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On the Preparation of *N*-Acylpyrroles and their Use in the Synthesis of Ketones

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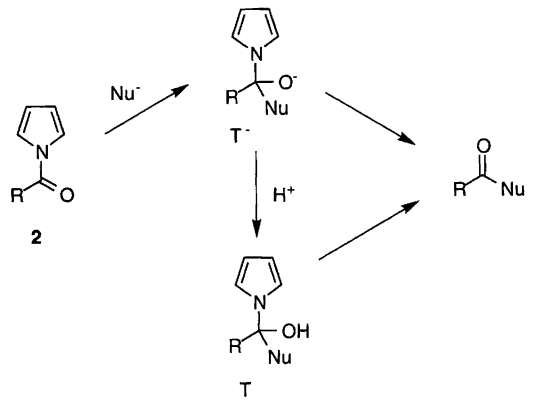
Two methods for the preparation of *N*-acylpyrroles have been studied: (a) the reaction between pyrrole and *N*-acylimidazoles and (b) the oxidation of amides of 3-pyrroline. The reactions between *N*-acylpyrroles and organolithium compounds can be directed to give ketones in good yields. The initially formed tetrahedral intermediates in these reactions are relatively stable and pyrrolylcarbinols are isolable intermediates. A Reformatsky–Claisen type ring-closure gave a more than doubled yield when an *N*-acylpyrrole group was used as an electrophile instead of an ester group; the increased stability of the initially formed tetrahedral intermediate presumably accounts for the observed result.

N-Acylpyrroles **2** can be regarded as activated carboxylic acids. They act as acylating agents in reactions with some *O*- and *N*-nucleophiles[1,2] and they *C*-acylate lithium ester enolates in a stepwise manner to form β-keto esters in high yields.[3] The efficiency of the latter synthesis is largely due to the relative stability of the initially formed tetrahedral intermediate T^- which becomes the main end product in the reaction mixtures (Scheme 1). A few other carboxylic acid derivatives of the type RCOX, notably *N*-methoxy-*N*-methyl amides,[4,5] 2-pyridyl thioates,[6] 3-acyloxazolidin-2-ones,[7] *N*-methyl-*N*-(2-pyridyl) amides[8] and tertiary amides,[9] also react with organometallic reagents to form long-lived intermediates of the T^- type and, on work-up, give ketones in good yields.[4] The T^- intermediates[10,11] derived from most other carboxylic acid derivatives are less stable. An even more striking property of *N*-acylpyrroles is the considerable and unusual stability of the *protonated* intermediates of the T type which are obtained on work-up (isolable 'pyrrolylcarbinols').[2,3,12] The smaller compounds in this series (Nu = H; R = H to



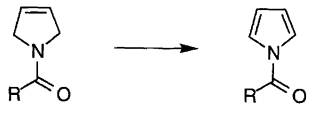
Scheme 1.

n-propyl) can be distilled at 60–80°C (under reduced pressure).[12] On the other hand, pyrrolylcarbinols can, if desired, be converted into ketones by basic reagents.[13,3] These properties motivate further studies of *N*-acylpyrroles and their use in organic synthesis. We here describe two methods for the preparation of *N*-acylpyrroles (**2**) and report new examples of their use in the synthesis of ketones.

Preparation of *N*-acylpyrroles

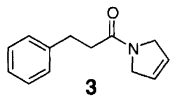
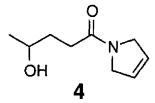
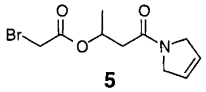
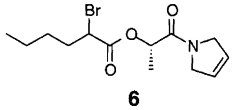
N-Acylpyrroles **2** can be formed in a number of ways but the general synthetic methods starting with carboxylic acids or their simple derivatives are few.[14] The classical route to **2** is the reaction between acid chlorides and pyrrolylpotassium.[15] However, this method sometimes gives only moderate yields with the aliphatic acid chlorides; a rhenium complex of pyrrole seems to be a better reaction partner for these.[16] The reaction between pyrrole, acetic anhydride and triethylamine (130°C, 16.5 h) afforded *N*-acetylpyrrole in an 80% yield.[17] Less direct is the reaction of primary amides with α-chloro ethers.[18,2] A single example of still another method is the preparation of *N*-acetylpyrrole from *N*-acetylimidazole in ca. 90% yield.[19] The latter was prepared from imidazole and acetic anhydride and then heated at ca. 130°C together with pyrrole. To find out whether this method could be used for other *N*-acylpyrroles as well, the conversion of dihydrocinnamic acid was first attempted by a modified technique. Sequential treatment of this acid with carbonyldiimidazole[20] and pyrrole, without purification of the intermediate *N*-acylimidazole, indeed afforded 1-(3-phenylpropanoyl)pyrrole (**7**), crystallised in a 72% overall yield. This modified procedure is advantageous since imidazole, which is formed as a by-product in the first step, seems[19] to catalyse the reaction between the *N*-acylimidazole and pyrrole. An α-branched carboxylic acid like 2-phenylbutanoic acid could also be transformed into the corresponding *N*-acylpyrrole although somewhat more reluctantly; longer heating (3 h) was necessary to obtain an acceptable yield (69%). This synthetic route to *N*-acylpyrroles from carboxylic acids via the imidazolides thus seems fairly general. It is simple, it avoids the strongly basic conditions due to pyrrolylpotassium and it may in many cases be the method of choice.

