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HETEROCYCLISATIONS INDUCED BY THALLIUM(III) ACETATE. EFFECT OF VARYING THE INTERNAL NUCLEOPHILE

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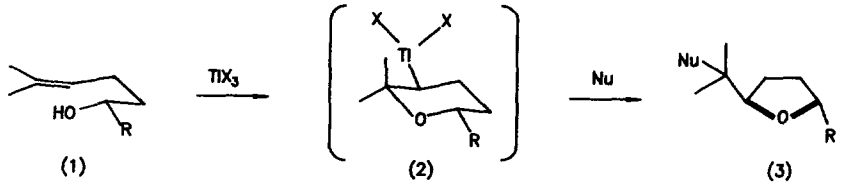
Abstract. The stereochemistry of the 2,5-disubstituted tetrahydrofuran formed on treating 5-methyl-1-phenylhex-4-en-1-ol [**6**] with thallium(III) acetate in appropriate solvents has been established as *trans* by means of nuclear Overhauser experiments. Replacement of the hydroxy group of [**6**] by ether, ester, amide or carbamate functionalities suppresses intramolecular nucleophilic participation during oxythallation. Instead, products of acetoxythallation followed by solvolysis of the C-Tl bond or by methyl group migration are isolated.

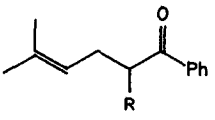
We recently showed[1] that 4-alkenols bearing alkyl substituents on the vinylic carbon atoms can undergo highly stereoselective cyclisation to 2,5-*trans*-disubstituted tetrahydrofurans in the presence of thallium(III) as electrophile. Although details of the mechanism are speculative, one can view the reaction as proceeding formally through Markovnikov oxythallation of the C=C bond of substrate [**1**], the OH group serving as internal nucleophile (Scheme 1). Stereocontrol comes from conformational bias in a putative chair-like transition state in which the bulky group R preferentially adopts the equatorial position. The ring oxygen, which is antiperiplanar to thallium in the intermediate [**2**], is well placed for a 1,2-shift in what amounts to an internal S_N2 displacement of the nucleofugal metal species. The incipient carbocation generated by the migration of oxygen is simultaneously, or subsequently, captured by an external nucleophile, which may be the solvent or the counter-ion on thallium, thereby yielding the observed product with complete *trans*- stereochemical integrity. The reaction complements the growing number of procedures for the synthesis of *cis*-2,5-disubstituted tetrahydrofurans[2], and it has much synthetic potential in view of the wide variety of natural products that contain tetrahydrofuran rings[3] (for example, the polyether antibiotics[4]). It has now been used by other workers for the synthesis of specific targets[5,6]. A similar ring-contraction process has been exploited in the synthesis of some showdomycin analogues[7].



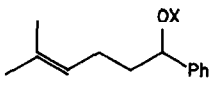
(1) (2) (3)

Scheme 1

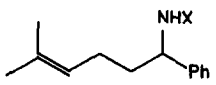
In our previous report[1], we described how the outcome of the reaction changes as the location of alkyl substituents on the 4-alkenol substrates is varied. In this study we have chosen to keep the isopropylidene terminus of the alkene unchanged while varying the internal nucleophile from alcohol to ester, ether, amide and carbamate. For convenience of synthesis, we have elected to work with compounds in which the R group is the more accessible phenyl, rather than cyclohexyl, which we had used before. These compounds, [4] to [13] in the diagrams below, are made by conventional procedures (see Experimental). A pivotal compound in these syntheses is 5-methyl-1-phenylhex-4-en-1-one [5], itself made[8] by alkylating the anion of ethyl benzoylacetate with prenyl bromide followed by hydrolysis and decarboxylation of the product [4]. It is necessary to avoid contact with acid during the removal of the ethoxycarbonyl group, since protonation of the trisubstituted alkene results in undesirable by-products that are difficult to separate from [5]. Similar caution is needed in preparing the other substrates. In control experiments, for example, we have found that exposure of alcohol [6] to hydrochloric acid yields the dichloro compound [14], while treatment of amine [10] with hydrochloric acid gives the *HCl* addition product as the hydrochloride salt [15]. Other workers have isolated different products on exposing ketone [5] or alcohol [6] to various acids[8,9].



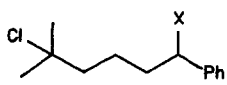
(4) R = $CO_2C_2H_5$
(5) R = H



(6) X = H
(7) X = CH_3
(8) X = $COCH_3$

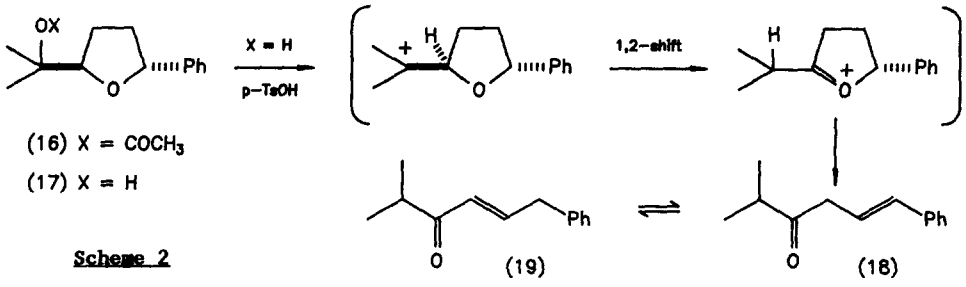


(9) X = CHO
(10) X = H
(11) X = COPh
(12) X = $COCH_3$
(13) X = $CO_2C_2H_5$



(14) X = Cl
(15) X = NH_2·HCl

The alcohol [6] itself undergoes the expected cyclisation with thallium(III) acetate in acetic acid or in aqueous acidic acetone to give the tetrahydrofurans [16] and [17] in 62% and 42% yields respectively, somewhat lower than those from the cyclohexyl substrates [1, R = c-C_6H_{11}][1]. (By contrast, cyclisation of [6] with palladium(II) acetate has been reported to give 2,2-dimethyl-6-phenyl-5,6-dihydropyran[10].) That compounds [16] and [17] belong to the same stereochemical series has been established by base-induced hydrolysis of the former to the latter in 81% yield. The tertiary alcohol [17] slowly decomposes on standing, and more rapidly on heating with a trace of acid. The product isolated is a mixture (4:1; 44%) of the unsaturated ketones [18] and [19]. Presumably, 1,2-hydride shift to the tertiary carbocation produced by loss of water is assisted by lone-pair donation from the ring oxygen. The ring is cleaved in the ensuing β-elimination; and under the reaction conditions, some shift of C=C double bond position occurs (Scheme 2).



Scheme 2

The *trans*-disposition of ring substituents, previously assumed[1] by comparison of ^{1}H and ^{13}C spectra with those of related compounds[11], has been established unambiguously for [17] in the following way. Epoxidation of alkenol [6] with *m*-chloroperoxybenzoic acid followed by treatment of the crude product with boron trifluoride gives two products: the tetrahydropyranol [20] (29%), and a 3:2 mixture (by n.m.r.; see Figure, spectrum **b**) of two stereoisomeric tetrahydrofurans (35%), the minor isomer of which is the same as product [17] from thallium-induced cyclisation (Figure, spectrum **a**). In the mixture, the signals for the hydrogen atoms flanking the ring oxygen are well separated, allowing irradiation at each in turn. Nuclear Overhauser enhancement between these positions is not observed for signals corresponding to [17] (Figure, spectra **c** and **e**), but is observed between 2-H and 5-H for the dominant tetrahydrofuran isomer (Figure, spectra **d** and **f**). These hydrogen atoms must therefore be in a 2,5-*cis* relationship, leaving the 2,5-*trans*-disposition of substituents in the thallium-derived product beyond doubt.

