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Synthesis of (±) Wine Lactone and Its Analogues by a Diels–Alder Approach

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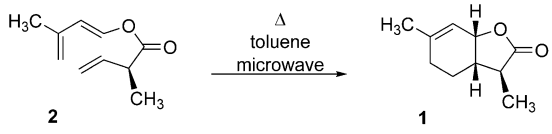
A novel route to (±)-wine lactone (**1**) by a *cis*-selective kinetically controlled intramolecular Diels–Alder (IMDA) cycloaddition of the linear triene **2** is reported. The triene precursor was synthesised by TBAF-catalysed coupling of an acyl fluoride with an silyl enol ether. Four butadienyl but-3-enoates were prepared and cyclised under mild conditions to give a series of wine lactone analogues. The diastereoselectivity of the IMDA cycloadditions was determined by NMR spectroscopy and GC-MS, whereby the formation of the natural *cis*-configured wine lactone (**1**) was established. The diastereomeric IMDA transition states were optimised by using density functional theory at the B3LYP/6-31+G(d) level, and the Boltzmann populations of the electronic energies were found to correlate well with the experimentally observed diastereoselectivity.

Introduction

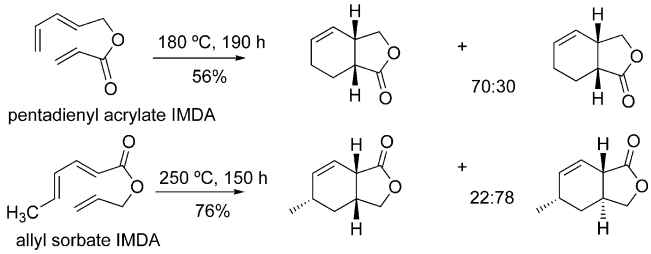
Wine lactone (**1**) is a sweetly scented organic compound with a coumarinic coconut-like odor, which was first isolated by Southwell in 1975.[1] Since its isolation it has been identified as a significant odorant in a variety of natural sources ranging from black pepper to orange juice to various essential oils.[2] The natural product derives its name from the recognition of **1** as an important flavour constituent of several white wines, specifically those made from the Gewürztraminer, Scheurebe and Riesling grape varieties.[3] Of the eight possible stereoisomers, (3*S*,3a*S*,7a*R*)-**1** has the lowest odour detection threshold, a remarkable value of 0.02 pg/L in air, while its enantiomer, *ent*-**1**, has the highest (1.0 μg/L); the difference in potency spans eight orders of magnitude. The monoterpenoid wine lactones originate from a biosynthetic pathway involving a cation-initiated cascade cyclisation.[4] Whereas the natural product has been the subject of numerous synthetic reports,[5] we present here a novel approach wherein the cyclohexene ring is assembled by an intramolecular Diels–Alder (IMDA) cycloaddition of an appropriately functionalised linear triene precursor **2**.

There are several reports concerning the synthesis of bicyclo[4.3.0] lactones by using an IMDA cycloaddition of 1,3,8-nonatrienes,[6] notably the work of Sherburn and Paddon-Row, who recently carried out extensive experimental and computational studies on the pentadienyl acrylate system (Scheme 1).[7] The complementary allyl sorbate IMDA cycloaddition has also been reported.[8]



Scheme 1. IMDA route to wine lactone (**1**).

However, to the best of our knowledge the regioisomeric IMDA cycloaddition manifold involving butadienyl butenoates (Scheme 2) has not yet been investigated. In order to test the feasibility and elucidate the π-diastereofacial selectivity of this novel system, we sought to synthesise the linear trienes depicted in Scheme 2 where R^1 and R^2 = Me or H.



Scheme 2. Selected 1,3,8-nonatriene ester IMDA scaffolds.

