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# Chiral auxiliaries as docking/protecting groups: biohydroxylation of selected ketones with *Beauveria bassiana* ATCC 7159

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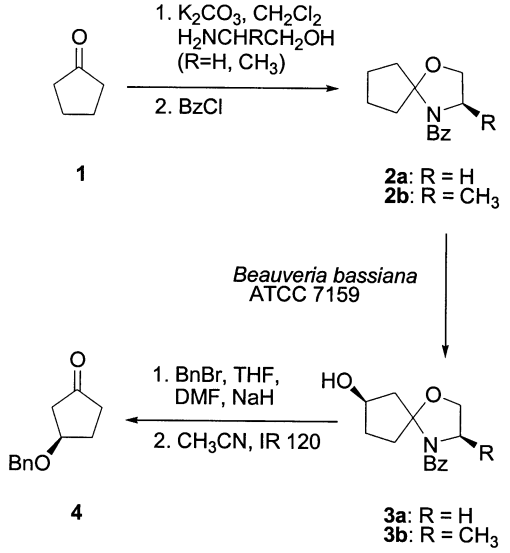
**Abstract**—The concept of chiral docking/protecting groups for biohydroxylation was extended from cyclopentanone to other ketones. Reaction of cyclohexanone, (*R*)-3-methylcyclohexanone, cycloheptanone, 5-methyl-2-hexanone and 4-methyl-2-pentanone with (*R*)-2-amino-1-propanol and subsequent in situ benzoylation afforded the corresponding *N*-benzoylated oxazolidine derivatives. All substrates were hydroxylated with the fungus *Beauveria bassiana* ATCC 7159, one of which was diastereoselectively hydroxylated with a d.e. of 99%. In this manner, access to the corresponding hydroxylated ketones was provided. 

## 1. Introduction

The regio- and stereoselective hydroxylation of non-activated carbon atoms in organic compounds remains a challenge in organic chemistry,[1] especially when enantio- or diastereomerically pure secondary alcohols are desired. Such compounds are, of course, interesting in their own right as valuable intermediates for synthetic work. Surprisingly, although the use of microorganisms to hydroxylate steroids and terpenes has been practised for decades, this approach has been little exploited in other areas of synthetic organic chemistry.[2] In an effort to change this dissatisfying situation, the principle of docking/protecting (d/p) groups was introduced into the field of biohydroxylation.[3] This concept enables the biohydroxylation of substrate classes such as carboxylic acids, aldehydes, alcohols and ketones with a defined set of microorganisms.

This approach is demonstrated in Scheme 1 using cyclopentanone **1** as a model compound and the fungus *Beauveria bassiana* ATCC 7159[2] (*B. bassiana*). Before the biohydroxylation step, ketone **1** is derivatised to **2a** in order to help facilitate and direct the hydroxylation as well as prevent undesired transformations which arise through the use of whole cell systems (hence the terms 'docking' and 'protecting' groups). The subsequent biotransformation gives **3a** which is then benzylated to improve final product (**4**) stability. Finally, the d/p group is simply removed to afford (*R*)-ketone derivative **4**. In the progress of this work it was also found that the use of chiral auxiliaries as d/p groups enhanced hydroxylation stereoselectivity, improved yield and eased product identification by virtue of the




**Scheme 1.**

*Keywords*: *Beauveria bassiana* ATCC 7159; biohydroxylation; biotransformations; chiral auxiliaries; ketones.