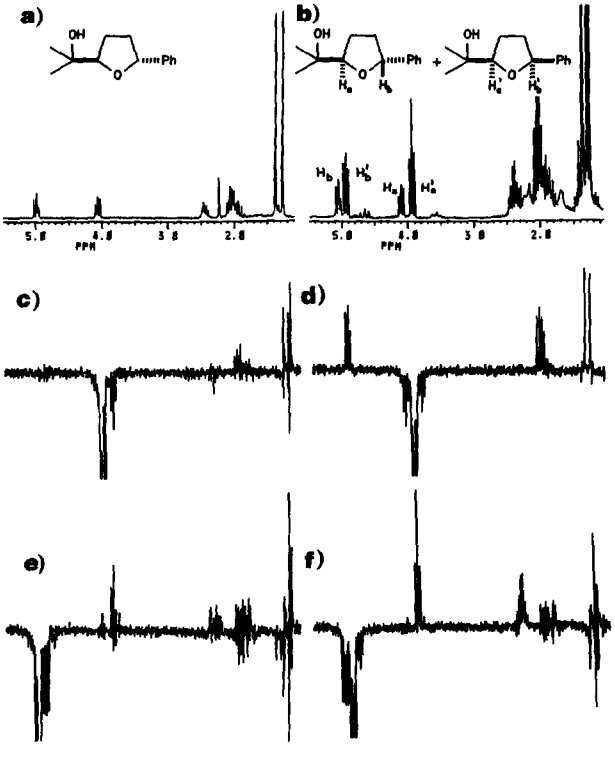
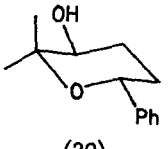
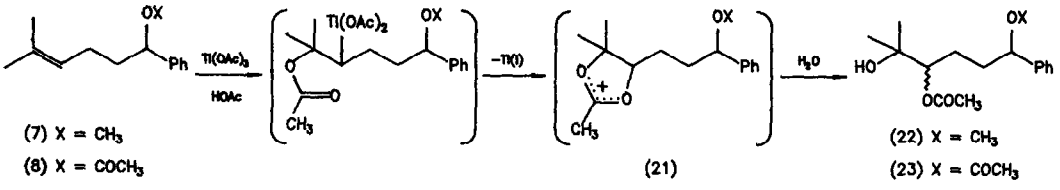


Figure. ^{1}H-n.m.r. spectra (200 MHz), excluding aromatic region, of (a): 2,5-*trans*-2-(1-hydroxy-1-methylethyl)-5-phenyltetrahydrofuran [17], from $Tl(OAc)_3$ cyclisation; (b): compound [17] and its *cis* isomer, from cyclisation of epoxide; (c), (d), (e) and (f): isomer mixture from (b), showing nuclear Overhauser effects arising from irradiation at positions labelled as H_a, H_a', H_b and H_b' respectively.



(20)

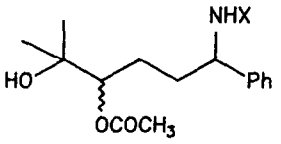
The successful reagent/solvent combination of thallium(III) acetate in acetic acid has been retained for studies with compounds [7] - [13]. Underlying our choice of functionality in these compounds are the many well-documented electrophilically-initiated cyclisations of functionalised alkenes in which the internal nucleophile is an ether, ester, amide or carbamate[12]. Intramolecular oxythallation, however, seems never to have been studied with participating groups other than OH[13] or, rarely, carboxylic acids and some of their derivatives[14]. We find that, on replacing hydroxy by methoxy or acetoxy (substrates [7] and [8]), the formation of tetrahydrofuran products is suppressed. While the reactions are not clean, it is clear that the major product isolated in each case arises solely from acetoxythallation at the C=C bond without any participation by the internal nucleophile. Furthermore, the 1,2-shift of substituents that is a hallmark of most oxythallations[15] does not occur. Instead, neighbouring group participation by the newly introduced acetoxy group probably assists in the cleavage of the labile C-Tℓ bond (Scheme 3), and regiospecific hydrolysis of the cyclic intermediate [21] during workup gives rise to the observed products [22] and [23] (56% and 44% respectively). The locations of OH and OAc substituents follow from a consideration of ^{13}C n.m.r. shifts. No diastereoselectivity is observed, or expected, in these reactions.



Scheme 3

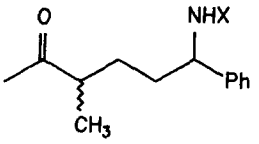
Current interest[16] in the stereocontrolled synthesis of 2,5-disubstituted pyrrolidines, several of which are constituents of ant venoms[17], has prompted extension of our cyclisation studies to amine derivatives [9] - [13]. The formamide [9], prepared by Leuckart amination[18] of ketone [5], serves as the precursor of the other substrates. However, with these compounds, too, we fail to observe cyclisation. Reactions with amine [10] or benzamide [11] and thallium(III) acetate do not give identifiable products; while the formamide [9], like the ether [7] and the ester [8], gives the product of acetoxythallation and hydrolysis, [24], as a 1:1 mixture of diastereomers (46%). The n.m.r. spectra of this mixture of isomers are complicated further by the presence of rotamers about the amide bond. With the acetamide [12] a different outcome is seen: the addition product [25] is now isolated (40%) alongside the more conventional product of solvothallation and 1,2-methyl shift, [26] (15%). Both occur as 1:1 diastereomeric mixtures, a finding that is once more clearly indicated by the duplication of signals in their ^{13}C n.m.r. spectra. When the reaction is performed in

aqueous acidic tetrahydrofuran, [26] becomes the only isolable product (47%). The carbamate [13] gives ketone [27] as the only identifiable product (42%) even when acetic acid is used as solvent.



(24) X = CHO

(25) X = $COCH_3$



(26) X = $COCH_3$

(27) X = $CO_2CH_2CH_3$

EXPERIMENTAL

Routine measurements were on Kofler micro hot-stage (m.p.), Pye-Unicam SP3-300 or PU 9512 (i.r.), Varian MAT 212 (m.s.), Varian EM-360A and Bruker WP80, AC200 or AM500 (n.m.r.) spectrometers. DEPT and CH-correlated spectra were routinely used for the complete assignment of n.m.r. signals. Unless otherwise stated, ^{1}H spectra were recorded at 200.13 MHz, and ^{13}C spectra at 50.32 MHz. T.l.c. was on pre-coated silica gel plates (Merck F254), and column chromatography was on Merck silica gel (particle size 0.063 - 0.200 mm) or Merck silica gel (particle size 0.040 - 0.063 mm) for flash chromatography[19]. Gas chromatograms were obtained on a Varian 3300 instrument with nitrogen as carrier gas and a bonded phase fused silica capillary column (25 m × 0.22 mm internal diameter, BP20 phase, thickness 0.25 μm) supplied by Scientific Glass Engineering (Australia).

Ethyl 2-benzoyl-5-methylhex-4-enoate [4]

Ethyl benzoylacetate (31.0 g, 161 mmol) and prenyl bromide (26.0 g, 174 mmol) were heated under reflux in freshly distilled acetone (400 ml) in the presence of anhydrous potassium carbonate (27.0 g, 0.195 mol) for 6 h. Solids were removed by filtration, solvents were removed *in vacuo*, and the residue was distilled at 132-134°C/1 torr (lit.[8], 144-145°C/2 torr) to give ethyl 2-benzoyl-5-methylhex-4-enoate [4] as a clear liquid (34.05 g, 75%); ν_{max} (liquid film) 1740, 1690, 1450, 700 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 8.05-7.9 (2H, m, *o*-Ar-H), 7.6-7.25 (3H, m, *m*- and *p*-Ar-H), 5.12 (1H, t with allylic coupling, *J* 7.3 and 1.5 Hz, =CH), 4.30 (1H, t, *J* 7.3 Hz, COCHCO), 4.13 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 2.69 (2H, t, *J* 7.1 Hz, $=CHCH_2$), 1.64 (6H, s, $=C(CH_3)_2$), 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C ($CDCl_3$) 194.9 (COPh), 169.6 (CO_2Et), 136.2 (arom C-1), 134.4 ($Me_2C=$), 133.3 (arom C-4), 128.5 and 128.4 (arom C-2, C-3), 120.0 (=CH), 61.1 (OCH_2), 54.3 (COCHCO), 27.6 ($=CHCH_2$), 25.6 (*E*-Me), 17.6 (*Z*-Me), 13.8 (OCH_2CH_3).