Another preparative method is the oxidative route **1**→**2**. This route represents a conversion of a relatively weak electrophile, the tertiary amide **1**, into a stronger electrophile, the *N*-acylpyrrole. Such a preparative method may be useful for reversion of site selectivities in polyfunctional compounds. Scattered examples of this type of oxidation can be found in the literature.[21–23] The first example was probably the oxidation of 1-benzoyl-3,4-bis(*p*-methoxyphenyl)-2,5-dihydropyrrole to the corresponding *N*-acylpyrrole (85%) with selenium(IV) oxide in refluxing dioxane.[21] We have found that several reagents bring about the oxidation **1**→**2**. Particularly attractive oxidants are manganese(IV) oxide and 2,3-dichloro-5,6-dicyano-1,4-*p*-benzoquinone (DDQ). These reagents are cheap and give high yields of **2** (Table 1). Some starting amides **1** were prepared from 3-pyrroline[24] and carboxylic acids via their imidazolides.[20] Others were prepared directly from 3-pyrroline and reactive esters (α-hydroxy esters[25] or lactones). Oxidations with manganese(IV) oxide require reflux in toluene for 1–16 h, while oxidations with DDQ (1.3 equiv.) can be performed in refluxing ethyl acetate for 4–5 h. Sodium hydrogencarbonate can be used in the work-up to remove excess DDQ and its reduction product DDQH since it turned out that *N*-acylpyrroles are fairly stable to aqueous sodium hydrogencarbonate. Thus *N*-isobutyrylpyrrole, dissolved in diethyl ether, was shaken for 3 min (23°C) with a saturated aqueous solution of sodium hydrogencarbonate (large excess) without any noticeable loss of the *N*-acylpyrrole. During the oxidation of **4** some ring-closure to lactone occurred, probably mainly from the *N*-acylpyrrole. The extent of lactone formation seems to be related to the heating; thus the yields of lactone were 22% and 54% in the oxidations with DDQ and MnO_2, respectively. Smaller amounts of lactone would probably



1 **2**

Table 1. Yields (%) of *N*-acylpyrroles obtained by oxidation of amides **3–6**

Starting amide	Oxidant	
	MnO_2	DDQ
 **3**	91	94
 **4**	83[a,b]	77[c]
 **5**	78	88[c]
 **6**	85	–

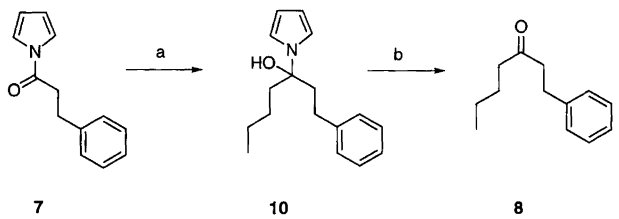
[a] At ca. 93% conversion. [b] Combined yield of the *N*-acylpyrrole and γ-valeroactone. [c] At ca. 92% conversion.

have been obtained if more DDQ had been used in a more concentrated solution to enable a shortening of the heating time. Both reagents showed good chemoselectivity but some oxidation of the secondary hydroxy group in **4** may have occurred with DDQ. There were two small singlets (δ 2.26 and 2.27) in the ^{1}H NMR spectrum of the crude oxidation product which may be due to methyl ketones; the intensities correspond to a combined yield of ca. 5%. On the other hand, Swern oxidation[26] of **4** led to selective oxidation of the hydroxy group; no reaction of the amide group was seen.

