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


Keywords: Lewis acids / Cyclization / Epoxidation / Methyl migration

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], resiniferatoxin (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 (−)-prespherene[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.

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-
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(2H)-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 [tBHP 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 AlCl3, SnCl4, TiCl4 and BF3OEt2 selected as the panel of Lewis acids.

Treatment of epoxy alcohol 9a with AlCl3 (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 aspects 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 SnCl4 (5 equiv.) and TiCl4 (5 equiv.) at room temperature for 24 h. For these reactions, the compounds were not isolated; instead the spectroscopic data from the AlCl3 reaction were used to establish the ratio of 10a and 13a. In the case of treatment with SnCl4 tricycle 10a and chlorohydrin 13a were obtained in 91% yield in a ratio of 6:1. After treatment with TiCl4, tricycle 10a was the only isolated product in 92% yield.

Treatment of epoxy alcohol 9a with BF3·OEt2 (5 equiv.) at 20 °C for 3 h afforded compound 14b as white needles. Surprisingly, analysis by 13C NMR showed the absence of the carbonyl of the expected cyclization product. Consideration of both 1H and 13C 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 BF3·OEt2 was not included in further studies. Instead SnCl4, TiCl4, and AlCl3 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 epoxy 9b with SnCl4 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 TiCl4 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 epoxy 9b with AlCl3 gave the same 3 products observed in the SnCl4 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 AlCl3 and TiCl4

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

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>R</th>
<th>Lewis acid</th>
<th>Product (yield [%])</th>
<th>Product (yield [%])</th>
<th>Product (yield [%])</th>
<th>Product (yield [%])</th>
<th>Product (yield [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>H</td>
<td>SnCl4</td>
<td>10a (79)[a]</td>
<td>10a (92)[a]</td>
<td>10a (23)[b]</td>
<td>10a (30)[b]</td>
<td>10a (34)[b]</td>
</tr>
<tr>
<td>9a</td>
<td>OMe</td>
<td>SnCl4</td>
<td>10b (33)[a]</td>
<td>11b (11)[a]</td>
<td>11b (9)[a]</td>
<td>11b (7)[a]</td>
<td>11b (6)[a]</td>
</tr>
<tr>
<td>9b</td>
<td>OMe</td>
<td>TiCl4</td>
<td>10b (86)[a]</td>
<td>11b (9)[a]</td>
<td>11b (7)[a]</td>
<td>11b (6)[a]</td>
<td>11b (6)[a]</td>
</tr>
<tr>
<td>9b</td>
<td>OMe</td>
<td>AlCl3</td>
<td>10b (55)[a]</td>
<td>11b (8)[a]</td>
<td>11b (7)[a]</td>
<td>11b (5)[a]</td>
<td>11b (5)[a]</td>
</tr>
<tr>
<td>9c</td>
<td>Cl</td>
<td>SnCl4</td>
<td>10c (49)[a]</td>
<td>10c (51)[a]</td>
<td>10c (30)[b]</td>
<td>10c (30)[b]</td>
<td>10c (30)[b]</td>
</tr>
<tr>
<td>9c</td>
<td>Cl</td>
<td>TiCl4</td>
<td>10c (51)[a]</td>
<td>10c (30)[b]</td>
<td>10c (30)[b]</td>
<td>10c (30)[b]</td>
<td>10c (30)[b]</td>
</tr>
<tr>
<td>9d</td>
<td>Me</td>
<td>SnCl4</td>
<td>10d (14)[a]</td>
<td>12d (34)[a]</td>
<td>12d (34)[a]</td>
<td>12d (34)[a]</td>
<td>12d (34)[a]</td>
</tr>
<tr>
<td>9d</td>
<td>Me</td>
<td>TiCl4</td>
<td>10d (55)[a]</td>
<td>12d (35)[a]</td>
<td>12d (35)[a]</td>
<td>12d (35)[a]</td>
<td>12d (35)[a]</td>
</tr>
</tbody>
</table>