Results and Discussion

Two synthetic approaches to the desired racemic butadienyl butenoates were found to proceed in useful yields. In the first case direct acylation of unsaturated potassium aldehyde enolates with acyl chlorides afforded the desired trienes in moderate yields.[9] However, a somewhat higher yielding procedure was later employed whereby TBAF-catalysed *O*-acylation of conjugated silyloxydienes with acyl

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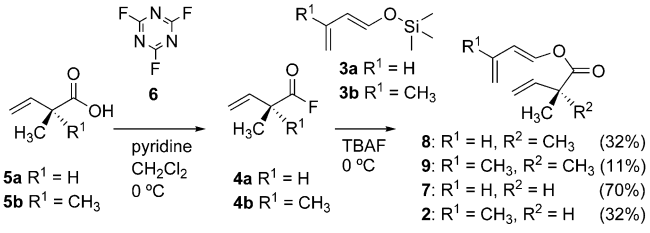
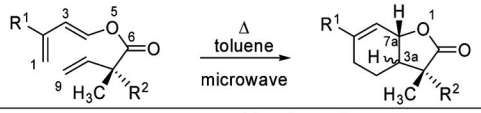
fluorides reproducibly delivered the desired trienes.[10] The requisite silyloxydienes **3a**–**b** were prepared from the corresponding unsaturated aldehydes,[11] whereas acyl fluorides **4a**–**b** were synthesised from their parent acids **5a**–**b** by using cyanuric fluoride (**6**) (Scheme 3).[12] Despite the fact that the reaction appeared relatively clean by TLC analysis, the isolated yields of trienes **2** and **7**–**9** after chromatography were somewhat disappointing. The low yields were attributed to hydrolytic sensitivity and high volatility, which also hampered characterisation efforts. The trienes were therefore directly employed in the subsequent cycloaddition step.



Scheme 3. Synthesis of butadienyl but-1-enoates.

With four linear trienes in hand, the IMDA cycloaddition was next attempted. Gratifyingly, microwave irradiation of trienes **7** and **2** in a sealed tube in toluene at 218–250 °C resulted in complete consumption of the starting material after 16 h, while the two analogues **8** and **9** possessing two C7 methyl groups required slightly shorter reaction times, presumably because of the *gem*-dimethyl effect.[13a–13c] In all cases the reaction was accompanied by a sweet woody coconut-like odor, which could be detected in the laboratory even before the "sealed" vessel was opened. Although isolation proved to be difficult owing to the high volatility of the lactone products, purification was eventually facilitated by careful removal of toluene by distillation followed by silica gel chromatography. According to Guth's ^{1}H NMR spectroscopic analysis of the wine lactones,[5a] the configuration of each purified diastereomer was determined by measurement of the multiplicity and coupling constants of the methine resonances (Table 1). The reaction diastereoselectivity was then determined by GC-MS analysis of the crude mixture. The purified cycloaddition products were found to be stable to heating, indicating that the reaction was under kinetic control.

Table 1. Experimental and theoretical IMDA product distribution.



Entry	Triene	Diels–Alder products	Experimental parameters Yield (%)[a] GCMS distribution	Gas-phase computationally predicted ratio
1	**8**	**10** **11**	180 °C, 10 h ca. 18 % **10**/**11** = 79:21	69:31[b] 70:30[c]
2	**9**	**12** **13**	250 °C, 6 h 17 % **12**/**13** = 88:12	72:28[b] 72:28[c]
3	**7**	**14** **15** **16** **17**	218 °C, 15 h 18 % **14**/**15**/**16**/**17** = 56:23:5:17	70:9:3:18[b] 69:10:3:18[c]
4	**2**	Wine Lactone (**1**) **18** **19** **20**	250 °C, 16 h 25 % **1**/**18**/**19**/**20** = 70:18:0:12	70:10:3:18[b] 69:11:3:17[c]

[a] Combined yield of racemic diastereomers after silica gel chromatography. [b] Unscaled ZPVE-corrected B3LYP/6-31+G(d)//B3LYP/6-31+G(d). [c] Unscaled ZPVE-corrected B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p).