N-acylpyrroles as acylating agents

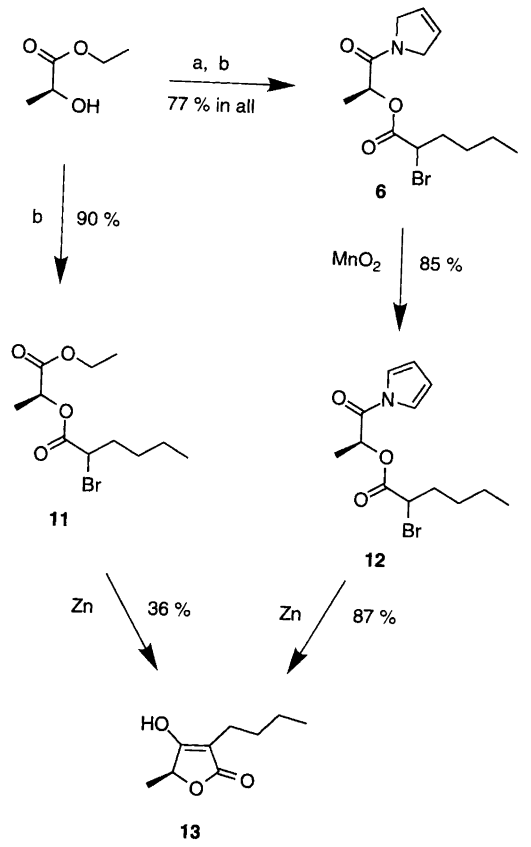
The carbon nucleophiles that have previously been allowed to react with *N*-acylpyrroles are butyllithium,[2] phenylmagnesium chloride[2] and lithium ester enolates.[3] More than two equiv. of the two first reagents were used and the final reaction temperatures were 0 °C or room temperature. The only reported products were tertiary alcohols, obtained in 55–72% yield.[2] In order to investigate the possibility of stopping the reaction at the T^- stage at lower temperatures, we mixed cooled (− 78 °C) solutions of *N*-acylpyrrole **7** in THF and butyllithium (2.2 equiv.) in hexane–THF (Scheme 2). After 30 min at − 78 °C the reaction was quenched with acetic acid. Despite the large excess of butyllithium, the pyrrolylcarbinol **10** was formed as the sole major product. Small amounts of the starting *N*-acylpyrrole **7**, ketone **8**, and a tertiary alcohol (**9**) were also detected (≤5% each; ^{1}H and ^{13}C NMR). Since the separation of **9** and **10** on silica gel was inefficient, the crude **10** was treated with K_2CO_3 (s) at 65 °C to convert[3] it into 1-phenyl-3-heptanone (**8**). Ketone **8** was isolated in an 82% yield, calc. from the *N*-acylpyrrole. *N*-Acylpyrroles are thus suitable reagents for the acylation of not only lithium ester enolates[3] but also alkyllithium compounds.

Another use of *N*-acylpyrroles in synthesis is shown in Scheme 3. We prepared, starting from ethyl L-lactate, the tetronic acid **13** by two different methods. Compound **13** was recently prepared by asymmetric synthesis[27] as part of a study related to an antibiotic. Here we used the chiral pool strategy. Our two-step route to **13** gave an overall yield of 33%, whereas the overall yield in the four-step



7 10 8

Scheme 2. Synthesis of a ketone from an *N*-acylpyrrole via an isolable pyrrolylcarbinol. Reagents: *a*, *n*-BuLi (2.2 equiv, −78 °C), then HOAc; *b*, K_2CO_3 (s), 65 °C. Overall yield, 82%.



Scheme 3. Different routes from (*S*)-ethyl lactate to the tetronic acid **13**. Reagents: *a*, 3-pyrroline; *b*, 2-bromohexanoyl bromide. Owing to a higher efficiency in its cyclisation step, the longer route, via the *N*-acylpyrrole **12**, gave a higher overall yield (57%) than the shorter route (33%).

route (Scheme 3) was 57%. This difference is mainly due to the intramolecular steps of the Reformatsky–Claisen type. The cyclisation of **11** gave **13** in a 36% yield (ester group as electrophile) while the cyclisation of **12** produced **13** in an 87% yield (*N*-acylpyrrole as the electrophile). The cyclisation of **11** leads to acidic compounds, *viz.*, ethanol or **13** (or its keto tautomer), both of which can destroy an equivalent of the Reformatsky reagent obtained from **11**. If this destruction reaction is much faster than the cyclisation, then the yield in the cyclisation will at best only slightly exceed 50%. Yields in the range 20–43%,[28] 42%,[29] and 55%[30] have been reported for this kind of cyclisation. The destruction of the Reformatsky reagent by protonation should lead to ethyl 2-(hexanoyloxy)propanoate, and the fact that this ester was isolated as a by-product in 39% yield in the reaction between **1** and zinc suggests that the destruction reaction is indeed a serious side-reaction. On the other hand, the cyclisation of **12** probably stops to a large extent at the tetrahedral intermediate of the T^- type. The result is less formation of acidic products, less destruction of the Reformatsky reagent and a higher yield of cyclisation product.

