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# Asymmetric Synthesis of *cis*-7-Methoxycalamenene via the Intramolecular Buchner Reaction of an *α*-Diazoketone

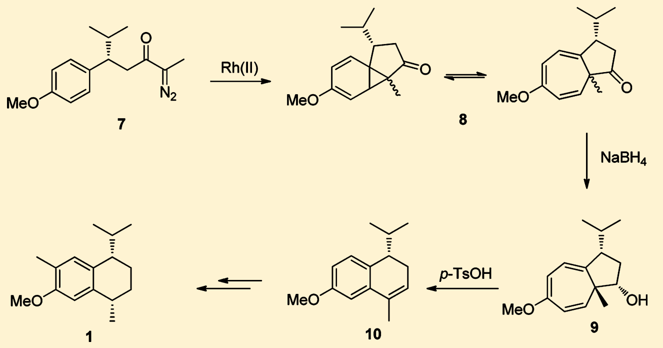
Paul A. McDowell,[†] David A. Foley,[†] Patrick O'Leary,[†,§] Alan Ford,[†] and Anita R. Maguire*[,‡]

[†]Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

[‡]Department of Chemistry & School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

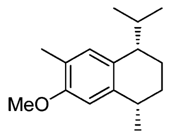
Ⓢ *Supporting Information*

**ABSTRACT:** The asymmetric synthesis of *cis*-7-methoxycalamenene **1** has been accomplished using the intramolecular Buchner reaction of *α*-diazoketone **7** as the key step in the synthetic route. Upon reduction of the equilibrating azulenone structure **8**, the resulting azulenol **9** rearranges to dihydronaphthalene **10** containing the 6,6-membered bicyclic ring system characteristic of **1**, by means of an acid-catalyzed aromatization process. Transformation of **10** to **1** is accomplished through a three-step reaction sequence.



The intramolecular version of the transition-metal-catalyzed Buchner reaction of *α*-diazoketones was first reported by Julia et al.[1] This process, involving the rhodium-catalyzed reaction of an *α*-diazoketone and addition of the resulting carbenoid to an aromatic system has been extensively studied over many years.[2−6] Many aspects of this transformation have been investigated, including diastereo-, regio-, and enantioselectivity.[2−6] The proposed mechanism for the cyclization involves initial cyclopropanation of the aromatic ring to form the norcaradiene tautomer, which is in dynamic equilibrium with the cycloheptatriene tautomer by means of a reversible electrocyclic ring-opening process.[7,8] Upon ring-opening, the relative stereochemistry between the substituent at the C(3) position and the bridgehead methyl group remains intact.

Our interest in the intramolecular Buchner process has extended to the synthesis of compounds possessing the bicyclo[5.3.0]decane skeleton, characteristic of many sesquiterpenoid natural products, from readily available dihydrocinnamic acid precursors. Synthetic approaches to this ring system have been extensively reviewed.[9,10] The asymmetric synthesis of *cis*-7-methoxycalamenene **1** using the intramolecular Buchner process is outlined.



*cis*-7-Methoxy-calamenene **1**

*cis*-7-Methoxycalamenene **1**, a cadinane sesquiterpene, contains the bicyclo[4.4.0]decane carbon framework. The cis calamenene sesquiterpenoid family are found as natural products in the foliage of *Cupressus bakeri*, a species of cypress native to the United States. The isolation of this sequiterpene family from the Madagascan shrub, *Tarenna madagascariensis*, has been reported.[11] The isolation of **1** in particular from a cell culture of liverwort has been documented.[12] The synthesis of **1** has been described in the literature as a single enantiomer,[13] while other synthetic routes have also been documented involving the preparation of **1** as a racemic mixture of cis and trans isomers[14] and as the individual cis and trans isomers in racemic form.[15]

The enantioenriched dihydrocinnamic acid **6** was synthesized from **5**, which had been described by Hruby et al.[16−18] as part of their synthesis of novel amino acids (Scheme 1). Hydrolysis of the *β*-substituted acyl oxazolidinone **5** following the procedure described by Evans et al.[19] afforded acid **6** with an enantiopurity of 96% ee determined by chiral HPLC (Scheme 1).

The *α*-diazocarbonyl precursor **7** was generated in two synthetic steps from **6** via initial acid chloride formation followed by treatment with diazoethane.[20] Cyclization of **7** to azulenone **8** was performed via the standard procedure for this transformation[2−6] (Scheme 2). The cyclization is found to be rapid, with reaction completion obtained once the diazoketone addition is complete. The synthesis of the corresponding racemic series was conducted in parallel with the enantiopure series as shown in Scheme 2. The synthesis of the racemic dihydrocinnamic acid (±)-**6** and subsequent transformation to the corresponding azulenone (±)-**8** have been previously described by our research team.[4]