[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 SnCl₄ 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 AlCl₃ or TiCl₄ cyclizations. Although chlorohydrin 13b was not isolated, peaks in the crude ¹H NMR spectra correlated with the R₂CH-Cl and R₂CH-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 AlCl₃ 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 AlCl₃ 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 ¹H 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 SnCl₄ and TiCl₄ 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 ¹H 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 SnCl₄ 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 TiCl₄ 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 ¹H NMR spectroscopy. Surprisingly, treatment of epoxy alcohol 9d with AlCl₃ 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 P2₁/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 12d also crystallizes in the monoclinic space group P2₁/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 CH₃ group is positioned away from the
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 affording 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 Weyland 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]azulene-3(2H)-ones has been established via a linear 3-step route: i) annulation with 2-cyclopentenone, ii) stereo-
selective epoxidation, iii) Lewis acid catalyzed cyclization. TiCl₄ and SnCl₄ were identified as the preferred Lewis acids for catalyzing the final cyclization step and afforded primarily the desired tricylic compounds while AlCl₃ 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 BF₃·OEt₂ 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 CDCl₃ 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 DuraSampler accessory, yields are judged to be determined using ultra-violet light. Column chromatography was performed on Merck HPTLC plates and visualized using ultra-violet light. Column chromatography was performed by using an AnaLogix Intelliflash 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 (2 × 20 mL). The resulting mixture was filtered and the organic layer was dried with MgSO₄ and concentrated under reduced pressure. This yielded 5b (3.9 g, 68.9 %) as a colourless oil, \(R_f \) [heptane/ethyl acetate (1:1)] = 0.72. IR (film): \(\tilde{\nu} = 2951, 2723, 1721, 1597, 1573, 1476, 1436, 1408, 1388, 1314, 1257, 1157, 1036, 944, 872, 779, 640, 553 \text{ cm}^{-1}\). \(^1\)H NMR (400 MHz): \(\delta = 8.49; \text{found C} 79.62, \text{H} 9.39. \) 1H NMR (400 MHz): \(\delta = 7.17 \text{ (t, } J = 7.5 \text{ Hz, } 1 \text{ H), } 7.05-6.92 \text{ (m, } 3 \text{ H), } 3.65 \text{ (t, } J = 6.5 \text{ Hz, } 2 \text{ H), } 2.71-2.60 \text{ (m, } 2 \text{ H), } 2.32 \text{ (s, } 3 \text{ H), } 1.93-1.83 \text{ (m, } 2 \text{ H), } 1.47 \text{ (s, } 1 \text{ H) ppm.} \) 13C NMR (101 MHz): \(\delta = 142.0, 138.2, 129.5, 128.6, 126.9, 125.7, 62.6, 35.4, 32.5, 21.6 \text{ ppm.} \)

3-(3-Methylphenyl)propan-1-ol (5d): A solution of 3-(3-methylyl)propiolic 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 MgSO₄ 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): \(\tilde{\nu} = 3306, 2935, 1607, 1485, 1449, 1377, 1043, 912, 779, 694 \text{ cm}^{-1}\). \(^1\)H NMR (400 MHz): \(\delta = 7.17 \text{ (t, } J = 7.5 \text{ Hz, } 1 \text{ H), } 7.05-6.92 \text{ (m, } 3 \text{ H), } 3.65 \text{ (t, } J = 6.5 \text{ Hz, } 2 \text{ H), } 2.71-2.60 \text{ (m, } 2 \text{ H), } 2.32 \text{ (s, } 3 \text{ H), } 1.93-1.83 \text{ (m, } 2 \text{ H), } 1.67 \text{ (s, } 1 \text{ H) ppm.}\) 13C NMR (101 MHz): \(\delta = 140.2, 138.2, 129.5, 128.6, 125.7, 62.6, 35.4, 32.5, 21.6 \text{ ppm.} \)
3-(Methylphenyl)propional (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. NaHCO3 (3 x 20 mL) and water (50 mL), dried with MgSO4, filtered, and concentrated under reduced pressure. This yielded 6d (0.68 g, 89%) as a colourless oil, Rf [heptane/ethyl acetate (1:1)] = 0.72. IR (film): ν = 3021, 2920, 2722, 1721, 1608, 1589, 1488, 1447, 1307, 1171, 1094, 1055, 906, 883, 781, 697, 572, 534 cm−1. 1H NMR (400 MHz): δ = 7.43 (t, J = 7.5 Hz, 1 H), 7.24–7.13 (m, 3 H), 7.11–7.06 (m, 1 H), 2.88–2.78 (m, 3 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), 2.04–1.95 (m, 2 H) ppm. 13C NMR (101 MHz): δ = 201.5, 201.6, 140.2, 138.2, 129.0, 128.5, 127.0, 125.2, 42.8, 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 (0.021 g, 0.8 mmol) in refluxing benzene (90 mL) in a Dean–Stark apparatus. The solution was heated at reflux for 5 h. Reaction mixture was cooled, then washed with saturated sodium bisulfate solution (2 x 20 mL) and water (20 mL), dried with MgSO4, 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 8a (2.2 g, 84%) as a pale yellow oil, Rf [heptane/ethyl acetate (1:1)] = 0.31. IR (film): ν = 3408, 2920, 2858, 1629, 1495, 1452, 1438, 1339, 1252, 1070, 999, 919, 788, 747, 698 cm−1, C15H18O3 (246.31): calcd. C 77.75, H 7.46; found C 78.58, H 7.88. 1H NMR (400 MHz, CDCl3): δ = 4.48–4.43 (m, 1 H), 2.85–2.64 (m, 3 H), 2.64–2.57 (m, 2 H), 2.43 (dd, J = 4.2, 2.7, 1.1 Hz, 2 H), 2.05–1.93 (m, 2 H) ppm. 13C NMR (101 MHz): δ = 210.0, 157.9, 147.3, 143.7, 134.1, 129.6, 128.7, 126.7, 126.1, 76.0, 36.8, 35.2, 31.3, 26.6 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, Rf [heptane/ethyl acetate (1:1)] = 0.31. IR (film): ν = 3409, 3059, 2920, 2860, 1681, 1629, 1572, 1476, 1433, 1341, 1253, 1197, 1076, 998, 919, 878, 783, 696, 682 cm−1. C15H18O2 (230.31): calcd. C 78.23, H 7.88; found C 77.98, H 8.00. 1H 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 (dd, J = 4.2, 2.7, 1.1 Hz, 2 H), 2.05–1.93 (m, 2 H) ppm. 13C NMR (101 MHz): δ = 210.0, 157.9, 147.3, 143.7, 134.1, 129.6, 128.7, 126.1, 76.0, 36.8, 35.2, 31.3, 26.6 ppm.
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, \( R_s [\text{heptane/ethyl acetate (1:1)}] = 0.20 \), recrystallized from diethyl ether, m.p. 65–66 °C. IR (film): \( \nu = 3491, 2949, 1727, 1599, 1467, 1452, 1292, 1257, 1164, 1036, 951, 897, 865, 781, 730, 697, 564 \text{ cm}^{-1} \). \( \text{C}_8\text{H}_8\text{O}_2 \) (262.30): calcd. C 68.68, H 6.92; found C 68.89, H 7.32. 