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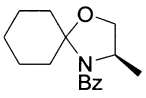
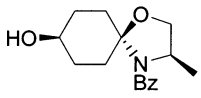
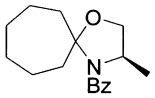
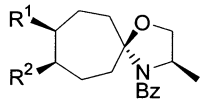
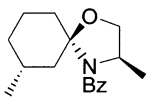
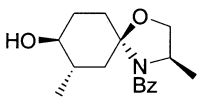
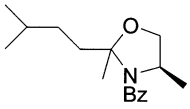
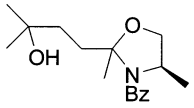
**Table 1.**

| Substrate | Product | Substrate | Product |
|---|---|---|---|
|  |  |  |  |
| **5** | **6** | **9** | **10a**; $R^1$ = H, $R^2$ = OH<br>**10b**; $R^1$ = OH, $R^2$ = H |
|  |  |  |  |
| **7** | **8** | **11** | **12** |

known chiral centre present.[4] These findings are also illustrated in Scheme 1; whereas substrate **2a** was converted to **3a** in 60% yield with a low d.e. (40%) with *B. bassiana*, substrate **2b** was hydroxylated to give **3b** in 84% yield and good d.e. (90%). Moreover, the d.e. of product **3b** could be raised even further to over 99% by recrystallization and, owing to the presence of a known chiral centre, the absolute configuration of all asymmetric centres could be elucidated by X-ray crystal structure analysis. Bearing these results in mind, we then endeavoured to investigate the scope and limitations of the chiral d/p group concept with respect to other ketone substrates. Our findings in this respect will be disclosed in this report.

## 2. Results and discussion

In order to investigate the applicability of the chiral d/p group concept to other ketones, investigations concentrated on substances related to model compound cyclopentanone **1**. For this purpose the following ketones were chosen; cyclohexanone, (*R*)-3-methylcyclohexanone, cycloheptanone, 4-methyl-2-pentanone (**13**) and 5-methyl-2-hexanone. Concerning the choice of chiral d/p group, previous studies had shown[4] that the highest yields and biohydroxylation selectivities could be obtained with the chiral d/p group present in substrate **2b**. Consequently, the aforementioned ketones were reacted with (*R*)-2-amino-1-propanol in a similar manner to that described[4] for compound **2b** to give the corresponding derivatives. With respect to the conditions employed for the biohydroxylation, for preliminary experiments it was thought appropriate to take the same conditions which had been found for the optimal conversion of derivative **2b**.

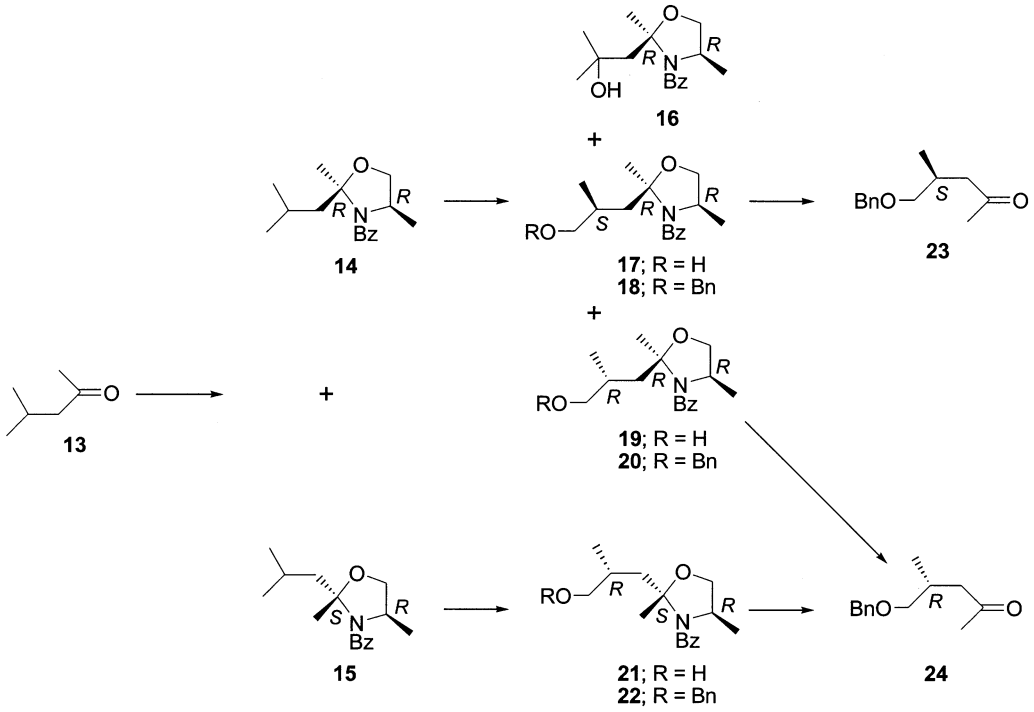
### 2.1. Biohydroxylation of cycloalkanones