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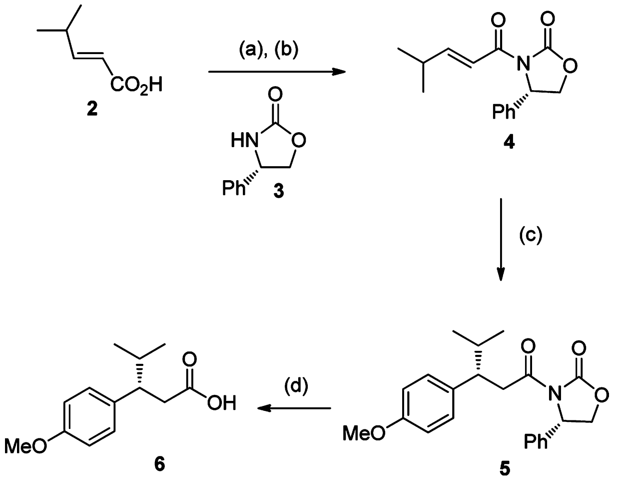
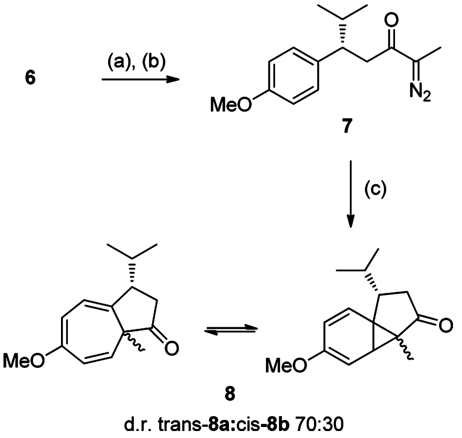
**Scheme 1. Synthesis of 6**



(a) $(COCl)_2$, $Et_2O$, 0 °C to rt, 64%. (b) **3**, *n*-BuLi, THF, −78 to 0 °C, 72%. (c) *p*-MeOPhMgBr, CuBr·$SMe_2$, THF, −15 °C to rt, 68%. (d) 30% $H_2O_2$, LiOH·$H_2O$, THF/$H_2O$, 0 °C, **6**, 84%, ee = 96%.

**Scheme 2. Synthesis of 8**



(a) $(COCl)_2$, $Et_2O$, 0 °C to rt. (b) $CH_3CHN_2$, $Et_2O$, −20 °C to rt, 65% in two steps. (c) $Rh_2(OAc)_4$, $CH_2Cl_2$, reflux, **8**, 84%.

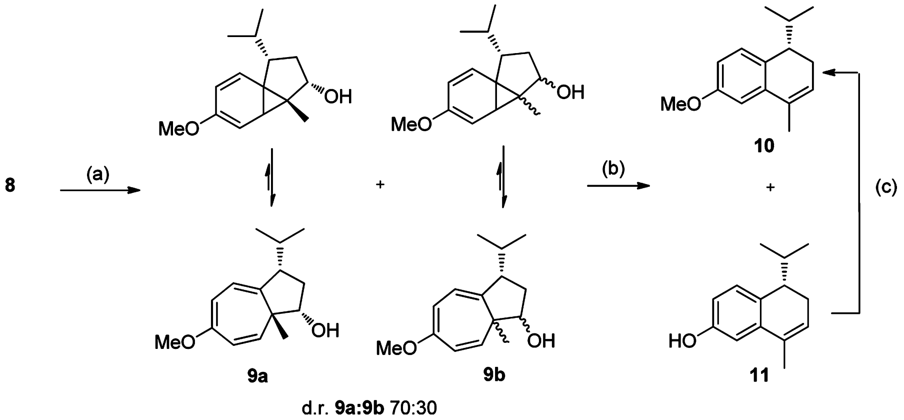
In general, the cyclization of related $\alpha$-diazoketones with unsubstituted phenyl rings are found to be highly diastereoselective with the trans isomer predominating, whereby the substituent at the C(3) position and the bridgehead methyl group are trans to each other. Although the cyclization proceeds with high diastereocontrol, equilibration of the trans and cis isomers initiated by the presence of the methoxy group takes place,[4] resulting in the formation of the trans and cis isomers in an approximate ratio of 70:30.

Reduction of **8** to azulenol **9** was conducted as illustrated in Scheme 3. The azulenol **9** exists as an inseparable mixture of diastereomers, the major diastereomer **9a** being where the hydroxyl substituent and the bridgehead methyl group are trans to each other. This major diastereomer, **9a**, is derived from the trans azulenone isomer **8a**. The stereochemistry of the minor diastereomer **9b** has not been determined. It is envisaged that **9b** could either be the epimer of **9a** at C(1) or that formation of **9b** is due to reduction of the cis azulenone isomer **8b**. Upon reduction, the complex dynamic nature of the bicyclic system is greatly simplified. The two diastereomers **9a**/**9b** can no longer interconvert, and even though both exist in dynamic equilibrium with their norcaradiene tautomers, the cycloheptatriene tautomer predominates to a very large extent.

On exposure to *p*-toluenesulfonic acid, azulenol **9** is found to undergo an interesting rearrangement resulting in the formation of dihydronaphthalenes **10** and **11**. The crude mixture of **10** and **11** was then conveniently methylated in situ, forming the methoxy dihydronaphthalene **10** (Scheme 3), which has been reported by Gatti et al. as an intermediate in the latter stages of their asymmetric synthesis of **1**.[13] While the synthesis undertaken clearly leads to (*S*)-**10**, it is worth noting that the sign of the specific rotation is opposite to that described by Gatti et al. for the same compound $\{[\alpha]_D^{20} = +68.45$ (*c* 1.0, $CHCl_3$); lit.[13] $[\alpha]_D^{20} = -40.5$ (*c* 1.03, $CHCl_3$)$\}$.[13] However, transformation of **10** through to **1** proceeded as expected giving (−)-**1**, confirming the absolute stereochemistry of the intermediate and the final product.