5-Methyl-1-phenylhex-4-en-1-one [5]

The preceding compound [4] (10.0 g, 38 mmol) was heated under reflux in ethanol (50 ml) containing aqueous sodium hydroxide solution (2M, 100 ml) for 4 h. The resulting two-phase mixture was cooled and extracted with dichloromethane (3 × 20 ml). The combined extracts were dried ($MgSO_4$), solvent was removed *in vacuo*, and the residue obtained was distilled at 142-145°C/15 torr to give 5-methyl-1-phenylhex-4-en-1-one [5] as a pale yellow liquid (5.21 g, 73%) that solidified on standing; m.p. 29-32°C (lit.[8], 32-33°C); R_F (hexane - ethyl acetate 9:1) 0.43; ν_{max} (liquid film) 1680 (C=O), 1600, 1450, 700 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 8.0-7.9 (2H, m, *o*-Ar-H), 7.6-7.25 (3H, m, *m*- and *p*-Ar-H), 5.18 (1H, t with allylic coupling, *J* 7.1 and 1.5 Hz, =CH), 2.99 (2H, t, *J* 7.1 Hz, CH_2CO), 2.41 (2H, q, *J* 7.3 Hz, $=CHCH_2$), 1.68 and 1.63 (6H, 2 × s, Me); δ_C ($CDCl_3$) 199.5 (C=O), 136.8 (arom C-1), 132.6 (arom C-4), 132.3 ($Me_2C=$), 128.3 and 127.8 (arom C-2, C-3), 122.8 (=CH), 38.5 (CH_2CO), 25.4 (*E*-Me), 22.7 ($=CHCH_2$), 17.4 (*Z*-Me).

5-Methyl-1-phenylhex-4-en-1-ol [6]
(A synthesis from ketone [5] and lithium aluminium hydride has been reported[8].) Ketone [5] (1.97 g, 10 mmol) and sodium borohydride (0.50 g, 13 mmol) were heated under reflux in methanol (100 ml) for 2 h. Once the solution had cooled, aqueous hydrochloric acid (2M, 100 ml) was added, and the mixture was rapidly extracted with dichloromethane (3 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product (1.90 g) was purified by chromatography on silica gel with hexane - ethyl acetate (17:3) as eluant. 5-Methyl-1-phenylhex-4-en-1-ol [6] was obtained as a colourless oil (1.84 g, 92%); R_F (hexane - ethyl acetate 17:3) 0.30; ν_{max} (liquid film) 3400 (br, OH), 1600, 1500, 1460, 1080, 780, 710 cm^{-1}; δ_H (80 MHz, $CDC\ell_3$) 7.32 (5H, br s, Ar-H), 5.15 (1H, br t, *J* 6.8 Hz, =CH), 4.66 (1H, t, *J* 6.1 Hz, CHOH), 2.25-1.8 (5H, m), 1.70 and 1.58 (6H, 2 × s, Me); δ_C ($CDC\ell_3$) 144.8 (arom C-1), 132.1 (Me_2C=), 128.3 and 125.8 (arom C-2, C-3), 127.3 (arom C-4), 123.8 (=CH), 74.1 (CHOH), 39.0 (CH_2CHOH), 25.6 (*E*-Me), 24.4 (=$CHCH_2$), 17.6 (*Z*-Me).

1-Methoxy-5-methyl-1-phenylhex-4-ene [7]
To 5-methyl-1-phenylhex-4-en-1-ol [6] (500 mg, 2.63 mmol), stirred with sodium hydride (50% in mineral oil, 230 mg, 4.8 mmol) in dry tetrahydrofuran (15 ml), was added methyl iodide (2 ml). The mixture was heated under reflux for 3 h, after which the solvent was removed *in vacuo*. Water (20 ml) was added, and the mixture was extracted with dichloromethane (3 × 25 ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. Bulb-to-bulb distillation of the crude product at 80-90°C/1 torr gave *1-methoxy-5-methyl-1-phenylhex-4-ene* [7] (520 mg, 97%) as a pale yellow liquid; R_F (hexane - ethyl acetate 19:1) 0.38; ν_{max} (liquid film) 1440, 1100, 750, 690 cm^{-1}; δ_H ($CDC\ell_3$) 7.45-7.15 (5H, m, Ar-H), 5.09 (1H, t with allylic coupling, *J* 7.1 and 1.4 Hz, =CH), 4.07 (1H, dd, *J* 7.4 and 5.8 Hz, CHOMe), 3.19 (3H, s, OMe), 2.01 (2H, q, *J* 7.1 Hz, =$CHCH_2$), 1.9-1.75 (2H, m, $MeOCHCH_2$), 1.68 (3H, s, Me), 1.56 (3H, s, Me); δ_C ($CDC\ell_3$) 142.4 (arom C-1) 131.9 (Me_2C=), 128.3 and 126.7 (arom C-2, C-3), 127.4 (arom C-4), 123.9 (=CH), 83.4 (MeOCH), 56.6 (OMe), 38.2 ($OCHCH_2$), 25.7 (*E*-Me), 24.3 (CH_2CH=), 17.6 (*Z*-Me); *m/z* 121 ($PhCHOCH_3^+$, 31%), 111 (26), 97 (41), 71 (65), 69 (61), 57 (100), 55 (80), 43 (97), 41 (87) (Found: M^+ - C_6H_{11}, 121.0653. C_8H_9O requires 121.0653).

5-Methyl-1-phenylhex-4-en-1-yl acetate [8]
A solution of 5-methyl-1-phenylhex-4-en-1-ol [6] (500 mg, 2.63 mmol) in acetic anhydride (3 ml) and pyridine (2 ml) was kept overnight at room temperature. The solvent was removed *in vacuo*, and the residue was distilled (bulb-to-bulb) at 140-160°C/1 torr to give *5-methyl-1-phenylhex-4-en-1-yl acetate* [8] as a colourless liquid (570 mg, 93%); R_F (hexane - ethyl acetate 1:1) 0.64; ν_{max} (liquid film) 1735 (C=O), 1240, 1020, 760, 700 cm^{-1}; δ_H ($CDC\ell_3$) 7.35-7.25 (5H, m, Ar-H), 5.71 (1H, dd, *J* 7.3 and 6.7 Hz, CHOAc), 5.10 (1H, br t, *J ca.* 7 Hz, =CH), 2.06 (3H, s, OAc), 2.05-1.8 (4H, m), 1.68 (3H, s, Me), 1.54 (3H, s, Me); δ_C ($CDC\ell_3$) 170.3 (C=O), 140.7 (arom C-1), 132.4 (Me_2C=), 128.3 and 126.5 (arom C-2, C-3), 127.8 (arom C-4), 123.1 (=CH), 75.6 (CHOAc), 36.3 ($OCHCH_2$), 25.7 (*E*-Me), 24.1 (=$CHCH_2$), 21.2 ($COCH_3$), 17.6 (*Z*-Me); *m/z* 172 (M^+ - CH_3CO_2H, 19%), 157 (20), 129 (56), 107 (27), 105 (18), 104 (23), 91 (21), 79 (20), 77 (26), 69 (18), 43 (100) 41 (39) (Found: M^+ - CH_3CO_2H, 172.1251. $C_{13}H_{16}$ requires 172.1252).