Experimental

3-Pyrroline was prepared as described.[24] (*S*)-Ethyl lactate was purchased from Fluka. THF (tetrahydrofuran) was distilled over $LiAlH_4$. Commercial carbonyldiimidazole was used. Its m.p. (ca. 75–82°C; lit.[31] m.p. 116–118°C) indicated low purity and an excess was therefore used in some experiments. Kieselgel 60 (70–230 mesh, Merck) was used for column chromatography and DC Fertigplatten Kieselgel 60 (Merck) for thin layer chromatography. ^1H and ^{13}C NMR spectra were run using a JEOL GSX 270 spectrometer. $CDCl_3$ was used as the solvent and tetramethylsilane as an internal reference.

*1-(3-Phenylpropanoyl)-2,5-dihydropyrrole (**3**).* Hydrocinnamic acid (1.50 g, 10.0 mmol) in dichloromethane (15 ml) was allowed to react with carbonyldiimidazole (1.62 g, ≤10.0 mmol) at 23°C (15 min) with stirring. 3-Pyrroline (0.76 g, 11.0 mmol) was added and after 15 min the reaction mixture was washed twice with aqueous sodium hydrogencarbonate, then twice with 0.1 M hydrochloric acid, and finally with brine. Drying (Na_2SO_4) and concentration led to a crude product which was crystallised from diethyl ether (−18°C); 61%; m.p. 71–73°C; ^1H NMR; δ 7.4–7.1 (m, 5 H), δ_A 5.86 and δ_B 5.75 (twelve lines, apparent AB part of ABX_2Y_2 system, 2 H, J_{AB} 6.4 Hz, J_{AX} 2.1 Hz; J_{BY} 2.0 Hz), δ_X 4.24 and δ_Y 4.14 (four lines, apparent X_2Y_2 part of ABX_2Y_2 system, 4 H, J_{XA} 4.0 Hz, J_{YB} 4.0 Hz), 3.02 (t-like, 2 H, measured *J*s 7.3 and 8.4 Hz), 2.57 (t-like, 2 H, measured *J*s 8.1 and 7.7 Hz).

*1-(4-Hydroxypentanoyl)-2,5-dihydropyrrole (**4**).* A mixture of γ-valerolactone (2.00 g, 20.0 mmol), 3-pyrroline (2.07 g, 30.0 mmol) and methanol (10 ml) was heated under reflux for 20 h. Concentration and purification on a silica gel column (10 × 2 cm; diethyl ether–methanol 9:1) gave **4** in an 81% yield; crystallised from diethyl ether (−18°C), m.p. 32–35°C; ^1H NMR: δ 5.9–4.1 similar to that of **3**, 4.01 (s, 1 H), 3.84 (br s, 1 H), 2.45 (disregarding four satellites: dt, 2 H, *J* 3.3 and 6.8 Hz), 1.81 (m, 2 H), 1.21 (d, 3 H, *J* 6.2 Hz); ^{13}C NMR: δ 172.2, 126.2, 125.0, 67.3, 53.5, 53.0, 33.4, 31.1, 23.7.

1-(3-Hydroxybutanoyl)-2,5-dihydropyrrole was prepared by heating a mixture of ethyl 3-hydroxybutanoate (7.50 g, 56.8 mmol) and 3-pyrroline (5.88 g, 85.1 mmol) at 100°C in an ampoule (42 h). Evaporation of ethanol and the excess of pyrroline (200°C) gave a crude product (9.31 g; 8.81 g = 100%) which contained (GLC) 3-pyrroline (5%), starting ester (4%) and amide (87%) (ethanol was not analysed). ^1H NMR (100 MHz): δ 5.86 (m, 2 H), 4.59 (br s, 1.3 H), 4.24 (s, 5 H), 2.6–2.0 (m, 2 H), 1.24 (d, 3 H); estimated yield, 92%.

*1-[3-(bromoacetoxy)butanoyl]-2,5-dihydropyrrole (**5**).* The above crude alcohol (9.31 g and *N,N*-dimethylaniline (9.63 g, 79.5 mmol) was dissolved in stirred dichloromethane (25 ml, 0°C). A solution of bromoacetyl bromide (14.8 g, 73.3 mmol) in dichloromethane (10 ml) was added over 15 min. After further reaction at 23°C (2 h), the reaction mixture was washed with hydrochloric acid (0.3 M, 100 ml) and then water, and finally dried (Na_2SO_4). The solvent was evaporated off and the residue further concentrated (ca. 200 Pa, 30°C, 20 min). Some contaminants were removed by silica gel chromatography (15 × 6 cm column) eluting with hexane-diethyl ether (1:3); **5** was eluted with diethyl ether and finally ethyl acetate (81% yield; ^1H NMR purity >95%). ^1H NMR: δ 6.0–5.7 (nine lines, 2 H), 5.42 (sextet, 1 H), 4.4–4.2 (m, 4 H), 3.80 (s, 2 H), δ_A 2.72 and δ_B 2.46 (2 H, AB part of ABX system, J_{AB} 15.3 Hz, J_{AX} 6.9 Hz, J_{BX} 6.1 Hz), 1.40 (d, 3 H, *J* 6.2 Hz); ^{13}C NMR: δ 167.6, 166.4, 126.3, 124.8, 70.3, 53.5, 52.9, 40.2, 26.2, 19.9.