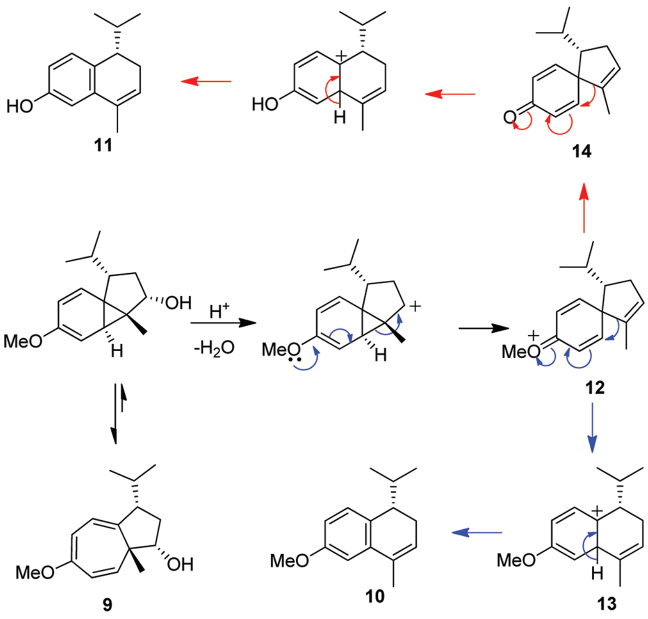
The formation of dihydronaphthalenes from azulenol precursors has not previously been described in the literature. Although **9** exists predominantly as the cycloheptatriene form, the aromatization process presumably takes place via the minor norcaradiene tautomer (Scheme 4). Protonation of **9** followed by loss of water leads to a cyclopropane-stabilized carbocation, which undergoes ring-opening to give the cationic spiro intermediate **12**, enabled by the presence of the electron donating methoxy substituent. Ring expansion of **12** to the bicyclic cationic intermediate **13** is followed by rearomatization, giving **10**. The intermediate **12** can also undergo

**Scheme 3. Synthesis of 10**



(a) $NaBH_4$, EtOH, 0 °C to rt, 95%. (b) *p*-TsOH·$H_2O$, toluene, rt. (c) $CH_3I$, $K_2CO_3$, acetone, reflux, **10**, 53% in two steps.

**Scheme 4. Formation of Dihydronaphthalenes 10 and 11 from 9**

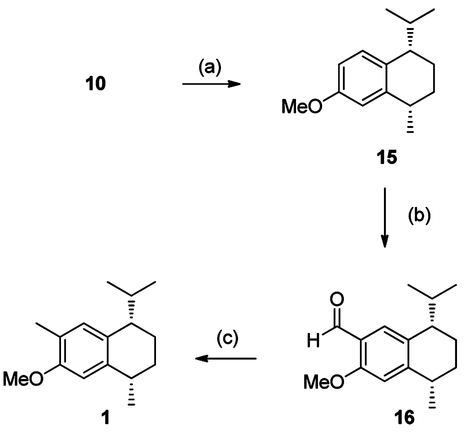


demethylation or exchange with water, forming the spiro dienone **14**, which can rearrange and rearomatize as before, yielding **11**. This demethylation occurs in competition with the skeletal rearrangement resulting in the formation of both products **10** and **11**.

Thus, while the intramolecular Buchner reaction of $\alpha$-diazoketones provides a facile route to the bicyclo[5.3.0]decane ring system characteristic of many sesquiterpenoid natural products, this transformation also allows access to the bicyclo[4.4.0]-decane skeleton, characteristic of **1**, via the same azulenone intermediate **8**. The reduction of **8** and subsequent acid-catalyzed aromatization of **9** forming dihydronaphthalenes **10** and **11** is a novel and convenient way of obtaining a 6,6-membered fused ring system from the corresponding 7,5-membered bicyclic structure. The tautomerisation between the norcaradiene and cycloheptatriene tautomers is critical in allowing the formation of both ring systems from the same azulenone structure **8**.

The remaining steps in the synthesis were conducted following the route described by Gatti et al.[13] (Scheme 5). Hydrogenation of **10** over palladium on carbon gave the cis diastereomer **15**. The formyl group was regioselectively introduced to the aromatic ring using Vilsmeier chemistry followed by reduction of the resulting aldehyde **16** to the final product **1** over palladium on carbon. The observed specific rotation of $[\alpha]_D^{20} = -32.0$ (*c* 1.0, $CHCl_3$) was in good agreement with the corresponding value of $[\alpha]_D^{20} = -30.3$ (*c* 0.92, $CHCl_3$) reported in the literature.[13] The enantiopurity of (−)-**1** was determined to be 95% ee by chiral HPLC.