N-(5-Methyl-1-phenylhex-4-en-1-yl)formamide [9]
5-Methyl-1-phenylhex-4-en-1-one [5] (530 mg, 2.82 mmol) and ammonium formate (709 mg, 11.2 mmol) were heated without solvent in an oil bath at 150-155°C. When frothing ceased, the temperature was raised to 180-185°C. After 4 h, the mixture was cooled, and water (20 ml) was added. The aqueous phase was extracted with dichloromethane (3 × 40 ml), and the extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography of the residue with hexane - ethyl acetate mixtures gave *N-(5-methyl-1-phenylhex-4-en-1-yl)formamide* [9] (390 mg, 64%) as a pale yellow liquid in which two geometrical isomers about the amide bond, in a ratio of approximately 3:1, were discernible by n.m.r.: R_F (hexane - ethyl acetate 3:2) 0.52; ν_{max} (liquid film) 3300 (NH), 1670 (C=O), 1540, 1390, 710 cm^{-1}; δ_H ($CDC\ell_3$) major isomer: 8.13 (1H, s with further fine coupling, CHO), 7.45-7.15 (5H, m, Ar-H), 6.32 (1H, br d, *J ca.* 7.4 Hz, NH), 5.09 and 5.02 (2H; t with allylic coupling, *J* 6.9 and 1.5 Hz, =CH; and q?, *J ca.* 7 Hz, CHNH), 2.05-1.9 (2H, m), 1.9-1.7 (2H, m), 1.67 and 1.51 (6H, 2 × s, Me); discernible peaks for minor isomer: 8.07 (d, *J* 11.9 Hz, CHO), 6.66 (br t, *J ca.* 7 Hz, NH), 4.67 and 4.42 (br d, *J ca.* 7 Hz; and q, *J ca.* 6.5 Hz; =CH and CHNH), 1.70 and 1.55 (2 × s, Me); δ_C ($CDC\ell_3$) major isomer: 160.4 (NHC=O), 141.7 (arom C-1), 132.6

($Me_2\underline{C}$=), 128.6 and 125.5 (arom C-2, C-3), 127.4 (arom C-4), 123.0 (=CH), 51.9 (NH$\underline{C}$H), 36.1 (CHNH$\underline{C}H_2$), 25.7 (*E*-Me), 24.7 ($\underline{C}H_2$CH=), 17.7 (*Z*-Me); minor isomer: 164.5 (NHC=O), 142.0 (arom C-1), 133.0 ($Me_2\underline{C}$=), 128.8 and 126.1 (arom C-2, C-3), 127.6 (arom C-4), 122.5 (=CH), 55.9 (NH$\underline{C}$H), 37.1 (CHNH$\underline{C}H_2$), 25.7 (*E*-Me), 24.4 ($\underline{C}H_2$CH=), 17.8 (*Z*-Me); *m/z* 217 (M^+, 18%), 173 (M^+ - NHCHO, 13), 172 (80), 157 (45), 135 (20), 134 (51), 129 (100), 106 (40), 104 (47), 91 (22), 79 (37), 77 (25), 41 (37) (Found: M^+, 217.1465. $C_{14}H_{19}NO$ requires 217.1467).

5-Methyl-1-phenylhex-4-en-1-amine [10]

5-Methyl-1-phenylhex-4-en-1-one [5] (1.40 g, 7.44 mmol) and ammonium formate (1.91 g, 30.3 mmol) were heated without solvent on an oil bath at 180-185°C for 4 h. The reaction mixture was cooled, treated with sodium hydroxide solution (10M, 30 ml), and heated under reflux for 2 h. The solution was extracted with dichloromethane (3 × 20 ml); the combined extracts were dried ($MgSO_4$), and evaporated *in vacuo*. Bulb-to-bulb distillation of the crude product (90-100°C/10 torr) gave *5-methyl-1-phenylhex-4-en-1-amine* [**10**] as a colourless liquid (920 mg, 65%); ν_{max} (liquid film) 3400 (br), 3300 (br), 1600, 1490, 1450, 1375, 760, 700 cm^{-1}; δ_H ($CDC\ell_3$) 7.35-7.15 (5H, m, Ar-H), 5.11 (1H, t with allylic coupling, *J* 7.0 and 1.4 Hz, =CH), 3.88 (1H, t, *J* 6.9 Hz, C$\underline{H}NH_2$), 2.0-1.7 (6H, m), 1.68 (3H, d, *J* 1.0 Hz, Me), 1.54 (3H, s, Me); δ_C ($CDC\ell_3$) 146.4 (arom C-1), 131.6 ($Me_2\underline{C}$=), 128.2 and 126.2 (arom C-2, C-3), 126.4 (arom C-4), 123.8 (=CH), 55.6 ($CHNH_2$), 39.4 (Ph$\underline{C}HCH_2$), 25.5 (*E*-Me), 24.9 ($\underline{C}H_2$CH=), 17.5 (*Z*-Me); *m/z* 189 (M^+, 2%), 172 (M^+ - NH_3, 8), 157 (4), 132 (15), 106 (100), 77 (10) (Found: M^+, 189.1513. $C_{13}H_{19}N$ requires 189.1518).

N-(5-Methyl-1-phenylhex-4-en-1-yl)benzamide [11]

5-Methyl-1-phenylhex-4-en-1-amine [**10**] (350 mg, 1.85 mmol), suspended in aqueous sodium hydroxide solution (2M, 25 ml), was shaken with benzoyl chloride (1 ml) until no further precipitation of product occurred. The product was filtered and recrystallised from ethanol to give *N-(5-methyl-1-phenylhex-4-en-1-yl)benzamide* [**11**] (314 mg, 58%) as colourless needles, m.p. 122-123°C (Found: C, 81.91; H, 7.97; N, 4.82. $C_{20}H_{23}NO$ requires C, 81.87; H, 7.90; N, 4.77%); R_F (hexane - ethyl acetate 7:3) 0.59; ν_{max} (KBr) 3320 (NH), 1625 (C=O), 1520, 695 cm^{-1}; δ_H ($CDC\ell_3$) 7.76 (1H, d with further fine coupling, *J* 6.5 and *ca.* 1.7 Hz, benzoyl *o*-ArH), 7.5-7.2 (8H, m, Ar-H), 6.52 (1H, br d, *J* 7.8 Hz, NH), 5.20 and 5.15 (2H, overlapping t, *J* 7.4 Hz, =CH), 2.15-1.9 (4H, m), 1.68 (3H, s, Me), 1.52 (3H, s, Me); δ_C ($CDC\ell_3$) 166.6 (C=O), 142.3 (arom C-1), 134.6 (arom C-1'), 132.5, ($Me_2\underline{C}$=), 131.2 and 127.2 (arom C-4, C-4'), 128.5, 128.4, 126.9 and 126.5 (arom C-2, C-2', C-3, C-3'), 123.4 (=CH), 53.6 (CHNH), 36.1 (NHCH$\underline{C}H_2$), 25.6 (*E*-Me), 24.8 ($\underline{C}H_2$CH=), 17.6 (*Z*-Me).

N-(5-Methyl-1-phenylhex-4-en-1-yl)acetamide [12]

5-Methyl-1-phenylhex-4-en-1-amine [**10**] (840 mg, 4.44 mmol) and acetic anhydride (4 ml) were heated under reflux for 15 min. Water (50 ml) was added, and the mixture was heated briefly. When cool, the solution was extracted with dichloromethane (3 × 40 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography of the crude product on silica gel with hexane - ethyl acetate mixtures gave *N-(5-methyl-1-phenylhex-4-en-1-yl)-acetamide* [**12**] as a liquid (720 mg, 70%); R_F (hexane - ethyl acetate 2:3) 0.39; ν_{max} (liquid film) 3240 (br, NH), 1630 (C=O), 1530, 1430, 1360, 740, 685 cm^{-1}; δ_H ($CDC\ell_3$) 7.4-7.15 (5H, m, Ar-H), 5.80 (1H, br d, *J* 7.4 Hz, NH), 5.10 (1H, t with allylic coupling, *J* 6.9 and 1.4 Hz, =CH), 4.96 (1H, q, *J* 7.4 Hz, $CH_2\underline{C}HNH$), 2.1-1.7 and 1.98 (7H, m and s, COMe), 1.68 (3H, d, *J* 0.7 Hz, Me), 1.52 (3H, s, Me); δ_C ($CDC\ell_3$) 169.4 (C=O), 142.4 (arom C-1), 132.2 ($Me_2\underline{C}$H=), 128.4 and 126.5 (arom C-2, C-3), 127.0 (arom C-4), 123.3 (=CH), 53.3 (CHNH), 36.1 (NHCH$\underline{C}H_2$), 25.6 (*E*-Me), 24.7 ($\underline{C}H_2$CH=), 23.1 ($CO\underline{C}H_3$), 17.5 (*Z*-Me); *m/z* 231 (M^+, 23%), 172 (M^+ - CH_3NH_2, 45), 157 (30), 149 (38), 148 (21), 129 (60), 120 (19), 106 (100), 104 (27), 91 (15), 79 (20), 43 (29), 41 (23) (Found: M^+, 231.1623. $C_{15}H_{21}NO$ requires 231.1623).