(S)-1-(2-hydroxypropanoyl)-2,5-dihydropyrrole. (*S*)-Ethyl lactate (2.36 g, 20.0 mmol) and 3-pyrroline (1.80 g, 26.0 mmol) were heated together in an ampoule (90°C, 16 h). Concentration (40°C, 0.5 h, 2 kPa) and purification on a silica gel column (10 × 2 cm), first eluting with diethyl ether and then with ethyl acetate, yielded the pure (>95%, ^1H NMR) amide (89%); ^1H NMR: δ 5.84 (m, 2 H), 4.24 (m, 5 H), 3.34 (s, 1 H), 1.36 (d, 3 H); ^{13}C NMR: δ 173.5, 125.9, 124.8, 65.5, 53.5, 52.6, 20.4.

*1-[(2S)-2-(2-bromohexanoyloxy)propanoyl]-2,5-dihydropyrrole (**6**).* A solution of 2-bromohexanoyl chloride (3.78 g, 17.7 mmol) in dichloromethane was added dropwise over a period of 20 min to an ice-cooled and stirred solution of the above hydroxy amide (2.08 g, 14.7 mmol) and pyridine (5.82 g, 73.8 mmol in dichloromethane (10 ml). After 2 h the reaction mixture was diluted with diethyl ether and washed three times with hydrochloric acid (1 M), then sequentially with water, aqueous $NaHCO_3$ and brine to neutral pH. The organic phase was dried (Na_2SO_4) and the solvents were evaporated off. Further evaporation at ca. 200 Pa afforded **6** (4.23 g) as a mixture (approximately 4:5) of diastereomers (4.67 g = 100%); purity >95% (^1H and ^{13}C NMR); estimated yield, 87%; ^1H NMR: δ 6.0–5.6 (m, 2 H), 5.20 (q) and 5.14 (q) (in all 1 H), 4.6–4.0 (m, 5 H), 2.2–1.8 (m, 2 H), 1.7–1.2 (m, 7 H), including a d at δ 1.50), 0.92 (t-like, 3 H); ^{13}C NMR: δ 169.7, 169.4, 168.0, 167.7, 126.0, 124.7, 69.4, 53.4, 52.8, 45.9, 45.6, 34.6, 34.4, 29.2, 21.9, 16.2, 13.8.

*1-(3-Phenylpropanoyl)pyrrole (**7**).* Hydrocinnamic acid (4.63 g, 30.8 mmol) was dissolved in dry dichloromethane (50 ml) and carbonyldiimidazole (6.00 g, ≤37.0 mmol) was then added. After 20 min the solvent was evaporated off, pyrrole (3.10 g, 46.3 mmol) was added and the mixture was heated for 90 min (150°C). The reaction mixture was cooled, dichloromethane (50 ml) was added and the solution was washed with water (130 ml) containing 70 mmol of HCl then with water (100 ml) containing 2 mmol of HCl and finally with saturated aqueous sodium hydrogencarbonate (ca. 5 ml); the resultant pH in

the last wash was ca. 7.5. Drying (Na_2SO_4) and evaporation of the solvent gave a crystalline residue. Two coevaporations with toluene under reduced pressure removed most of the pyrrole. Purification on silica gel (5 × 35 cm) with hexane–Et_2O (10:1) as the eluant, followed by crystallisation (−18 °C) from Et_2O or hexane–Et_2O (5:1) yielded 4.42 g (72%) of **7**; m.p. 52–53 °C. ^1H NMR: δ 7.4–7.2 (m, 7 H), 6.28 (t, 2 H, *J* 2.4 Hz), 3.2–2.9 (m, 4 H). ^{13}C NMR: δ 169.6, 140.2, 128.6, 128.4, 126.4, 118.9, 113.1, 36.3, 30.3.

1-(2-Phenylbutanoyl)pyrrole. was prepared in the same way as **7** but on a 6 mmol scale and by using 2.0 equiv. of pyrrole and a longer heating time (3 h). After purification on silica gel [hexane as the eluant, then hexane–Et_2O (10:1)], the chromatographically pure (TLC) material corresponded to a 69% yield. Crystallisation from Et_2O–hexane (three crops; −18 °C) gave the product in a 64% yield; m.p. 52–54 °C. ^1H NMR: δ 7.33–7.25 (m, 7 H), 6.21 (t, 2 H, *J* 2.4 Hz), 4.07 (t, 2 H, *J* 7.3 Hz), 2.24 (7 resonances, 1 H), 1.89 (7 resonances, 1 H), 0.94 (t, 3 H, *J* 7.3 Hz). ^{13}C NMR: δ 170.9, 138.7, 129.0, 127.7, 127.5, 119.3, 113.0, 52.7, 27.7, 12.1.