Gas-phase DFT computation of the reaction transition states was performed with the Gaussian 03 suite of programs.[14] Transition-state optimisation and vibrational analyses were performed by using the B3LYP[15] hybrid functional with the 6-31+G(d) basis set, a model, which has been shown to give good results for a variety of pericyclic reactions.[7,16] Given the relative nonpolarity of both solvent and starting material, it was thought that the gas-phase calculation would provide acceptable results. The stationary points were verified as transition-state structures by observing that the vibrational mode of the single imaginary frequency corresponded to concerted bond formation along the reaction coordinate. Unscaled ZPVE-corrected electronic energies were used in place of free energies, as these parameters had been shown to give acceptable results for regioisomeric IMDA cycloadditions.[7c] Although the calculated Boltzmann populations at 180 °C accurately predicted the major and minor diastereomers, there appeared to be some deviation with respect to the ratios of **15/17** and **18/20** (Table 1). The close experimental isomer ratio **18/20** (18:12) observed experimentally is incorrectly predicted in Table 1. Reoptimisation of the transition-state structures by using a larger basis set generated an almost identical Boltzmann distribution ratio, thereby ruling out basis set effects as the cause of the discrepancy.

Notwithstanding possible systematic inaccuracies in the DFT functional,[17] a better agreement with experimental results may be obtained by comparing free energies computed by using a solvent model. Nevertheless, given the approximations, the computed transition states were in excellent agreement with the experimental results.

Discussion of IMDA *cis*/*trans* Selectivity

The transition-state geometry and weak preference for *cis* over *trans* diastereoselectivity for products illustrated in Figure 1 is consistent with the trends observed for similarly substituted pentadienyl acrylate IMDA cycloadditions.[7a] Overall, the transition states display varying degrees of asynchronicity with advanced internal bond formation. For both the *endo* and *exo* transition states, a significant energetic penalty is likely incurred due to the inherent inability of the three-atom tether to accommodate an ideal bonding arrangement between the diene and dienophile. For energetic reasons, the tether must maintain an approximate *syn*-coplanar or s-*cis* relationship with respect to the ester function (vide infra). The *exo* transition states are geometrically less able to meet these requirements, and consequently one observes a higher degree of asynchronicity, whereby the *exo* transition states are geometrically distorted to achieve the lowest-energy configuration. Asynchronicity can be defined by four parameters: bond-forming asynchronicity ($\Delta R_{as} = |R_{pr} - R_{in}|$, where R_{pr} and R_{in} are the lengths of newly forming peripheral and internal sp^3 bonds),[7a] and the magnitude of the two endocyclic dihedral angles about the two newly forming carbon bridgeheads, θ_{dh5} = O5–C4–C8–C7 and θ_{dh6} = C3–C4–C8–C9 (Table 2). The torsional angle θ_{as} = C1–C4–C8–C9 is defined by Houk et al.[18] as twist-mode asynchronicity and is recognised as an important parameter in defining asynchronous IMDA cycloadditions.[7] A general trend observed within the scope of this investigation is that the *exo* transition states leading to *trans*-lactones have consistently greater asynchronicity parameters ΔR_{as}, θ_{dh5}, θ_{dh6} and θ_{as} relative to *endo* transition states, which lead to the corresponding *cis*-lactones (Table 2). There is also a greater degree of deviation from the ideal s-*cis* ester configuration for the *exo* transition states.

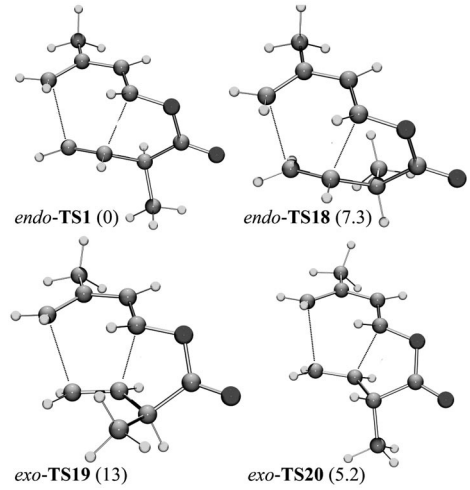


Figure 1. B3LYP/6-31+G(d)-optimised transition-state structures for linear triene **2**, relative ZPVE-corrected electronic energies [kJ/mol] shown in parentheses.