**Scheme 5. Synthesis of 1**



(a) $H_2$, 1 atm, Pd/C, EtOH, 89%. (b) $P_2O_3Cl_4$, DMF, 0 °C to reflux, 72%. (c) $H_2$, 1 atm, Pd/C, EtOH, **1** 89%, ee = 95% by chiral HPLC.

The synthetic plan outlined above involves six steps from the enantiopure dihydrocinnamic acid precursor **6** to the methoxy dihydronaphthalene **10** in a yield of 17%, a more concise synthesis than that previously reported.[13] The overall yield obtained for (−)-**1** of 7% from (*S*)-**6** also compares favorably with the corresponding yield of 3% in the synthesis described by Gatti et al.[13] All reaction steps in this work are simple and proceed with good yields. The work outlined above demonstrates the synthetic utility of the intramolecular Buchner cyclization of $\alpha$-diazoketones in the area of sesquiterpenoid natural product synthesis. The methoxy dihydronaphthalene **10** has also been used as an intermediate in a number of other syntheses.[21−23] Hence, the synthesis of (*S*)-**10** via this methodology could also be used as a route to other structurally related sesquiterpenes.

## ■ EXPERIMENTAL SECTION

**General Experimental Methods.** All reactions were carried out under a nitrogen atmosphere. Where necessary, solvents were routinely dried and distilled prior to use. Diazoethane solutions in ether were freshly prepared prior to use and were used undistilled. All commercial reagents were used as received unless otherwise stated. Rhodium(II) acetate dimer was kindly donated by Johnson Matthey. Organic phases were dried using anhydrous magnesium sulfate. Diastereomeric ratios (d.r.) were determined by $^1H$ NMR spectroscopy. In the cases of minor diastereomers, spectral characteristics reported are those that were easily distinguished from those due to the major diastereomer. Cyclization efficiency (%) was determined by $^1H$ NMR spectroscopy.

Infrared (IR) spectra were obtained as films on NaCl plates or as KBr disks, and wavelengths ($\nu$) are reported in $cm^{-1}$. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ (300 and 75.5 MHz, respectively) unless otherwise stated. Chemical shifts ($\delta$) are given downfield from tetramethylsilane. Melting points obtained are uncorrected. Flash column chromatography was carried out using Kieselgel 60, 0.040−0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 $PF_{254}$). Enantiopurity of chiral compounds was determined by chiral HPLC performed on a Chiralpak ASH or Chiralcel OJH column. Details of the column conditions and mobile phases employed are included under the corresponding compounds. Optical rotations were measured at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^{20}$ is the specific rotation of a compound and is expressed in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Specific rotations were employed to confirm the enantiomeric series. High resolution mass spectrometry (HRMS) was performed on a TOF instrument in electrospray ionization (ESI) mode; samples were made up in acetonitrile.

**(*E*)-4-Methyl-pent-2-enoic acid 2.**[24] This was prepared following the procedure described by Pirrung et al.[24] from isobutyraldehyde (5.48 g, $7.60 \times 10^{-2}$ mol), malonic acid (5.00 g, $4.80 \times 10^{-2}$ mol), pyridine (15 mL), and morpholine (75 $\mu$L) to give the *acid* **2** (5.00 g, 91%) as a colorless oil: IR (NaCl) 2967, 1699, 1652 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.08 (d, *J* = 6.9 Hz, 6H), 2.43−2.56 (m, 1H), 5.78 (dd, *J* = 15.6, 1.5 Hz, 1H), 7.07 (dd, *J* = 15.8, 6.9 Hz, 1H).

**(4*S*,2*E*)-3-(2′-Isohexenyl)-4-phenyl-2-oxazolidinone 4.**[16,18] Butyllithium (1.90 M in hexanes, 13.18 mL, $2.50 \times 10^{-2}$ mol) was added dropwise to a stirring solution of (4*S*)-4-phenyl-2-oxazolidinone **3** (4.09 g, $2.50 \times 10^{-2}$ mol) in THF (110 mL) at −78 °C. The resulting solution was stirred for 20 min at −78 °C. A solution of (*E*)-4-methylpent-2-enoyl chloride (3.69 g, $2.78 \times 10^{-2}$ mol) [prepared from **2** (4.97 g, 4.35 × $10^{-2}$ mol) in ether (50 mL) and oxalyl chloride (8.29 g, 6.53 × $10^{-2}$ mol) and purified by distillation at atmospheric pressure (158 °C)] in THF (10 mL) was added dropwise at −78 °C. The temperature was maintained at −78 °C for 30 min and was allowed to warm to 0 °C over 1.5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 mL), and the volatiles were removed under reduced pressure. Ethyl acetate (70 mL) was added, and the organic phase was separated and washed with saturated aqueous sodium bicarbonate (2 × 40 mL) and brine (60 mL), dried, and concentrated under reduced pressure to give the crude *oxazolidinone*. Purification by flash column chromatography on silica gel eluting with gradient ethyl acetate/hexane (20:80−40:60) gave the *oxazolidinone* **4** (4.64 g, 72%) as a white solid: mp 101−103 °C (lit.[16] 103−104 °C); $[\alpha]_D^{20}$ = +112.0 (*c* 1.0, CHCl$_3$) {lit.[16] $[\alpha]_D^{20}$ = +103.1 (*c* 1.0, CHCl$_3$)}; IR (KBr) 2965−2870, 1776, 1686, 1632 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 1.06, 1.07 (2 × d, 2 × *J* = 6.9 Hz, 2 × 3H), 2.45−2.58 (m, 1H), 4.26 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.68 (t, *J* = 8.7 Hz, 1H), 5.48 (dd, *J* = 8.7, 3.9 Hz, 1H), 7.05 (dd, *J* = 15.5, 6.9 Hz, 1H), 7.22 (dd, *J* = 15.5, 1.2 Hz, 1H), 7.28−7.43 (m, 5H).