Ethyl N-(5-methyl-1-phenylhex-4-en-1-yl)carbamate [13]

5-Methyl-1-phenylhex-4-en-1-amine [**10**] (860 mg, 4.54 mmol) and ethyl chloroformate (0.5 ml) were stirred at room temperature in aqueous sodium hydroxide solution (10M, 10 ml) for 10 min. The solution was extracted with dichloromethane (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The liquid product (990 mg, 83%) solidified on standing to give *ethyl N-(5-methyl-1-phenylhex-4-en-1-yl)carbamate* [**13**] as needles, m.p. 52-53°C (from ethyl acetate) (Found: C, 73.44; H, 9.09; N, 5.02. $C_{16}H_{23}NO_2$ requires C, 73.53; H, 8.87; N, 5.36%); R_F (hexane - ethyl acetate 4:1) 0.65; ν_{max} (liquid film) 3250 (br, NH), 1680 (C=O), 1510, 1240, 1040, 755, 690 cm^{-1}; δ_H ($CDC\ell_3$) 7.35-7.15 (5H, m, Ar-H), 5.25 (1H,

br d, *J* 8.2 Hz, NH), 5.10 (1H, t with allylic coupling, *J* 7.0 and 1.4 Hz, =CH), 4.66 (1H, br q, *J* 7.7 Hz, NHCHPh), 4.07 and 4.06 (2H, overlapping q, *J* 7.1 Hz, OCH_2CH_3), 1.98 (2H, q, *J* 7.1 Hz, CH_2CH=), 1.9-1.75 (2H, m, $CHCH_2CH_2$), 1.68 (3H, d, *J* 0.7 Hz, Me), 1.52 (3H, s, Me), 1.19 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C ($CDCl_3$) 155.9 (C=O), 142.8 (arom C-1), 132.3 (Me_2C=), 128.3 and 126.2 (arom C-2, C-3), 127.0 (arom C-4), 123.2 (=CH), 60.6 (OCH_2CH_3), 54.8 (PhCHNH), 36.6 ($NHCHCH_2$), 25.6 (*E*-Me), 24.6 (CH_2CH=), 17.5 (*Z*-Me), 14.4 (OCH_2CH_3); *m/z* 261 (M^+, 8%), 188 (M^+ - CO_2Et, 11), 178 (100), 172 (36), 157 (20), 129 (21), 106 (40), 104 (30), 79 (17) (Found: M^+, 261.1721. $C_{16}H_{23}NO_2$ requires 261.1729).

1,5-Dichloro-5-methyl-1-phenylhexane [14]

Hydrogen chloride gas was passed into a solution of 5-methyl-1-phenylhex-4-en-1-ol [**6**] (165 mg, 0.87 mmol) in methanol (20 ml) for several minutes. Solvent was removed *in vacuo*, and the crude product was purified by column chromatography on silica gel with hexane - ethyl acetate mixtures as eluant. *1,5-Dichloro-5-methyl-1-phenylhexane* [**14**] was obtained as a colourless oil (143 mg, 67%), R_F (hexane - ethyl acetate 9:1) 0.65 (Found: C, 64.19; H, 7.21. $C_{13}H_{18}Cl_2$ requires C, 63.68; H, 7.40%); ν_{max} (liquid film) 3020, 1450, 1370, 1120, 750, 700 cm^{-1}; δ_H ($CDCl_3$) 7.4-7.2 (5H, m, Ar-H), 4.86 (1H, dd, *J* 8.3 and 6.2 Hz, PhCH), 2.3-2.0 (2H, m), 1.85-1.65 (4H, m), 1.54 and 1.53 (6H, 2 × s, Me); δ_C ($CDCl_3$) 141.6 (arom C-1), 128.6 and 126.8 (arom C-2, C-3), 128.2 (arom C-4), 70.5 (Me_2CCl), 63.5 (PhCHCl), 45.1 ($CHClCH_2$), 39.9 (CH_2CClMe_2), 32.3 (2 × CH_3), 22.8 ($CH_2CH_2CH_2$); *m/z* 244 (M^+, 4%), 208 (M^+ - HCl, 10), 173 (M^+ - HCl - Cl, 60), 138 (27), 125 (60), 117 (91), 104 (100), 91 (76), 77 (23), 69 (48), 41 (28).

5-Chloro-5-methyl-1-phenylhexylammonium chloride [15]

Hydrogen chloride was bubbled into a solution of 5-methyl-1-phenylhex-4-en-1-amine [**10**] (930 mg, 4.91 mmol) in methanol (10 ml) for several minutes. Solvent was removed *in vacuo*, giving *5-chloro-5-methyl-1-phenylhexylammonium chloride* [**15**] (810 mg, 63%), as a solid, m.p. 180-181°C (from ether - methanol) (Found: C, 59.18; H, 8.12; N, 5.33. $C_{13}H_{21}Cl_2N$ requires C, 59.55; H, 8.07; N, 5.34%); ν_{max} (KBr) 3400 (br, NH), 2840 (br), 1560, 1475, 1420, 1355, 1315, 730, 670 cm^{-1}; δ_H ($CDCl_3$) 8.74 (2H, br s, NH_2, exchanges with D_2O), 7.5-7.25 (5H, m, Ar-H), 4.14 (1H, dd, *J* 9.4 and 5.6 Hz, PhCHN), 2.2-1.85 (2H, m), 1.85-1.55 (2H, m), 1.48 and 1.46 (6H, 2 × s, Me), 1.45-1.2 (2H, m); δ_C ($CDCl_3$) 135.8 (arom C-1), 129.1, 129.1 and 127.3 (arom C-2, C-3, C-4), 70.3 ($CClMe_2$), 56.2 (PhCHN), 45.1 (CH_2CHCl), 34.3 (CH_2CHN), 32.4 and 32.1 (2 × Me), 21.3 ($CH_2CH_2CH_2$).

General procedure for oxythallation experiments

Thallium(III) acetate sesquihydrate (1-2 mmol) was added to a solution of the appropriate alkene substrate (1 mmol) in acetic acid (1-5 ml). The mixture was stirred under conditions indicated in individual experiments below until starting material was consumed (t.l.c.). Solvent was removed under reduced pressure. Saturated sodium chloride solution (*ca.* 10 ml) was added, followed by sufficient solid K_2CO_3 to neutralise the mixture, and the Tl(I)-containing precipitate that formed was removed by filtration through Celite under suction. The precipitate was washed with brine solution and dichloromethane, and the filtrate was extracted with more dichloromethane (2-3 portions). The organic phases were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product thus obtained was purified further by column chromatography on silica gel with hexane - ethyl acetate mixtures as eluant.

2,5-trans-2-(1-Acetoxy-1-methylethyl)-5-phenyltetrahydrofuran [16]

Thallium(III) acetate sesquihydrate (1.167 g, 2.86 mmol) was added in one portion to a stirred solution of 5-methyl-1-phenylhex-4-en-1-ol [**6**] (543 mg, 2.85 mmol) in acetic acid (10 ml) at room temperature. After 1 h the solvent was removed *in vacuo*. Workup and column chromatography according to the general procedure gave *2,5-trans-2-(1-acetoxy-1-methylethyl)-5-phenyltetrahydrofuran* [**16**] (440 mg, 62%) as an isomerically pure (capillary g.c.) pale yellow liquid, R_F (hexane - ethyl acetate 9:1) 0.20; ν_{max} (liquid film) 1730 (C=O), 1370, 1250, 1070, 760, 705 cm^{-1}; δ_H ($CDCl_3$) 7.35-7.2 (5H, m, Ar-H), 5.00 (1H, dd, *J* 8.5 and 5.7 Hz, 5-H), 4.31 (1H, dd, *J* 8.2 and 6.8 Hz, 2-H), 2.4-2.3 (1H, m, 4-H), 2.1-1.65 and 2.02 (5H, m and s, OAc), 1.55 and 1.52 (6H, 2 × s, Me); δ_C ($CDCl_3$) 170.5 (C=O), 143.1 (arom C-1), 128.3 and 125.6 (arom C-2, C-3), 127.2 (arom C-4), 84.9 (C-5), 83.6 (CMe_2OAc), 81.7 (C-2), 35.7 (C-4), 27.3 (C-3), 22.5 ($COCH_3$), 22.1 and 21.8 (2 × Me); *m/z* 188 (M^+ - CH_3CO_2H, 22%), 147 (M^+ - Me_2COH, 37), 129 (21), 105 (16), 104 (39), 91 (36), 59 (20), 43 (100) (Found: M^+ - CH_3CO_2H, 188.1198. $C_{13}H_{16}O$ requires 188.1201).