Table 2. Geometric parameters for *endo* and *exo* transition states TS1 and TS10–TS20 calculated by using B3LYP/6-31+G(d).

Asynchronicity parameter	*endo*-*cis* range	*exo*-*trans* range
ΔR_{as}	0.138–0.194 Å	0.309–0.358 Å
θ_{dh5}	30.5–34.3°	36.6–39.2°
θ_{dh6}	36.4–37.6°	68.5–69.4°
θ_{as}	10.5–11.1°	14.6–15.6°
Ester dihedral angles		
$\theta_{E1} \approx$ s-*cis*	3.9–6.4°	7.0–9.1°
θ_{E2}	89.7–93.2°	139.8–141.1°

It is important to note that other steric and stereoelectronic factors may outweigh the inherent preference for *cis* stereochemistry, which, despite a significant degree of asynchronicity, may be as little as 4 kJ/mol.[18]

In all transition states, the ester dihedral angle θ_{E1} = C4–O5–C6–C7 adopts a near s-*cis* conformation in order to maximise the overlap of the O5 p-type lone pair with the C6 carbonyl group. It is well known that deviations from planar geometry about the ester R–O–CO–R torsional angle are highly unfavourable, and it has been estimated that rotation to a perpendicular arrangement would require approximately 42–54 kJ/mol.[19] The adjacent ester dihedral angle θ_{E2} = C3–C4–O5–C6 may also be important in de-

termining the degree of O5 lone-pair conjugation to the butadiene system. However, given the lone-pair conjugation with the carbonyl group and the seemingly unfavourable (for overlap) torsional angle θ_{E2} (Table 2), it seems unlikely that the O5 lone pair is conjugated to any significant degree into the butadienyl system. Further calculations are required to confirm this.

For trienes **7** and **2**, (Table 1) the two respective *endo* and *exo* transition states each have a high- and a low-energy conformer corresponding to the configuration of the C7 methyl group. Whereas high-energy conformations appear to have a weak $A^{1,3}$ allylic interaction,[20] this is not sufficient to account for the energy differences between the isomers ($E_{TS18} - E_{TS19}$) = 7.8 kJ/mol (Figure 1). It is likely that a significant contribution arises from a steric clash of the C7 methyl group with the C4 methine group (cf. structures **TS19** and **TS20**), or from a steric interaction of the C7 methyl group with the diene moiety (cf. structures **TS1** and **TS18**).

It is important to note that other factors such as van der Waals forces, electrostatic, and in some cases secondary orbital interactions may also influence the transition-state energy. For example, the IMDA reactions of regioisomeric pentadienyl acrylates[7] generally favour the formation of the *cis* isomer; however, substitution of the C9 carbonyl group can lead to complete reversal of selectivity in favour of the *trans* isomer. Whereas a priori knowledge of reaction diastereoselectivity may prove to be elusive, the subtle factors governing relative transition-state energies are reasonably well accounted for by gas-phase electronic energies computed at the B3LYP/6-31+G(d) level.

Conclusions

We have demonstrated the use of butadienyl butenoates as novel substrates for the 1,3,8-nonatriene IMDA cycloaddition. The diastereoselectivity of this reaction can be accurately predicted by DFT computational methods. Future work will involve the enantioselective synthesis and olfactory analysis of the scented Diels–Alder products.