**(3′*S*,4*S*)-3-[3′-(4″-Methoxyphenyl)-4′-methylpentanoyl)-4-phenyloxazolidin-2-one 5.**[17,18] This was prepared following the procedure outlined by Hruby et al.[17] from **4** (4.53 g, 1.75 × $10^{-2}$ mol), *p*-bromoanisole (5.89 g, 3.15 × $10^{-2}$ mol), magnesium (0.76 g, 3.15 × $10^{-2}$ mol), iodine (catalytic amount), and copper(I)bromide dimethylsulfide complex (6.48 g, 3.15 × $10^{-2}$ mol). Purification by flash column chromatograpy on silica gel eluting with gradient ethyl acetate/hexane (5:95−40:60) gave the *substituted acyl oxazolidinone* **5** (4.39 g, 68%) as a white solid: mp 78−80 °C (lit.[18] 85−86 °C); $[\alpha]_D^{20}$ = +55.6 (*c* 1.0, CHCl$_3$) {lit.[18] $[\alpha]_D^{20}$ = +54.7 (*c* 1.02, CHCl$_3$)}; IR (KBr) 2965−2834, 1786, 1726, 1611, 1515 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 0.72 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.75−1.89 (m, 1H), 2.82−2.92 (m, 1H), 3.06 (dd, *J* = 15.6, 5.1 Hz, 1H), 3.72 (dd, *J* = 15.9, 5.7 Hz, 1H), 3.78 (s, 3H), 4.05 (dd, *J* = 8.9, 4.2 Hz, 1H), 4.54 (t, *J* = 8.7 Hz, 1H), 5.28 (dd, *J* = 8.0, 3.3 Hz, 1H), 6.72−6.82 (m, 4H), 7.00−7.07 (m, 2H), 7.11−7.21 (m, 3H).

**(3*S*)-3-(4′-Methoxyphenyl)-4-methylpentanoic Acid 6.** To a −10 °C precooled solution of **5** (4.23 g, 1.15 × $10^{-2}$ mol) in THF (83 mL) and water (17 mL) was added hydrogen peroxide (30% w/w, 11.04 mL, 9.78 × $10^{-2}$ mol). A solution of lithium hydroxide monohydrate (1.26 g, 2.99 × $10^{-2}$ mol) in water (17 mL) was added dropwise to the resulting slurry. The reaction mixture was allowed to warm to 0 °C, stirred at 0 °C for 2 h, and quenched by the careful addition of aqueous sodium sulfite (1.6 M, 30 mL). The organic solvent was evaporated under reduced pressure, and the resulting aqueous suspension was extracted with dichloromethane (4 × 40 mL). The remaining aqueous phase was cooled to 0 °C, acidified to pH 1 with aqueous hydrochloric acid (10%), and again extracted with dichloromethane (5 × 40 mL). The combined organic extracts were dried and concentrated under reduced pressure to give the crude *acid* as an off-white solid. Purification by flash column chromatography on silica gel eluting with gradient ethyl acetate/hexane (10:90−40:60) gave the *acid* **6** (2.15 g, 84%, 96% ee) as a white solid: mp 71−73 °C; $[\alpha]_D^{20}$ = −26.6° (*c* 1.0, CHCl$_3$); spectral characteristics obtained for this compound were in agreement with that described for the corresponding racemate (±)-**6**;[4] IR (KBr) 2961−2835, 1721, 1610, 1514 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 0.73 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 1.74−1.86 (m, 1H), 2.50−2.62 (m, 1H), 2.71−2.87 (m, 2H), 3.77 (s, 3H), 6.77−6.84 (m, 2H), 7.01−7.07 (m, 2H). HPLC: $t_R$ (R) = 21.89 min, $t_R$ (S) = 26.33 min [Chiralpak ASH; flow rate 0.50 mL min$^{-1}$; UV detector ($\lambda$ = 252 nm); hexane/isopropanol (95:5); 25 °C].

**(5*S*)-2-Diazo-5-(4′-methoxyphenyl)-6-methylheptan-3-one 7.** This was prepared following the procedure described for the corresponding racemate (±)-**7**[4] from **6** (4.12 g, 1.85 × $10^{-2}$ mol) in ether (32 mL), oxalyl chloride (3.53 g, 2.78 × $10^{-2}$ mol), and a solution of diazoethane in ether[25] [prepared from *N*-ethyl-*N*-nitrosourea[26] (21.71 g, 1.85 × $10^{-1}$ mol)]. Purification by flash column chromatography on silica gel, using ethyl acetate/hexane (15:85) as eluant, gave the *α-diazoketone* **11** (3.12 g, 65%) as an orange oil: $[\alpha]_D^{20}$ = +41.7 (*c* 1.0, CHCl$_3$); spectral characteristics obtained for this compound were in agreement with that described for the corresponding racemate (±)-**7**;[4] IR (film) 2959−2836, 2072, 1634, 1513 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 0.73 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.72−2.01 (m, 4H), 2.65−2.81 (m, 2H), 2.84−2.95 (m, 1H), 3.78 (s, 3H), 6.76−6.84 (m, 2H), 7.00−7.08 (m, 2H).