2,5-trans-2-(1-Hydroxy-1-methylethyl)-5-phenyltetrahydrofuran [17]
(a) Thallium(III) acetate sesquihydrate (256 mg, 0.63 mmol) was added in one portion to a stirred solution of 5-methyl-1-phenylhex-4-en-1-ol [**6**] (99 mg, 0.52 mmol) in a mixture of water (1 ml), acetone (2 ml) and aqueous fluoroboric acid (50%, 0.5 ml) at 0°C. After 1 h the acetone was removed *in vacuo*. Workup and column chromatography according to the general procedure gave *2,5-trans-2-(1-hydroxy-1-methylethyl)-5-phenyltetrahydrofuran* [**17**] (49 mg, 46%) as an isomerically pure (capillary g.c.) colourless liquid, R_F (hexane - ethyl acetate 4:1) 0.23; ν_{max} (liquid film) 3460 (br, OH), 1440, 1365, 1140, 1050, 940, 745, 690 cm^{-1}; δ_H ($CDC\ell_3$) 7.4-7.25 (5H, m, Ar-H), 5.00 (1H, dd, *J* 8.6 and 6.1 Hz, 5-H; simplifies to d, *J* 7.7 Hz, on irradiation at δ 2.4), 4.04 (1H, dd with further fine coupling, *J* 8.6 and 6.9 Hz, 2-H), 2.45-2.35 (1H, m, 4-H), 2.17 (1H, s, OH), 2.15-1.75 (3H, m), 1.30 and 1.19 (6H, 2 × s, Me); δ_C ($CDC\ell_3$) 143.3 (arom C-1), 128.3 and 125.5 (arom C-2, C-3), 127.2 (arom C-4), 86.5 (C-2), 81.5 (C-5), 71.7 ($\underline{C}Me_2OH$), 36.1 (C-4), 27.4 (C-3), 27.2 and 24.0 (2 × Me); *m/z* 191 (M^+ - CH_3, 3%), 188 (M^+ - H_2O, 5), 147 (M^+ - Me_2COH, 26), 117 (15), 105 (17), 104 (100), 91 (22), 59 (43) (Found: M^+ - H_2O, 188.1202. $C_{13}H_{16}O$ requires 188.1201).
(b) 2,5-*trans*-2-(1-Acetoxy-1-methylethyl)-5-phenyltetrahydrofuran [**16**] (170 mg, 0.69 mmol) was heated under reflux for 2 h in a mixture of methanol (5 ml) and aqueous sodium hydroxide solution (2M, 10 ml). The solution was extracted with dichloromethane (3 × 20 ml). The extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Chromatography of the crude product on silica gel with hexane - ethyl acetate mixtures gave the alcohol [**17**] (115 mg, 81%) as a colourless liquid.

(E)-2-Methyl-6-phenylhex-5-en-3-one [18] and (E)-2-methyl-6-phenylhex-4-en-3-one [19]
A solution of 2,5-*trans*-2-(1-hydroxy-1-methylethyl)-5-phenyltetrahydrofuran [**17**] (200 mg, 0.97 mmol) and *p*-toluenesulphonic acid (20 mg) in benzene (20 ml) was heated under reflux for 16 h. Solvent was removed *in vacuo*. Water was added to the residue, and the mixture was extracted with dichloromethane (3 × 30 ml). The organic phases were combined, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography on silica gel with hexane - ethyl acetate mixtures gave recovered tetrahydrofuran [**17**] (34 mg, 17%) and a mixture of *(E)-2-methyl-6-phenylhex-5-en-3-one* [**18**] and *(E)-2-methyl-6-phenylhex-4-en-3-one* [**19**] (81 mg, 44%) in the ratio 4:1 (n.m.r.); R_F (hexane - ethyl acetate 4:1) 0.54; ν_{max} (liquid film) 3025, 1700 (C=O), 1455, 960, 725, 680 cm^{-1}; δ_H ($CDC\ell_3$) 7.4-7.15 (5H, m, Ar-H), 7.00 (0.2H, dt, *J* 15.6 and 6.8 Hz, 5-H of minor isomer), 6.47 (0.8H, d, *J* 16.0 Hz, 6-H of major isomer), 6.32 (0.8H, dt, *J* 16.0 and 6.6 Hz, 5-H of major isomer), 6.15 (0.2 H, dt, *J* 15.6 and 1.6 Hz, 4-H of minor isomer), 3.54 (0.4H, dd, *J* 6.8 and 1.6 Hz, 6-H of minor isomer), 3.38 (1.6H, dd, *J* 6.5 and 0.8 Hz, 4-H of major isomer), 2.82 and 2.71 (1H, 2 × septet, *J* 7.0 Hz, 2-H of minor and major isomers respectively), 1.15, 1.11 and 1.08 (6H, 3 × s, Me); δ_C ($CDC\ell_3$) major isomer: 212.3 (C=O), 136.9 (arom C-1), 133.2 (=$\underline{C}$HPh), 128.4 and 126.1 (arom C-2, C-3), 127.3 (arom C-4), 122.3 ($CH_2\underline{C}H$=), 44.4 ($\underline{C}H_2$), 40.4 ($\underline{C}HMe_2$), 18.1 (2 × Me); minor isomer: 204.0 (C=O), 145.0 ($CH_2\underline{C}H$=), 142.2 (arom C-1), 128.6 and 126.5 (arom C-2, C-3), 128.5 (CO$\underline{C}$H=), 127.7 (arom C-4), 38.6 ($\underline{C}H_2$), 38.3 ($\underline{C}HMe_2$), 18.3 (2 × Me); *m/z* 188 (M^+, 5%), 161 (M^+ - OH, 15), 149 (15), 147 (14), 122 (14), 105 (100), 77 (45), 61 (55), 43 (65) (Found: M^+, 188.1203. $C_{13}H_{16}O$ requires 188.1201).

(rel-3R,6R)-2,2-Dimethyl-6-phenyltetrahydropyran-3-ol [20]
m-Chloroperoxybenzoic acid (*ca.* 60%; 2.48 g, *ca.* 8.6 mmol) was added to a solution of 5-methyl-1-phenylhex-4-en-1-ol [**6**] (450 mg, 2.36 mmol) in dichloromethane (20 ml) containing a suspension of anhydrous Na_2HPO_4 (670 mg, 4.7 mmol), and the mixture was stirred at room temperature for 4 h before being filtered. A drop of boron trifluoride etherate was added to the filtrate. After 20 min, the solution was washed with aqueous $NaHSO_3$ (3 × 30 ml), then aqueous K_2CO_3 (3 × 25 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was separated into its components by column chromatography on silica gel with hexane - ethyl acetate mixtures. Two fractions were obtained: *(rel-3R,6R)-2,2-dimethyl-6-phenyltetrahydropyran-3-ol* [**20**] (140 mg, 29%) as prisms, m.p. 142-143°C (from ethyl acetate) (Found: C, 75.93; H, 8.87. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.79%); R_F (hexane - ethyl acetate 4:1) 0.15; ν_{max} (KBr) 3400 (br, OH), 1080, 1060, 985, 760, 700 cm^{-1}; δ_H ($CDC\ell_3$) 7.4-7.2 (5H, m, Ar-H), 4.59 (1H, dd, *J* 11.2 and 2.1 Hz, 6-H-ax), 3.56 (1H, dd, *J* 10.6 and 4.4 Hz, 3-H-ax), 2.0-1.6 (5H, m; reduces to 4H after addition of D_2O), 1.36 (3H, s, eq-Me), 1.30 (3H, s, ax-Me); δ_C ($CDC\ell_3$) 142.9 (arom C-1), 128.3 and 126.0 (arom C-2, C-3), 127.3 (arom C-4), 75.7 (C-2), 74.1 (C-3), 72.0 (C-6), 34.1 (C-5), 28.8 (C-4), 28.3 (eq-Me), 16.3 (ax-Me); and a mixture of *2,5-trans-2-(1-hydroxy-1-methylethyl)-5-phenyltetra-*

hydrofuran [17] and the *2,5-cis isomer* (2:3 by n.m.r.) (170 mg, 35%). Assignable signals for the *cis* isomer are: δ_H ($CDCl_3$) 4.86 (dd, *J* 8.5 and 6.7 Hz, 5-H), 3.87 (t, *J* 7.4 Hz, 2-H), 1.29 (s, Me), 1.21 (s, Me); δ_C ($CDCl_3$) 142.4 (arom C-1), 128.4 and 125.9 (arom C-2, C-3), 127.4 (arom C-4), 86.0 (C-2), 81.0 (C-5), 71.5 ($\underline{C}Me_2OH$), 34.2 (C-4), 27.1 (Me), 26.4 (C-3), 24.5 (Me).