\( \text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.23 (m, 1 H), 2.12 (ddd, 1 H), 2.72 (dd, 1 H) \) ppm. \( \text{C} \) NMR (101 MHz, CDCl\(_3\)): \( \delta = 210.5, 159.7, 143.1, 129.4, 120.8, 114.1, 111.4, 64.6, 64.5, 62.0, 55.1, 33.6, 32.3, 31.3, 22.0 \) ppm.

**syn-2,3-Oxirano-2-[1-hydroxy-3-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 acetylactonate (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 \( \times 25 \) 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, \( R_s [\text{heptane/ethyl acetate (1:1)}] = 0.44 \). IR (film): \( \nu = 3453, 2931, 1736, 1597, 1572, 1476, 1476, 1302, 1077, 1036, 988, 688, 783, 680, 571, 538 \text{ cm}^{-1} \). \( \text{C}_8\text{H}_{12}\text{O}_3 \) (172.24): calcd. C 62.92, H 6.35, Cl 13.17; found C 62.68, H 6.32, Cl 13.22. 1H NMR (400 MHz, CDCl\(_3\)): \( \delta = 2.46–2.35 (m, 1 H), 2.31–2.23 (m, 2 H), 2.19–2.09 (m, 1 H), 1.98–1.84 (m, 3 H) \) ppm.

**syn-2,3-Oxirano-2-[1-hydroxy-3-(3-chlorophenyl)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 (3.13 g, 13.0 mmol) and vanadyl acetylactonate (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 \( \times 25 \) 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 (1:0–1:1) as eluent. This yielded 9d (1.98 g, 62%) as a pale yellow oil, \( R_s [\text{heptane/ethyl acetate (1:1)}] = 0.51 \). IR (film): \( \nu = 3465, 2926, 2864, 1737, 1608, 1487, 1487, 1406, 1036, 866, 782, 570 \text{ cm}^{-1} \). \( \text{C}_8\text{H}_{12}\text{O}_3 \) (172.24): calcd. C 63.15, H 6.79; found C 63.08, H 6.84. \( \text{C}_8\text{H}_{12}\text{O}_3 \) (172.24): calcd. C 63.15, H 6.79; found C 63.08, H 6.84. 1H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.23–7.12 (m, 1 H), 6.83–7.06 (m, 2 H), 4.21 (t, 1 H, J = 6.2 Hz, 1 H) \) ppm. \( \text{C} \) NMR (101 MHz, CDCl\(_3\)): \( \delta = 159.7, 143.1, 129.4, 120.8, 114.1, 111.4, 64.6, 64.5, 62.0, 55.1, 33.6, 32.3, 31.3, 22.0 \) ppm.

(b) Using Tin(IV) Chloride: Tin(IV) chloride (2.15 mL, 2.15 mmol, 1 mol 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 \( \times 10 \) mL). The combined organic layers were washed with HCl (10 mL, 1 mol), 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 \( ^1\text{H} \) NMR spectroscopy.

(c) Using Titanium(IV) Chloride: Titanium(IV) chloride (2.15 mL, 2.15 mmol, 1 mol 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 \( \times 10 \) mL). The combined organic layers were washed with HCl (10 mL, 1 mol), 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 \( ^1\text{H} \) NMR spectroscopy.