Experimental Section

General: All reactions were carried out in flame- or oven-dried glassware under dry nitrogen or argon. Tetrahydrofuran and diethyl ether were dried with sodium wire, toluene was dried with molten sodium, pyridine and triethylamine were dried with calcium hydride. Glacial acetic acid was used without further purification. Flash column chromatography was carried out by using 0.063–0.1 mm silica gel with the desired solvent. Thin-layer chromatography (TLC) was performed by using UV fluorescence and/or staining with vanillin in ethanolic sulfuric acid or iodine. Merck silica gel 60 F_{254} plates were used. High-resolution mass spectra were recorded at a nominal resolution of 5000–10000. Infrared spectra were recorded with a Fourier transform infrared spectrometer and were reported as wavenumbers ($\tilde{\nu}$). GC analyses were performed by a system equipped with a DB-5MS column (30 m × 0.25 mm). Helium was used as the carrier gas with a flow rate of 1 mL/min. A programmed temperature ramp from 40 to 250 °C over 70 min was employed. NMR spectra were recorded with either a 300 MHz spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or a 400 MHz spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are reported in parts per million (ppm) relative to $CHCl_3$ at ^{1}H NMR (δ = 7.26 ppm). ^{1}H NMR spectroscopic data are reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; dq, doublet of quartets; t, triplet; m, multiplet), coupling constant (J in Hz) and assignment. Standard gradient-mode phase-sensitive 2DNOE and gradient-selected magnitude-mode 2DCOSY pulse sequences were employed.[21]

(±)-2-Methylbut-3-enoic Acid (5a): A single iodine crystal was added to a stirred suspension of activated magnesium (20 g, 0.82 mol) in dry tetrahydrofuran (200 mL). The mixture was heated to reflux, and a mixture of 3-chlorobut-1-ene (30 g, 0.33 mol) in tetrahydrofuran (30 mL) was slowly added at a rate sufficient to maintain a gentle reflux. The mixture was cooled to –78 °C, and dry CO_2 was bubbled through it for 1 h. The reaction mixture was then cooled to room temperature and filtered though Celite®. Water (200 mL) was added, and the pH was adjusted to 12 by the addition of 1 M NaOH. The organic layer was discarded, and the pH was re-adjusted to 2 by the addition of 1 M HCl. After extraction of the aqueous layer with Et_2O (3 × 100 mL), the combined organic extracts were washed with brine and dried with $MgSO_4$. The solvent was removed in vacuo, and the yellow, oily residue was distilled (b.p. 75–80 °C/14 Torr; ref.[22] 80 °C/14 Torr) to afford the title compound (23.4 g, 70%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.9 Hz, 3 H, CH_3), 3.16 (m, 1 H, 2-H), 5.22–5.13 (m, 2 H, 4-H), 5.88–6.00 (m, 1 H, 3-H), 11.8 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 43.5, 116.5, 136.4, 181.2 ppm. ^{1}H and ^{13}C NMR spectroscopic data agreed with published values.[23]

2,2-Dimethylbut-3-enoic Acid (5b):[24] Prenyl chloride (13.8 mL, 122 mmol) was dissolved in anhydrous tetrahydrofuran (55 mL) and added to a suspension of activated magnesium (12.0 g, 494 mmol) in anhydrous tetrahydrofuran (38 mL) at a rate sufficient to maintain a gentle reflux. An excess of dry carbon dioxide was bubbled through the reaction mixture for 2 h followed by direct addition of solid dry ice (ca. 15 g). Upon evaporation of excess dry ice, the reaction mixture was hydrolysed by the addition of concentrated hydrochloric acid (14 mL) in water (23.8 mL). After addition of sufficient NaCl to separate the remaining aqueous layer, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic solutions were dried with sodium sulfate, and the solvent was evaporated in vacuo. The crude product was distilled at reduced pressure (b.p. 85–90 °C/37–39 Torr) to give the title compound as a colourless liquid (5.1 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 6 H, CH_3), 5.11 (m, 2 H, 4-H), 6.05 (dd, J = 17.5, 10.6 Hz, 1 H, 3-H), 11.60 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 24.3, 44.6, 113.3, 141.9, 183.0 ppm. ^{1}H and ^{13}C NMR spectroscopic data agreed with literature values.[24]

1-Trimethylsilyloxy-3-methylbuta-1,3-diene (3b): To a stirred solution of 3-methylbut-2-enal (13.7 mL, 143 mmol), diethyl ether (25 mL), triethylamine (22 mL, 160 mmol) and zinc chloride (200 mg, 1.47 mmol) under argon was added trimethylsilyl chloride (20 mL, 157 mmol) dropwise at room temperature. The red-brown solution was then heated to reflux for 24 h. After cooling to room

temperature, *n*-pentane (150 mL) was added and the precipitate removed by filtration through silica. The solvent was removed in vacuo to give an oil that was distilled (b.p. 54 °C/15 Torr; ref.[25] 50 °C/15 Torr) to afford the title compound (13.8 g, 62%) as a colourless oil.