Oxidations

(a) With manganese(IV) oxide. A mixture of amide **1**, active manganese(IV) oxide (Merck, 6 equiv.) and dry toluene was stirred and heated under reflux. The oxidation was followed by TLC; the *N*-acylpyrroles showed clearly higher mobility, e.g., $R_F = 0.2$ for **3** and $R_F = 0.7$ for the corresponding *N*-acylpyrrole (**7**); ethyl acetate–2,2,4-trimethylpentane (1:1). Portions of fresh MnO_2 were added if necessary to complete the oxidation. Compound **3** was the most reactive (6 equiv. of MnO_2; reaction time, 1 h) while **6** was the least reactive (16 equiv., 16 h). The reaction mixtures were filtered through Celite, washed through with hot toluene and dichloromethane, and the solvent was evaporated off. The pure *N*-acylpyrrole was obtained by separation on a short column of silica gel.

(b) With DDQ. A solution of the amide (1.0 mmol) and DDQ (1.3 mmol) in ethyl acetate (15 ml) was heated under reflux (ca. 4–5 h). Compound **5** was more difficult to oxidize than the other compounds; 77% oxidation using 1.3 equiv. of DDQ and a reaction time of 4.2 h but 92% with 2.0 equiv. under the same conditions (^1H NMR). The work-up was performed at 0–5 °C to minimize hydrolysis of the *N*-acylpyrrole. The reaction mixture was diluted with diethyl ether (ca. 50 ml) and washed with half-saturated aq. $NaHCO_3$ (5–10 ml). After two back-extractions with diethyl ether, the combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated off and the product characterised by ^1H NMR spectroscopy. The pure *N*-acylpyrroles could be obtained by separation on a short column of silica gel. Only compound **7** was obtained crystalline (see above).

1-(4-Hydroxypentanoyl)pyrrole. ^1H NMR: δ 7.33 (s, 2 H), 6.29 (t, 2 H, *J* 2.4 Hz), 3.91 (m, 1 H), 2.99 (m, 2 H), 2.1–1.6 (m), 1.27 (d, 3 H, *J* 6.2 Hz).

1-[3-(bromoacetoxy)butanoyl]pyrrole. ^1H NMR: δ 7.32 (s, 2 H), 6.31 (t, 2 H, *J* 2.4 Hz), 5.51 (sextet, 1 H, *J* 6.3 Hz), 3.79 (s, 2 H), $\delta_A = 3.27$ and $\delta_B = 2.98$ (AB part of ABX spectrum, 2 H, J_{AB} 16.1 Hz, J_{AX} 7.0 Hz, J_{BX} 5.9 Hz), 1.44 (d, 3 H, *J* 6.2 Hz).

1-[(2S)-2-(2-bromohexanoyloxy)propanoyl]pyrrole (**12**). ^1H NMR: δ 7.30 (t-like, 2 H), 6.34 (t-like, 2 H), 5.73 (q, 1 H), 4.32 (t) and 4.27 (t) (in all 1 H), 2.3–1.8 (m, 2 H), 1.66 (d, 3 H), 1.6–1.0 (m, 4 H), 0.92 (t-like, 3 H); ^{13}C NMR: δ 169.3, 169.0, 167.4, 167.2, 119.1, 113.9, 69.6, 69.5, 45.2, 44.9, 34.5, 34.4, 29.2, 21.9, 17.2, 13.7.

Reactions between **7** *and butyllithium*. A solution of **7** (1.00 g; 5.0 mmol) in THF (50 ml) was placed in a flame-dried flask and the solution was stirred and cooled to −78 °C. Commercial butyllithium in hexane (1.6 M; 6.9 ml; 11.0 mmol) was cooled and diluted with THF (10 ml). After further cooling to −78 °C, the BuLi solution was added all at once; the temperature in the flask rose to −65 °C. After reaction at −78 °C for 30 min, a solution of acetic acid (0.90 g; 15 mmol) in THF (10 ml) was added over a period of 3 min. Then the cooling bath was removed and the reaction mixture was warmed to 22 °C (ca. 10 min). Most of the solvents were evaporated off and the residue was partitioned between dichloromethane (50 ml) and water (50 ml) containing $NaHCO_3$ (34 mmol). The organic phase was separated and washed twice with water, then dried (Na_2SO_4) and concentrated at ca. 0.1 kPa to an oil (1.31 g; 100% yield of **10** 1.29 g). ^{13}C NMR showed the pyrrolylcarbinol **10** to be the major product (>80%); three minor components (**7**, **8**, **9**, see below) were also detected but amounted (^{13}C NMR) to less than about 5% each. R_F-values with hexane–Et_2O (4:1, vol/vol) as the mobile phase: **7**, 0.60; **8**, 0.57; **9**, 0.33; **10**, 0.33).