***trans*-(3*S*,8a*R*)-3-Isopropyl-6-methoxy-8a-methyl-2,3-dihydroazulen-1(8a*H*)-one 8a and *cis*-(3*S*,8a*S*)-3-Isopropyl-6-methoxy-8a-methyl-2,3-dihydroazulen-1(8a*H*)-one 8b.** A solution of **7** (4.13 g, 1.59 × $10^{-2}$ mol) in dichloromethane (70 mL) was added dropwise over 2 h to a solution of rhodium(II) acetate (0.5 mg) in dichloromethane (100 mL) heated under reflux (another 0.5 mg of rhodium(II) acetate was added halfway through the diazoketone addition). The reaction progress was monitored by TLC and was complete once all the diazoketone had been added. Evaporation of the solvent at reduced pressure gave the crude product as a brown oil. A $^1$H NMR spectrum of the crude reaction mixture estimated the efficiency of the cyclization (% azulenone compared to aromatic byproduct) as 82%, and the diastereomeric ratio of the azulenones formed: diastereomeric ratio, *trans*-**8a**/*cis*-**8b**, 71:29. Purification by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (10:90) gave the azulenone **8a**/**8b** (3.11 g, 84%) as a pale yellow oil. The diastereomeric ratio of the purified product was estimated as *trans*-**8a**/*cis*-**8b** 70:30. Spectral characteristics obtained for this compound were in agreement with that described for the corresponding racemate (±)-**8**.[4] IR (film) 2958, 1746, 1712, 1645 cm$^{-1}$; $[\alpha]_D^{20}$ = +14.15 (*c* 1.0, CHCl$_3$). Spectral characteristics for *trans*-**8a**: $\delta_H$ (300 MHz, CDCl$_3$) 0.76 (s, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 1.61−1.72 (m, 1H), 1.99 (dd, *J* = 17.4, 6.9 Hz, 1H), 2.41−2.61 (m, 2H), 3.61 (s, 3H), 3.69 (br d, *J* = 7.5 Hz, 1H), 5.34 (br dd, *J* = 7.7, 2.1 Hz, 1H), 5.85 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.06 (d, *J* = 9.0 Hz, 1H). Spectral characteristics for *cis*-**8b**: $\delta_H$ (300 MHz CDCl$_3$) 0.84 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 2.30−2.37 (m, 2H), 2.67−2.77 (m, 1H), 3.63 (s, 3H), 4.70 (br d, *J* = 9.9 Hz, 1H), 5.74−5.78 (m, 2H), 6.16 (dd, *J* = 8.4, 1.5 Hz, 1H).

**(1*S*,3*S*,8a*R*)-3-Isopropyl-6-methoxy-8a-methyl-1,2,3,8a-tetrahydroazulen-1-ol 9a and (3*S*)-3-Isopropyl-6-methoxy-8a-methyl-1,2,3,8a-tetrahydroazulen-1-ol 9b.** A solution of **8a**/**8b** (3.03 g, *trans*-**8a**/*cis*-**8b** 70:30, 1.30 × $10^{-2}$ mol] in ethanol (30 mL) was added dropwise to a stirring suspension of sodium borohydride (2.47 g, 6.50 × $10^{-2}$ mol) in ethanol (40 mL) at 0 °C. The reaction mixture was stirred for 3.5 h while slowly returning to room temperature. The reaction was quenched by the dropwise addition of water (30 mL) at 0 °C. The volatiles were removed under reduced pressure, and the resulting aqueous suspension was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (35 mL) and dried, and the solvent was removed under reduced pressure to give the azulenols **9a**/**9b** (2.89 g, 95%) as a colorless oil. A $^1$H NMR spectrum of the crude reaction mixture estimated the diastereomeric ratio of the azulenols formed: diastereomeric ratio, **9a**/**9b**, 70:30. This material was used without any purification: $[\alpha]_D^{20}$ = +138.4 (*c* 1.0, CHCl$_3$); IR (film) 3383, 2956−2830, 1622, 1464 cm$^{-1}$. Spectral characteristics for the major diastereomer **9a**: $\delta_H$ (300 MHz CDCl$_3$) 0.56 (d, *J* = 6.6 Hz, 3H), 0.71 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.11−1.22 (m, 1H), 1.78−2.20 (m, 3H), 2.53−2.67 (br m, 1H), 3.65 (s, 3H), 4.00−4.14 (overlapping dd, *J* = 9.8, 6.0 Hz, 1H), 5.52 (d, *J* = 10.2 Hz, 1H), 5.79−5.85 (m, 1H), 5.92−6.00 (m, 2H). $\delta_C$ (CDCl$_3$, 75.5 MHz) 16.2 (CH$_3$), 17.2 (CH$_3$), 21.9 (CH$_3$), 28.2 (CH), 33.2 (CH$_2$), 46.0 (CH), 48.2 (C), 54.7 (CH$_3$), 80.5 (CH), 104.2 (CH), 116.4 (CH), 117.4 (CH), 119.1 (CH), 133.0 (C), 157.3 (C). Spectral characteristics for the minor diastereomer **9b**: $\delta_H$ (300 MHz, CDCl$_3$) 0.78 (s, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 3.61 (s, 3H), 5.20 (d, *J* = 10.5 Hz, 1H), 5.55−5.58 (m, 2H), 5.72 (dd, *J* = 7.4, 1.5 Hz, 1H); $\delta_C$ (CDCl$_3$, 75.5 MHz) 11.5 (CH$_3$), 15.8 (CH$_3$), 27.7 (CH), 31.3 (CH$_2$), 45.6 (CH), 54.5 (CH$_3$), 80.8 (CH), 101.4 (CH), 115.5 (CH), 123.0 (CH), 135.7 (CH), 143.1 (C), 157.0 (C). HRMS-TOF (*m*/*z*) [M + H]$^+$ calcd for $C_{15}H_{23}O_2$ 235.1698, found 235.1697.