Cyanuric Fluoride (6):[12] A dry 500 mL round-bottomed flask equipped with a mechanical stirrer, Vigreux column and distillation head was charged with cyanuric chloride (50.4 g, 273 mmol), sodium fluoride (68.3 g, 1.53 mol) and warm sulfolane (217 mL). The stirred mixture was gradually heated to a pot temperature of 250 °C while collecting the condensed vapor. The reaction was stopped when the head temperature reached 100 °C. The crude distillate was redistilled (71 °C; ref.[12] 72–73 °C) to yield the title compound (21.3 g, 58%) as a colourless liquid.

(±)-3-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-ones 14, 15 and 17: A solution of cyanuric fluoride (0.12 mL, 1.40 mmol) was added dropwise to a stirred solution of 2-methylbut-3-enoic acid (**5a**) (0.3 g, 3.0 mmol) and pyridine (0.113 mL, 1.4 mmol) in dry dichloromethane (10 mL) at 0 °C. The resulting white milky mixture was stirred for 2 h. A solution of 1-trimethylsilyloxybuta-1,3-diene (**3a**) (0.4 g, 2.8 mmol) in anhydrous tetrahydrofuran (20 mL) was added dropwise to the reaction mixture at 0 °C. To the resultant yellow solution was added solid tetra-*n*-butylammonium fluoride (ca. 30 mg, 95 μmol), and the mixture was stirred for 2 h. The reaction mixture was warmed to room temperature, and pentane (120 mL) was added. The solution was dried with $MgSO_4$, filtered through Celite®, and the solvent was removed in vacuo. The yellow oily residue was purified by flash chromatography by using pentane/diethyl ether (100:1) as eluent. Slow evaporation of the solvent to the atmosphere overnight afforded the crude linear triene **7** as a colourless oil. Crude triene **7** (470 mg, ca. 3.09 mmol) was taken up in toluene (4 mL) and stirred in a microwave reactor at 218 °C for 15 h. The toluene was carefully removed by distillation with a Kugelrohr apparatus, which left a resultant dark yellow residue. Purification by silica-gel flash chromatography (pentane/diethyl ether, 5:1) gave three separable fractions. Evaporation of the solvent to the atmosphere overnight afforded three sweetly scented (earthy coumarinic) diastereomers as colourless oils. **14** (47 mg, 10%),[26] **15** (17 mg, 4%), and **17** (17 mg, 4%).

(3*SR*,3a*SR*,7a*SR*)-3-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (14):[26] IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2933, 1765, 1172, 1161, 994 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, J = 7.3 Hz, 3 H, CH_3), 1.68–1.89 (m, 2 H, 4-H), 2.05–2.10 (m, 2 H, 5-H), 2.28–2.37 (m, 1 H, 3a-H), 2.45 (dq, J = 9.1, 7.3 Hz, 1 H, 3-H), 4.87–4.91 (m, 1 H, 7a-H), 5.77 (dq, J = 2.6, 10.2 Hz, 1 H, 7-H), 5.99 (dt, J = 10.3, 3.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.7, 21.8, 37.2, 41.1, 74.3, 124.3, 132.4, 179.7 ppm. HRMS (EI^+): m/z = 152.0833 [M^+]; $C_9H_{12}O_2$ requires 152.0837.