1-Phenyl-3-(1-pyrrolyl)-3-heptanol (**10**). ^1H NMR: δ 7.1–7.3 (m, 5 H), 6.83 (t, 2 H, *J* 2.1 Hz), 6.26 (d, 2 H, *J* 2.0 Hz), 2.90 (t, 2 H, *J* 7.3 Hz), 2.72 (t, 2 H, *J* 7.2 Hz), 2.38 (t, 2 H, *J* 7.4 Hz), 1.54 (m, 2 H), 1.30 (m, 2 H), 0.88 (t, 3 H, *J* 7.3 Hz). ^{13}C NMR: δ 141.4, 128.5, 128.3, 126.0, 117.6, 108.0, 88.0, 42.8, 40.9, 29.4, 25.0, 22.7, 13.9.

Synthesis of 1-phenyl-3-heptanone (**8**) *from* (**10**). Crude **10** (1.31 g) was heated with anhydrous potassium carbonate (0.15 g, 65 °C, 50 min). TLC showed full conversion into **8**. To hydrolyse the small amount of **7**, which was difficult to separate from **8** on silica gel, water (10 ml) and acetonitrile (20 ml) were added and the mixture was refluxed for 15 min. The acetonitrile was evaporated off and the residue was partitioned between water and dichloromethane. After drying (Na_2SO_4) and evaporation of the solvent, pyrrole was removed by coevaporation with tolu-

ene (3 × 10 ml) and the residue purified on silica gel using hexane–Et_2O (20:1) as the eluant. This left **8** (0.78 g) of high purity (> 98%; NMR); 82% yield from **7**. ^1H NMR: δ 7.1–7.3 (m, 5 H), 2.90 (m, 2 H), 2.72 (m, 2 H), 2.38 (t, 2 H, *J* 7.4 Hz), 1.54 (m, 2 H), 1.27 (sextet, 2 H, *J* 7.4 Hz), 0.88 (t, 2 H, *J* 7.3 Hz). ^{13}C NMR: δ 210.4, 141.2, 128.4, 128.3, 126.0, 44.2, 42.8, 29.8, 25.9, 22.3, 13.8. This compound has been synthesised many times before, see, e.g., Ref. 32, but not characterised by NMR spectroscopy.

*5-(2-Phenylethyl)-5-nonanol (**9**)* was obtained as a by-product from the reaction between BuLi and **7** but was also prepared for reference purposes from methyl 3-phenylpropanoate and 2.5 equiv. of BuLi: ^1H NMR: 7.1–7.4 (m, 5 H), 2.6–2.7 (m, 2 H), 1.7–1.8 (m, 2 H), 1.6–1.3 (m, 7 H), 0.93 (t, 3 H). ^{13}C NMR: δ 142.8, 128.4, 128.3, 125.7, 74.3, 41.4, 38.9, 30.0, 25.8, 23.3, 14.2.

*(2S)-Ethyl 2-(2-bromohexanoyloxy)propanoate (**11**).* A solution of 2-bromohexanoyl bromide (30.9 g; 0.12 mol) in dichloromethane (50 ml) was added over a period of 1.5 h to a cooled (0–5 °C) and stirred solution of (*S*)-ethyl lactate (11.8 g, 0.10 mol) and pyridine (39.5 g; 0.50 mol). After a further 1.5 h at the same temperature, the reaction mixture was diluted with Et_2O (250 ml) and then washed with 1 M hydrochloric acid (4 × 75 ml), then successively with water, dilute aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated. TLC showed that **11** was contaminated by a product of lower mobility on silica gel and part of **11** (4.0 g) was therefore purified on a silica gel column (4 × 25 cm) using light petroleum–ethyl acetate (5:1) as the eluant. The amount of chromatographically pure **11** corresponded to a 90% yield (mixture of diastereomers). ^1H NMR: δ 5.13 (q, 2 H, *J* 7.0 Hz), 4.29 (t, 0.5 H, *J* 7.7 Hz), 4.21 (t, 0.5 H, *J* 7.7 Hz), 4.22 (q, 2 H, *J* 7.4 Hz), 1.9–2.2 (m, 2 H), 1.54 (d, 1.5 H, *J* 7.0 Hz), 1.53 (d, 1.5 H, *J* 7.0 Hz), 1.3–1.5 (m, 4 H), 1.29 (t, 1.5 H, *J* 7.1 Hz), 1.28 (t, 1.5 H, *J* 7.1 Hz), 0.92 (t, 3 H, *J* 7.1 Hz); ^{13}C NMR ($CDCl_3$); δ 170.1, 170.0, 169.3, 169.1, 69.83, 59.78, 61.4, 45.4, 45.3, 34.6, 29.3, 22.0, 16.7, 14.1 and 13.8.