(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 \( \times 30 \) mL). The combined organic extracts were washed with water (2 \( \times 30 \) mL) and saturated sodium chloride solution (30 mL), dried (Na\(_2\)SO\(_4\)), 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, \( R_s [\text{CHCl}_3] = 0.70 \). IR (KBr disc): \( \nu = 3459 \) (br), 3067, 3017, 2947, 2870 and 1492 cm\(^{-1} \). \( \text{C}_8\text{H}_{12}\text{O}_3 \) (172.24): calcd. C 68.68, H 6.92; found C 68.48, H 6.74. H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.23–7.05 (m, 4 H), 4.34 (dt, 1 H, J = 11.5 \text{ and } 5.5 \text{ Hz}, 1 H), 3.59 (dd, 1 H, J = 12.5 \text{ and } 6.5 \text{ Hz}, 1 H), 2.79–2.57 (m, 4 H), 2.33–1.79 (m, 2 H) \) ppm. \( \text{C} \) NMR (101 MHz, CDCl\(_3\)): \( \delta = 141.4 \) (s), 136.4 (s), 131.3 (d), 129.5 (d), 127.1 (d), 126.7 (d), 112.5 (s), 87.9
Straightforward Synthesis of Octahydrobenzo[e]azulenes

(s). 75.0 (d), 50.9 (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(10bH)-one (26), syn-3a,4-Dihydroxy-10-methoxy-1,2,3a,4,5,6-hexahydrobenzo[e]azulen-3(10bH)-one (11b), and 3-Chloro-2-hydroxy-2-[1-hydroxy-3-(3-methylphenyl)propyl]cyclopentanone (13b): (a) Using Tin(IV) Chloride: Tin(IV) chloride (19.5 mL, 19.5 mmol, 1 mL 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 MgSO₄, 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 1H 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 MgSO₄, 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 1H 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, Rf (heptane/ethyl acetate (1:1)) = 0.41. IR (film): ν = 3490, 3360, 2950, 2923, 1736, 1596, 1573, 1476, 1406, 1305, 1207, 1170, 1135, 1087, 1047, 1041, 913, 902, 871, 822, 791, 763, 742, 701, 682, 639, 608, 558, 537 cm⁻¹. C₁₉H₁₄O₄ (295): calcd. C 68.68, H 6.92; found C 68.82, H 6.99. 1H NMR (400 MHz, CDCl₃): δ = 7.42–7.14 (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 (dd, 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. 13C NMR (101 MHz, CDCl₃): δ = 217.1, 143.6, 134.1, 129.6, 126.8, 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 mL solution in dichloromethane) was added dropwise to a solution of 9e (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 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 MgSO₄, filtered, and concentrated under reduced pressure. The crude material contained a mixture of products of cyclization 10e and 13e (0.048 g, 96% mass recovery), in a ratio of 14:13 by 1H NMR spectroscopy.

(c) Using Titanium(IV) Chloride: Titanium(IV) chloride (0.93 g, 0.94 mmol) was added dropwise to a solution of 9e (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 MgSO₄, filtered, and concentrated under reduced pressure to give a mixture of 10e and 13e (0.047 g, 95%), in a ratio of 6:5 by 1H 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(10bH)-one (10d), and 3-Chloro-2-hydroxy-2-[1-hydroxy-3-(3-methylphenyl)propyl]cyclopentanone (13d)

(a) Using Tin(IV) Chloride: Tin(IV) chloride (19.5 mL, 19.5 mmol, 1 mL 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 MgSO₄, 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 ¹H 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 (1:1) 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, R₉ [heptane/ethyl acetate (1:1)] = 0.31. IR (film): ν = 3473, 3343, 3397, 2953, 2926, 2851, 1519, 1466, 1443, 1400, 1333, 1295, 1277, 1219, 1191, 1157, 1094, 1047, 1034, 964, 944, 902, 812, 787, 705, 662, 590, 562, 542 cm⁻¹. C₁₅H₁₈O₃ (246.31): calcd. C 34.34, 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, 590, 562, 542 cm⁻¹. C₁₅H₁₈O₃ (246.31): calcd. C 34.34, 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, 590, 562, 542 cm⁻¹.

Acknowledgments

Prof. Charles M. Marson is thanked for his guidance and Prof. Peter Wipf for useful discussions and help in preparing this manuscript.

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.

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.

1H and 13C NMR spectra for compounds 9a, 9b, 9c, 9d, 10a, 10b, 10c, 10d, 11b, 12d and 13a.

References

Straightforward Synthesis of Octahydrobenzo[e]azulenes


[26] G. M. Sheldrick, SADABS, Program for Empirical Absorption Correction of Area Detector Data, University of Göttingen, Germany.

Received: April 10, 2015
Published Online: July 15, 2015
学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：
图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具