(3*RS*,3a*SR*,7a*SR*)-3-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (15): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 1672, 1171, 949, 883 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.7 Hz, 3 H, CH_3), 1.52–1.74 (m, 2 H, 4-H), 1.91–2.26 (m, 2 H, 5-H), 2.37–2.50 (m, 1 H, 3a-H), 2.91 (dq, J = 6.7, 7.3 Hz, 1 H, 3-H), 4.61–4.64 (m, 1 H, 7a-H), 5.92–5.98 (m, 1 H, 7-H), 6.16–6.21 (m, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.16, 19.2, 23.8, 38.4, 40.1, 73.3, 122.6, 135.2, 178.7 ppm. HRMS (EI^+): m/z = 152.0843 [M^+]; $C_9H_{12}O_2$ requires 152.0837.

(3*RS*,3a*RS*,7a*SR*)-3-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (17): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2934, 1774, 1648, 1134, 1016 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, J = 6.9 Hz, 3 H, CH_3), 1.53–1.88 (m, 2 H, 4-H), 1.99–2.07 (m, 1 H, 3a-H), 2.24–2.38 (m, 3 H), 4.37–4.44 (m, 1 H, 7a-H), 5.70 (dq, J = 10.24, 3.3 Hz, 1 H, 7-H), 6.09 (dq, J = 10.24, 3.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 22.9, 25.7, 41.4, 48.9, 79.4, 125.6, 129.5, 179.4 ppm. HRMS (EI^+): m/z = 152.0836 [M^+]; $C_9H_{12}O_2$ requires 152.0837. ^1H NMR data for compound **14** were in agreement with published values.[26]

(±)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-ones 1, 18 and 20: By the same procedure as described above for compound **14**, carboxylic acid **5a** (0.700 g, 7.00 mmol) and silyloxydiene **3b** (1.20 g, 7.68 mmol) afforded, after silica chromatography (pentane/diethyl ether, 150:1), the crude triene **2** as a colourless liquid. Triene **2** (512 mg, 2.83 mmol) was taken up in toluene (3 mL) and was stirred in a microwave reactor at 250 °C for 16 h. The toluene was carefully removed by distillation using a Kugelrohr apparatus leaving a dark yellow residue, which was purified by flash chromatography with pentane/diethyl ether (6:1) as eluent to afford three fractions. Evaporation of the solvent to the atmosphere overnight afforded three highly scented diastereomers as colourless oils. **1** (96 mg, 19%), **18** (26 mg, 5%), **20** (4 mg, 1%).

(3*SR*,3a*SR*,7a*RS*)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (1): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2923, 1764, 1174, 948, 908, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, J = 5.5 Hz, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 1.94–2.03 (m, 4 H, 4,5-H), 2.22–2.31 (m, 1 H, 3a-H), 2.35–2.47 (m, 1 H, 3-H), 4.88–4.91 (m, 1 H, 7a-H), 5.47–5.51 (m, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.3, 23.6, 26.0, 37.6, 40.4, 75.4, 118.9, 141.4, 179.4 ppm. HRMS (EI^+): m/z = 166.0999 [M^+]; $C_{10}H_{14}O_2$ requires 166.0994.

(3*RS*,3a*RS*,7a*RS*)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (20): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2916, 1981, 1769, 1016, 802 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, J = 7.3 Hz, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.96–2.23 (m, 4 H), 2.26–2.38 (m, 2 H, 3a,3-H), 4.33–4.41 (m, 1 H, 7a-H), 5.81–5.83 (m, 1 H, 7-H) ppm. HRMS (EI^+): m/z = 166.09880 [M^+]; $C_{10}H_{14}O_2$ requires 166.0994.

(3*RS*,3a*SR*,7a*RS*)-3,6-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (18): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2922, 1980, 1764, 1174, 948, 909 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17–1.36 (m, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 1.94–2.41 (m, 5 H, 4,5,3a-H), 2.95–2.86 (m, 1 H, 3-H), 4.62–4.65 (m, 1 H, 7a-H), 5.66–5.69 (m, 1 H, 7-H) ppm. HRMS (EI^+): m/z = 166.0991 [M^+]; $C_{10}H_{14}O_2$ requires 166.0994. ^1H NMR spectroscopic data were in agreement with published values.[5a]