*(5S)-3-Butyl-4-hydroxy-5-methyl-2(5H)-furanone (**13**) from **11**.* A magnetically stirred mixture of **11** (8.68 g, 29.4 mmol) and activated zinc dust[33] (7.69 g, 118 mmol) in dry THF (200 ml) was heated under reflux (70 min), generating a sticky mass. After cooling, the reaction mixture was added with stirring to hydrochloric acid (4 M, 60 ml). The resulting product was filtered, the THF was evaporated off and the resultant liquid was extracted with dichloromethane (2 × 100 ml). After drying (Na_2SO_4) and concentration of the organic phase the residue was chromatographed on a silica gel column (5 × 35 cm) using ethyl acetate-hexane (1:1) as the eluant. Ethyl 2-(hexanoyloxy)propanoate (2.49 g, 39%), indistinguishable from the authentic sample described below, was eluted first and then compound **13** (1.81 g, 36%) which crystallised on evaporation of the solvent, m.p. 56–63 °C; $[\alpha]^{22}_D$ + 15.2 (*c* 1.1, $CHCl_3$); lit.[27] values: m.p. 58–59 °C: $[\alpha]^{20}_D$ + 17.3° (*c* 1.0, $CHCl_3$). Attempted recrystallisation of **13** as indicated in Ref. 27 was unsuccessful. The main tautomer was the enol form, in $CDCl_3$ as well as in D_2O. ^{13}C NMR ($CDCl_3$): δ 178.1, 177.9, 100.8, 75.5, 30.3, 22.5, 20.8, 17.8, 13.9. ^1H NMR ($CDCl_3$): δ 10–9 (v br), 4.82 (q, 1 H, *J* 6.7 Hz), 2.19 (br t, 2 H, *J* 7.5), 1.7–1.2 (m, 7 H, inluding a doublet at δ 1.49, *J* 6.6 Hz), 0.90 (t, 3 H, *J* 7.2 Hz); the values given in Ref. 27 are very similar. ^1H NMR(D_2O): δ 4.91 (q, 1 H, *J* 6.7 Hz), 2.14 (t, 2 H, *J* 7.3 Hz), 1.7–1.2 (m, 7 H, inluding a doublet at δ 1.44, *J* 6.7 Hz), 0.87 (t, 3 H, *J* 7.3 Hz).

(S)-Ethyl 2-(hexanoyloxy)propanoate. (*S*)-Ethyl lactate (2.60 g; 22.0 mmol), hexanoyl chloride (2.72 g; 20.2 mmol) and pyridine (4.10 g, 51.8 mmol) were mixed (exothermic reaction) in dichloromethane (20 ml). The mixture was left overnight, diluted with dichloromethane and washed three times with dilute acid, twice with aq. $NaHCO_3$ and finally with water to neutrality. After drying (Na_2SO_4) and concentration of the organic phase the title compound was obtained in 91% yield. ^1H NMR: δ 4.24 (q, 1 H, *J* 7.1 Hz), 4.12 (q, 2 H, *J* 7.1 Hz), 2.4–2.2 (m, 2 H), 1.7–1.2 (m, 12 H), 0.89 (t, 3 H. ^{13}C NMR: δ 173.2, 171.0, 68.5, 61.3, 34.0, 31.3, 24.6, 22.4, 17.0, 14.1 and 13.9.

*(5S)-3-Butyl-4-hydroxy-5-methyl-2(5H)-furanone (**13**) from **12**.* A magnetically stirred mixture of **12** (1.55 g, 4.90 mmol) and activated zinc dust[33] (2.1 g, 32 mmol) in dry THF (40 ml) was heated under reflux (N_2 atmosphere). When the mixture became difficult to stir, dry acetonitrile (10 ml) was added. After being heated for 4 h, the mixture was stirred at 23 °C overnight. Most of the solvent was evaporated off and ethyl acetate was added. The organic phase was extracted twice with saturated aq. $NaHCO_3$ and the combined aqueous phases were acidified and extracted three times with ethyl acetate. The combined extracts were dried (Na_2SO_4), the solvent was evaporated off and the residue dissolved in a small volume of diethyl ether. This solution was filtered through a plug (1 cm) of silica gel and the solvent was evaporated off to give pure (TLC, ^1H and ^{13}C NMR) **13** (0.73 g, 87%). The product was indistinguishable (^1H and ^{13}C NMR) from that obtained from **11**. The optical rotation of this product was not measured.

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