**(1*S*)-1-Isopropyl-6-methoxy-4-methyl-1,2-dihydronaphthalene 10.**[13] Solid *p*-toluenesulfonic acid monohydrate (4.68 g, 2.46 × $10^{-2}$ mol) was added to a solution of **9a**/**9b** [2.89 g, **9a**/**9b** 70:30, 1.23 × $10^{-2}$ mol] in toluene (200 mL), and the suspension was stirred at room temperature for 24 h. The reaction mixture was then washed with water (50 mL), saturated aqueous sodium bicarbonate (2 × 50 mL), water (50 mL), and brine (70 mL). The organic phase was dried and concentrated under reduced pressure to give the crude *dihydronaphthalenes* **10** and **11** (3.26 g) as a dark brown oil. A $^1$H NMR spectrum of the crude reaction mixture estimated the ratio of dihydronaphthalenes formed as **10**/**11** 1:0.95.

Potassium carbonate (1.88 g, 1.36 × $10^{-2}$ mol) was added to a solution of **10** and **11** (3.23 g, **10**/**11** 1:0.95) in acetone (100 mL). Methyl iodide (1.02 mL, 1.64 × $10^{-2}$ mol) was then added dropwise. The reaction mixture was heated under reflux for 22 h. The suspension was cooled to room temperature, filtered, and rinsed with acetone. The organic washings were combined and concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate/hexane (10:90), to give the *dihydronaphthalene* **10** (1.41 g, 53%) as a pale brown oil: $[\alpha]_D^{20}$ = +68.45 (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{20}$ = −40.5 (*c* 1.03, $CHCl_3$)}; spectral characteristics obtained for this compound were in agreement with that described in the literature;[13] IR (film) 2955−2833, 1604, 1571 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.79 (d, *J* 6.9 Hz, 3H), 0.88 (d, *J* 6.9 Hz, 3H), 1.79−1.92 (m, 1H), 2.01 (d, *J* 1.8 Hz, 3H), 2.26−2.40 (br m, 3H), 3.81 (s, 3H), 5.74 (br s, 1H), 6.69 (dd, *J* 8.4, 2.7 Hz, 1H), 6.80 (d, *J* 2.7 Hz, 1H), 7.02 (d, *J* 8.4 Hz, 1H); $\delta_C$ ($CDCl_3$, 75.5 MHz) 19.1 ($CH_3$), 20.3 ($CH_3$), 21.4 ($CH_3$), 25.8 ($CH_2$), 30.3 (CH), 43.6 (CH), 55.3 ($CH_3$), 109.4 (CH), 110.5 (CH), 124.7 (CH), 129.2 (CH), 131.4 (C), 131.6 (C), 136.6 (C), 158.2 (C). $C_{15}H_{20}O$ requires C, 83.28; H, 9.32%. Found: C, 83.32; H, 9.41.

**(1*S*,4*S*)-1-Isopropyl-6-methoxy-4-methyl-1,2,3,4-tetrahydronaphthalene 15.**[13] This was prepared following the procedure described by Gatti et al.[13] from **10** (1.15 g, 5.32 × $10^{-3}$ mol) and palladium on carbon (116 mg, 5% by wt) in ethanol (20 mL). Purification by flash column chromatography on silica gel eluting with ethyl acetate/hexane (5:95) gave the *tetrahydronaphthalene* **15** (1.04 g, 89%) as a colorless oil: $[\alpha]_D^{20}$ = −30.8 (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{20}$ = −34.8 (*c* 2.47, $CHCl_3$)}; spectral characteristics obtained for this compound were in agreement with that described in the literature;[13] IR (film) 2957, 1611, 1502 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.76 (d, *J* 6.9 Hz, 3H), 1.02 (d, *J* 6.9 Hz, 3H), 1.27 (d, *J* 6.9 Hz, 3H), 1.57−1.88 (m, 4H), 2.14−2.27 (m, 1H), 2.53−2.64 (m, 1H), 2.80−2.92 (m, 1H), 3.78 (s, 3H), 6.65−6.73 (m, 2H), 7.12 (d, *J* = 9.6 Hz, 1H); $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.5 ($CH_3$), 19.7 ($CH_2$), 21.3 ($CH_3$), 23.3 ($CH_3$), 28.6 ($CH_2$), 31.1 (CH), 33.2 (CH), 43.0 (CH), 55.1 ($CH_3$), 111.3 (CH), 113.3 (CH), 129.1 (CH), 132.1 (C), 144.2 (C), 157.2 (C). $C_{15}H_{22}O$ requires C, 82.52; H, 10.16%. Found: C, 82.67; H, 9.91.