(±)-3,3,6-Trimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-ones 12 and 13: By the same procedure as described above for compound **14**, carboxylic acid **5b** (1.5 g, 13.1 mmol) and silyloxydiene **3b** (2.04 g, 13.1 mmol) afforded, after silica chromatography (pentane/diethyl ether, 150:1), the title compound (260 mg, 11%) as a volatile unstable liquid. A quantity of triene **9** (180 mg, 1.00 mmol) was taken up in toluene (6 mL), and the reaction mixture was stirred in the microwave reactor at 200 °C for 6 h. The toluene was carefully removed by distillation using a Kugelrohr apparatus, and the dark yellow residue left behind was purified by flash chromatography (hexanes/diethyl ether, 5:1) to give two fractions. Evaporation of the solvent to the atmosphere overnight afforded two diastereomers. **12** (20 mg, 11%), and **13** (11 mg, 6%) as colourless oils.

(3a*SR*,7a*SR*)-3,3,6-Trimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (12): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 1773, 1107 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 6 H, CH_3), 1.19–1.73 (m, 4 H, 4,5-H), 1.79 (s, 3 H, CH_3), 1.92–1.99 (m, 1 H, 3a-H), 4.78 (d, J = 4.9 Hz, 1 H, 7a-H), 5.66 (m, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 21.5, 23.8, 24.8, 29.4, 73.5, 117.3, 143.7, 181.4 ppm. HRMS (EI^+): m/z = 180.114855 [M^+]; $C_{11}H_{16}O_2$ requires 180.1150.

(3a*RS*,7a*SR*)-3,3,6-Trimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (13): IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2932, 1774, 1107 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 6 H, CH_3), 1.47–1.60 (m, 2 H, 4-H), 1.69 (s, 3 H, CH_3), 1.76–1.93 (m, 2 H, 5-H), 2.14–2.27 (m, 1 H, 3a-H), 4.53 (d, J = 9.8 Hz, 1 H, 7a-H), 5.81–5.85 (m, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 19.5, 22.9, 23.5, 30.9, 51.4, 77.7, 120.8, 137.6, 182.5 ppm. HRMS (EI^+): m/z = 180.1152 [M^+]; $C_{11}H_{16}O_2$ requires 180.1150.

(3a*SR*,7a*SR*)-3,3-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (10): By the same procedure as described above for compound **14**, carboxylic acid **5b** (1.2 g, 10.5 mmol) and silyloxydiene **3a** (1.5 g, 10.1 mmol) afforded, after silica chromatography (pentane/diethyl ether, 250:1), the unstable volatile triene **8** (800 mg, 32%). A quantity of triene **8** (101 mg, 0.60 mmol) was taken up in toluene (2.5 mL) and stirred in a microwave reactor at 180 °C for 10 h. The toluene was carefully removed by distillation using a Kugelrohr apparatus, and the dark yellow residue left behind was purified by flash chromatography (pentane/diethyl ether, 10:1) to give a single isolable fraction. Evaporation of the solvent to the atmosphere overnight afforded the title compound (18.1 mg, 18%) as a sweet (earthy coumarinic) smelling colourless liquid. IR ($CDCl_3$): $\tilde{\nu}_{max}$ = 2924, 1768, 1219, 1135, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.47–2.10 (m, 4 H, 4,5-H), 2.15–2.24 (m, 1 H, 3a-H), 4.80 (dd, J = 9.35, 4.6 Hz, 1 H, 7a-H), 5.93–5.99 (m, 1 H, 7-H), 6.15–6.20 (m, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 24.1, 24.8, 29.7, 44.9, 72.0, 122.9, 134.8, 179.93 ppm. HRMS (EI^+): m/z = 167.10793 [M^+]; $C_{10}H_{15}O_2$ requires 167.10720.

Supporting Information (see footnote on the first page of this article): Cartesian coordinates for computed transition states with electronic and zero-point energy (hartrees); ^1H NMR coupling constants and chemical shifts required for identification of IMDA product structure, and reaction diastereoselectivity as determined by GC-MS analysis.

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