1-(1-Hydroxy-1-methylethyl)-4-methoxy-4-phenylbutyl acetate [22]
1-Methoxy-5-methyl-1-phenylhex-4-ene [7] (200 mg, 0.98 mmol) and thallium(III) acetate sesquihydrate (560 mg, 1.38 mmol) were heated under reflux in acetic acid (2 ml) for 2 h. Workup and chromatography according to the general procedure gave *1-(1-hydroxy-1-methylethyl)-4-methoxy-4-phenylbutyl acetate* [22] (155 mg, 56%), a pale yellow liquid, as a 1:1 mixture of diastereomers (n.m.r.); R_F (hexane - ethyl acetate 4:1) 0.45; ν_{max} (liquid film) 3450 (br, OH), 1720 (C=O), 1445, 1365, 1240, 1100, 1040, 760, 700 cm^{-1}; δ_H ($CDCl_3$) 7.4-7.25 (5H, m, Ar-$\underline{H}$), 4.84 and 4.38 (1H, 2 × dd?; *J* 10.4 and 4.6 Hz; *J* 8.3 and 4.4 Hz; $C\underline{H}OAc$), 4.15 and 4.08 (1H, t and dd; *J* 3.8 Hz; *J* 7.2 and 4.9 Hz; $C\underline{H}OMe$), 3.21 and 3.19 (3H, 2 × s, OMe), 2.10 and 2.08 (3H, 2 × s, COMe), 1.9-1.6 and 1.62 (5H, m and s, OH), 1.19, 1.18 and 1.16 (3H, 3 × s, ratio 1:2:1, Me); δ_C ($CDCl_3$) 171.2 and 171.1 (C=O), 142.0 and 141.8 (arom C-1), 128.4, 126.5 and 126.4 (arom C-2, C-3), 127.6 and 127.5 (arom C-4), 83.7 and 83.1 ($\underline{C}HOMe$), 79.7 and 79.1 ($\underline{C}HOAc$), 72.3 and 72.2 ($\underline{C}OH$), 56.6 and 56.5 (OMe), 34.6 and 34.5 ($MeOCH\underline{C}H_2$), 26.6, 26.5, 24.8 and 24.7 (Me), 25.8 and 25.5 ($\underline{C}H_2CHOAc$), 21.0 ($OCO\underline{C}H_3$); *m/z* 202 ($M^+ - H_2O - CH_3CO_2H$, 10%), 130 (10), 121 (100), 104 (40), 91 (15), 77 (10), 59 (10), 43 (39) (Found: $M^+ - H_2O - CH_3CO_2H$, 202.1346. $C_{14}H_{18}O$ requires 202.1358).

1,4-Diacetoxy-5-methyl-1-phenylhexan-5-ol [23]
A solution of 5-methyl-1-phenylhex-4-en-1-yl acetate [8] (200 mg, 0.86 mmol) in acetic acid (4 ml) was treated with thallium(III) acetate sesquihydrate (702 mg, 1.72 mmol). The mixture was stirred overnight at 60°C before workup and chromatography according to the general procedure. *1,4-Diacetoxy-5-methyl-1-phenylhexan-5-ol* [23] (117 mg, 44%), a yellow liquid, was obtained as a 1:1 mixture of diastereomers (n.m.r.); R_F (hexane - ethyl acetate 1:1) 0.49; ν_{max} (liquid film) 3380 (br, OH), 1730 (C=O), 1380, 1280, 1040 cm^{-1}; δ_H ($CDCl_3$) 7.32 (5H, br s, Ar-$\underline{H}$), 5.78 and 5.69 (1H, 2 × dd; *J* 8.1 and 5.2 Hz; *J* 7.6 and 5.7 Hz, $PhC\underline{H}$), 4.85 and 4.81 (1H, 2 × dd; *J* 8.6 and 3.9 Hz; *J* 10.1 and 2.7 Hz; $CH_2C\underline{H}OAc$), 2.11, 2.09, 2.08 and 2.06 (6H, 4 × s, $COC\underline{H}_3$), 2.0-1.5 and 1.80 (5H, m and s; latter exchanges with D_2O), 1.16 and 1.15 (6H, 2 × s, $C\underline{H}_3$); δ_C ($CDCl_3$) 171.1, 170.4 and 170.3 (C=O), 140.3 and 140.1 (arom C-1), 128.5, 126.5 and 126.3 (arom C-2, C-3), 128.0 and 127.9 (arom C-4), 79.3 and 79.0 ($C(OH)\underline{C}HOAc$), 75.9 and 75.3 ($Ph\underline{C}HOAc$), 72.3 and 72.2 ($\underline{C}OH$), 32.9 and 32.8 ($PhCH\underline{C}H_2$), 26.6, 26.4, 25.5 and 25.3 (Me), 25.1 and 25.0 ($CH_2\underline{C}H_2CHOAc$), 21.2 and 21.0 ($CO\underline{C}H_3$); *m/z* 290 ($M^+ - H_2O$, 2%), 188 (10), 130 (12), 120 (12), 105 (18), 104 (60), 91 (16), 59 (20), 43 (100) (Found: $M^+ - H_2O$, 290.1509. $C_{17}H_{22}O_4$ requires 290.1518).

4-Formylamino-1-(1-hydroxy-1-methylethyl)-4-phenylbutyl acetate [24]
N-(5-Methyl-1-phenylhex-4-en-1-yl)formamide [9] (210 mg, 0.97 mmol) and thallium(III) acetate sesquihydrate (790 mg, 1.94 mmol) were stirred in acetic acid (4 ml) at room temperature for 3 h. Workup and column chromatography according to the general procedure gave *4-formylamino-1-(1-hydroxy-1-methylethyl)-4-phenylbutyl acetate* [24] (131 mg, 46%), a pale yellow oil, as a 1:1 mixture of diastereomers (n.m.r.) containing a minor quantity of a geometrical isomer about the amide N-CO bond. The product slowly crystallised on standing, giving needles, m.p. 126-127°C (from ethyl acetate) (Found: C, 65.46; H, 8.00; N, 4.75. $C_{16}H_{23}NO_3$ requires C, 65.51; H, 7.90; N, 4.77%); R_F (ethyl acetate) 0.28; ν_{max} (liquid film) 3450 (br, OH), 3250 (br, NH), 1720 (C=O of ester), 1660 (C=O of amide), 1530, 1390, 1255, 1050, 710 cm^{-1}; δ_H ($CDCl_3$) 8.13 (1H, s, $NHC\underline{H}O$), 7.45-7.15 (5H, m, Ar-$\underline{H}$), 6.66 (0.5H, br d, *J ca.* 7 Hz, NH), 6.50 (0.5H, br d, *J ca.* 7 Hz, NH), 5.2-4.95 (1H, br m, *J ca.* 7.7 Hz, $PhC\underline{H}NH$), 4.95-4.8 (1H, m, $C\underline{H}OAc$), 2.09 and 2.08 (3H, 2 × s, $COCH_3$), 1.95-1.6 (5H, m), 1.15 and 1.14 (6H, 2 × s, Me); δ_C ($CDCl_3$) diastereomers of major rotamer: 171.4 and 171.2 ($O\underline{C}OMe$), 160.7 (NHCHO), 141.5 and 141.4 (arom C-1), 128.8 and 126.4 (arom C-2, C-3), 127.8 (arom C-4), 79.5 and 78.9 ($\underline{C}HOAc$), 72.0 and 71.9 ($\underline{C}$-OH), 52.2 and 51.8 ($\underline{C}HNH$), 32.7 and 32.6 ($NHCH\underline{C}H_2$), 26.4 and 25.9 ($\underline{C}H_2CHOAc$), 25.8 and 25.7 (Me), 21.0 ($CO\underline{C}H_3$); discernible signals for diastereomers of minor rotamer: 171.2, 164.6 and 164.5, 141.9, 128.9, 127.5, 126.0, 79.0 and 78.4, 71.3 and 71.0, 56.6 and 55.9, 33.6, 25.5 and 25.3, 20.8; *m/z* 275 ($M^+ - H_2O$, 5%), 215 ($M^+ - H_2O - CH_3CO_2H$, 14), 175 (14), 147 (48), 134 (100), 117 (18), 106 (36), 104 (65), 91 (21), 79 (21), 59 (17), 43 (60) (Found: $M^+ - H_2O$, 275.1518. $C_{16}H_{21}NO_3$ requires 275.1521).