**(5*S*,8*S*)-8-Isopropyl-3-methoxy-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde 16.**[13] This was prepared following the procedure described by Gatti et al.[13] from **15** (1.02 g, 4.67 × $10^{-3}$ mol) and pyrophosphoryl chloride (1.03 mL, 7.47 × $10^{-3}$ mol) in DMF (0.54 mL, 7.00 × $10^{-3}$ mol). Purification by flash column chromatography on silica gel eluting with ethyl acetate/hexane (5:95) gave the *aldehyde* **16** (0.83 g, 72%) as a white solid: mp 64−66 °C (lit.[13] 54−56 °C); $[\alpha]_D^{20}$ = −61.0 (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{20}$ = −72.0 (*c* 0.9, $CHCl_3$)}; spectral characteristics obtained for this compound were in agreement with that described in the literature;[13] IR (film) 2958, 1675, 1607 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.74 (d, *J* 6.6 Hz, 3H), 1.02 (d, *J* 6.6 Hz, 3H), 1.30 (d, *J* 7.2 Hz, 3H), 1.61−1.90 (m, 4H), 2.23−2.36 (m, 1H), 2.57−2.67 (m, 1H), 2.85−2.98 (m, 1H), 3.90 (s, 3H), 6.72 (s, 1H), 7.69 (s, 1H), 10.40 (s, 1H); $\delta_C$ ($CDCl_3$, 75.5 MHz) 17.2 ($CH_3$), 19.0 ($CH_2$), 21.1 ($CH_3$), 23.0 ($CH_3$), 28.3 ($CH_2$), 30.9 (CH), 33.9 (CH), 42.7 (CH), 55.5 ($CH_3$), 111.3 (CH), 122.7 (C), 128.3 (CH), 132.4 (C), 152.4 (C), 159.5 (C), 189.8 (COH). $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%. Found: C, 77.98; H, 8.77.

**(1*S*,4*S*)-1-Isopropyl-6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene 1.**[13] This was prepared following the procedure described by Gatti et al.[13] from **16** (0.77 g, 3.13 × $10^{-3}$ mol) and palladium on carbon (77 mg, 5% by wt) in ethanol (20 mL). Purification by flash column chromatography on silica gel eluting with ethyl acetate/hexane (2:98) as eluent gave **1** (0.65 g, 89%, 95% ee) as a colorless oil: $[\alpha]_D^{20}$ −32.0 (*c* 1.0, $CHCl_3$) {lit.[12] $[\alpha]_D^{20}$ −29.0 (*c* 0.2, $CHCl_3$), lit.[13] $[\alpha]_D^{20}$ −30.3 (*c* 0.92, $CHCl_3$)}; spectral characteristics obtained for this compound were in agreement with that described in the literature;[13] IR (film) 2957, 1503, 1464 cm$^{-1}$; $\delta_H$ (300 MHz $CDCl_3$) 0.75 (d, *J* 6.9 Hz, 3H), 1.02 (d, *J* 6.9 Hz, 3H), 1.27 (d, *J* 7.2 Hz, 3H), 1.57−1.88 (m, 4H), 2.13−2.29 (m, 1H), 2.17 (s, 3 H), 2.50−2.60 (m, 1H), 2.78−2.92 (m, 1H), 3.80 (s, 3H), 6.58 (s, 1H), 6.97 (s, 1H); $\delta_C$ ($CDCl_3$, 75.5 MHz) 16.0 ($CH_3$), 17.5 ($CH_3$), 19.6 ($CH_2$), 21.4 ($CH_3$), 23.4 ($CH_3$), 28.8 ($CH_2$), 31.1 (CH), 33.1 (CH), 42.9 (CH), 55.2 ($CH_3$), 109.7 (CH), 123.6 (C), 130.3 (CH), 131.4 (C), 141.3 (C), 155.5 (C). $C_{16}H_{24}O$ requires C, 82.70; H, 10.41%. Found: C, 82.61; H, 10.37. HPLC: $t_R$ (S,S) = 18.41 min, $t_R$ (R,R) = 21.72 min [Chiralcel OJH; flow rate 0.25 mL min$^{-1}$; UV detector ($\lambda$ = 254 nm); hexane/isopropanol (99.5:0.5); 25 °C].

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H NMR spectra for all compounds. $^{13}$C NMR spectra for compounds **9**, **10**, **15**, **16**, and **1**. HPLC traces for compounds **6** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: a.maguire@ucc.ie.

### Present Address

[§]School of Chemistry, National University Of Ireland, Galway, University Road, Galway, Ireland.

### Notes

The authors declare no competing financial interest.

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