL of ice water and extracted with dichloromethane (2× 50 mL). The combined organic layers were washed with HCl (50 mL, 1 M), water (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of **10d**, **12d** and **13d** (0.048 g, 96% mass recovery), in a ratio of 11:7:1 by ^{1}H NMR spectroscopy.

(c) Using Aluminium(III) Chloride: Aluminium(III) chloride (0.135 g, 1.01 mmol) was added dropwise to a solution of **9d** (0.05 g, 0.20 mmol) in dichloromethane (4 mL) at 0 °C. The solution was stirred at room temperature for 24 h. The reaction mixture was poured onto 10 mL of ice water and extracted with dichloromethane (2× 5 mL). The combined organic layers were washed with HCl (5 mL, 1 M), water (5 mL), and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of **10d**, **12d** and **13d** (0.047 g, 95%), in a ratio of 7:5:1 by ^{1}H NMR spectroscopy.

X-ray Data Collection: Data collections for all samples were carried out on a Bruker Apex II diffractometer with SMART CCD area detector utilizing Mo-K_α radiation (λ = 0.71073) and a graphite monochromator. The data collection, cell refinement, and data reduction were performed using SHELXTL.[25] The absorption corrections were made by redundant data using SADABS.[26] All structures were solved employing direct methods and expanded by Fourier techniques.[27] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms bonded to carbon atoms were placed in calculated positions and refined using a riding model with fixed isotropic U values. Hydrogen atoms bonded to oxygen atoms were located in the difference map and their positions refined using fixed isotropic U values. In Table S1 full crystal and refinement details are given, while selected bond lengths and angles are given in Table S2. Hydrogen bond data are presented in Table S3.

CCDC-788542 (for **9b**), -788543 (for **10b**), -788546 (for **11b**), -788544 (for **10d**), -788545 (for **12d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Detailed discussion of molecular structure and lattice packing for compounds **20**, **26**, **27**, **31** and **32** along with crystal data, selected bond lengths and angles, and hydrogen bonding parameters. ^{1}H and ^{13}C NMR spectra for compounds **9a**, **9b**, **9c**, **9d**, **10a**, **10b**, **10c**, **10d**, **11b**, **12d** and **13a**.

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Disclosure

Adrian D. Hobson and Donald B. Konopacki are employees at AbbVie. The design, study conduct, and financial support for the research were provided by AbbVie. Kelley C. Shortsleeves, and Mark M. Turnbull are employees at Clark University. Jan L. Wikaira is an employee of the University of Canterbury. AbbVie, Clark University and the University of Canterbury participated in the interpretation of data, review, and approval of the publication.

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