Reaction of N-(5-methyl-1-phenylhex-4-en-1-yl)acetamide with $Tl(OAc)_3$
The amide [**12**] (200 mg, 0.86 mmol) and thallium(III) acetate sesquihydrate (400 mg, 0.98 mmol) were heated under reflux in acetic acid (10 ml) for 4 h. Workup and chromatography according to the general procedure gave two products: *4-acetylamino-1-(1-hydroxy-1-methylethyl)-4-phenylbutyl acetate* [**25**] (106 mg, 40%), an oil, as a 1:1 mixture of diastereomers (n.m.r.); R_F (hexane - ethyl acetate 1:9) 0.27; ν_{max} (liquid film) 3450 (br, OH), 3280 (br, NH), 1725 (ester C=O), 1670 (amide C=O), 1540, 1385, 1370, 1245, 1045, 710 cm^{-1}; δ_H ($CDCl_3$) 7.4-7.2 (5H, m, Ar-H), 6.08 (0.5H, d, *J* 8.4 Hz, NH), 5.90 (0.5H, d, *J* 8.7 Hz, NH), 5.1-4.85 (2H, m, PhCHNH and CHOAc), 2.11 (3H, s, $CHCOCH_3$), 1.97 (3H, s, $NHCOCH_3$), 1.95-1.3 (5H, m), 1.14 (6H, s, Me); δ_C ($CDCl_3$) 171.4 and 171.2, and 171.1 and 169.8 (ester and amide C=O), 142.1 and 141.9 (arom C-4), 128.7 and 126.3 (arom C-2, C-3), 127.2 (arom C-1), 79.6 and 79.0 (CHOAc), 71.9 and 71.8 (CMe_2OH), 53.5 (PhCHNH), 32.6 ($NHCH_2CH_2$), 26.4 and 25.9 (CH_2CHOAc), 23.6 and 23.4 ($C(CH_3)_2OH$), 23.0($NHCOCH_3$), 21.0 and 20.7 ($OCOCH_3$) (Found: M^+, 307.1780. $C_{17}H_{25}NO_4$ requires 307.1784); and *N-(4-methyl-5-oxo-1-phenylhexyl)acetamide* [**26**] (29 mg, 15%) as a 1:1 mixture of diastereomers (n.m.r.); R_F (hexane - ethyl acetate 1:9) 0.63; ν_{max} (liquid film) 3240 (br, NH), 1725 (ketone C=O), 1635 (amide C=O), 1530, 1360, 1215, 1005, 685 cm^{-1}; δ_H ($CDCl_3$) 7.4-7.2 (5H, m, Ar-H), 6.25 (1H, br m, *J ca.* 8 Hz, NH), 4.92 and 4.90 (1H, overlapping q, *J* 7.4 and 6.7 Hz, PhCHNH), 2.53 and 2.51 (1H, overlapping q, *J* 6.7 Hz, MeCHCO), 2.10 and 2.08 (3H, 2 × s, $CHCOCH_3$), 1.97 and 1.95 (3H, 2 × s, $NHCOCH_3$), 1.9-1.15 (4H, m), 1.08 and 1.06 (3H, 2 × d, *J* 7.0 Hz, $CHCH_3$); δ_C ($CDCl_3$) 212.5 (ketone C=O), 169.5 and 169.4 ($MeCONH$), 142.1 and 141.8 (arom C-1), 128.6, 126.5 and 126.4 (arom C-2, C-3), 127.3 and 127.3 (arom C-4), 53.4 and 53.3 (CHNH), 46.6 and 46.5 (COCHMe), 33.7 and 33.3 ($NHCHCH_2$), 29.1 and 28.9 (CH_2CHMe), 28.1 and 28.0 ($COCH_3$), 23.2 ($NHCOCH_3$), 16.4 and 16.1 ($CHCH_3$); *m/z* 247 (M^+, 8%), 204 (M^+ - COMe, 39), 148 (44), 106 (100), 104 (20), 43 (34) (Found: M^+, 247.1565. $C_{13}H_{21}NO_2$ requires 247.1572).

Alternative synthesis of N-(4-methyl-5-oxo-1-phenylhexyl)acetamide [26]
N-(5-Methyl-1-phenylhex-4-en-1-yl)acetamide [**12**] (169 mg, 0.73 mmol) and thallium(III) acetate sesquihydrate (326 mg, 0.78 mmol) were stirred at room temperature in a mixture of tetrahydrofuran (5 ml), water (1 ml) and aqueous fluoroboric acid (50%, 0.5 ml) for 4 h. Workup and chromatography according to the general procedure gave the keto-amide [**26**] (77 mg, 47%) as a slightly brown oil; characterisation as above.

Ethyl N-(4-methyl-5-oxo-1-phenylhexyl)carbamate [27]
Ethyl N-(5-methyl-1-phenylhex-4-en-1-yl)carbamate [**13**] (148 mg, 0.57 mmol) and thallium(III) acetate sesquihydrate (245 mg, 0.60 mmol) were stirred in acetic acid (5 ml) at room temperature for 16 h. Workup and chromatography according to the general procedure gave *ethyl N-(4-methyl-5-oxo-1-phenylhexyl)carbamate* [**27**] (67 mg, 42%) as a pale yellow oil; R_F (hexane - ethyl acetate 1:1) 0.47; ν_{max} (liquid film) 3290 (br, NH), 1680 (C=O), 1500, 1230, 1035, 740, 685 cm^{-1}; δ_H ($CDCl_3$) 7.4-7.2 (5H, m, Ar-H), 4.95 (1H, br d, *J ca.* 7 Hz, NH), 4.65 (1H, br m, NHCH), 4.07 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 2.50 (1H, m, *J* 6.7 Hz?, CHCOMe), 2.10 (3H, s, $COCH_3$), 1.75-1.45 (4H, m), 1.21 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.08 and 1.07 (3H, 2 × d, *J* 7.0 Hz, $CHCH_3$); δ_C ($CDCl_3$) 212.3 (ketone C=O), 156.0 (amide C=O), 142.2 (arom C-1), 128.4 and 126.2 (arom C-2, C-3), 127.3 (arom C-4), 60.7 (OCH_2CH_3), 55.1 (PhCHNH), 46.5 (COCHMe), 33.9 ($NHCHCH_2$), 29.0 (CH_2CHCO), 28.0 ($COCH_3$), 16.2 ($CHCH_3$), 14.5 (OCH_2CH_3); *m/z* 317 (M^+, 23%), 277 (62), 259 (30), 231 (30), 218 (30), 178 (100), 117 (23), 111 (22), 104 (48) (Found: M^+, 277.1671. $C_{16}H_{23}NO_3$ requires 277.1678).

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