Taking cyclohexanone as the first example, reaction of this ketone with (*R*)-2-amino-1-propanol gave product **5** in moderate yield (Table 1, 70%). Treatment of **5** with *B. bassiana* under standard conditions[4] gave **6** in 44% yield. NMR experiments and X-ray crystal structure analysis confirmed that hydroxylation had taken place as shown. At this point it should be mentioned that structurally similar compounds have also been observed to be hydroxylated in this position by *B. bassiana*.[5] Owing to the stability of the expected end product, **6** was not benzylated prior to removal of the d/p group. Subjecting **6** to mildly acidic conditions[4] furnished the known[6] ketone 4-hydroxy-cyclohexanone in moderate yield (59%).

Introducing a methyl group into the six-membered ring and thereby forming an additional chiral centre was not found to influence the site of hydroxylation. Reacting (*R*)-3-methylcyclohexanone with (*R*)-2-amino-1-propanol afforded a mixture of diastereoisomers, whereby major isomer **7** was isolated by simple crystallisation (67%). The absolute configuration of **7** was determined by X-ray crystal structure analysis. This substrate was hydroxylated (NMR, X-ray crystal structure analysis) to give **8** as the sole product in fair yield (43%, d.e. 95%). D/p removal furnished the previously unknown ketone, (3*S*, 4*S*)-4-hydroxy-3-methylcyclohexanone (43%).

Homologation of the six-membered ring by an additional carbon atom resulted in a pronounced loss in hydroxylation selectivity, lowered isolated yield and promoted ketone formation via biooxidation of the initially formed alcohol. Substrate **9**, obtained from cycloheptanone in modest yield (25%), afforded an inseparable mixture of alcohols **10a** and **10b** (29%, a waxy solid), in addition to small amounts (7%) of the corresponding ketone derivative. Due to the complexity of the NMR data obtained for alcohols **10a** and **10b**, structure elucidation could only be achieved by X-ray crystal structure analysis of the corresponding crystalline *N*-phenylurethane derivative.[7] In strong contrast to the five-membered ring analogue **3b** (d.e. 90%), products **10a** and **10b** were formed in only equal amounts (HPLC). Ketone formation and yield reduction upon ring expansion has also been observed for similar compounds, namely cycloheptyl-*N*-phenylcarbamates.[8] Due to these discouraging results d/p group removal was not carried out.

It is interesting to note that in all of the examples above (**6**, **8**, **10a** and **10b**) hydroxylation always occurred *anti* to the nitrogen moiety. This observation has been frequently made with *B. bassiana* employing other *N*-benzoylated spirooxazolidines[4] as well as related compounds.[2]




**Scheme 2.**

### 2.2. Biohydroxylation of acyclic derivatives

Derivatives of acyclic ketones were also found to be suitable candidates for *B. bassiana*, as can be seen from substrates **11** (Table 1), **14** and **15** (Scheme 2). Derivatising 5-methyl-2-hexanone with (*R*)-2-amino-1-propanol produced a mixture of diastereoisomers in low yield (34%, 2.4:1). Subjecting major isomer **11** to *B. bassiana* gave compound **12** in good yield (67%). Because the expected end product from **12**, 5-hydroxy-5-methyl-2-hexanone, can be prepared more efficiently by chemical means,[9] **12** was not further investigated.

As can be seen from Scheme 2, reacting 4-methyl-2-pentanone **13** with (*R*)-2-amino-1-propanol and subsequent benzoylation afforded a mixture of diastereoisomers **14** and **15** (1.8:1). Subjecting major isomer **14** to *B. bassiana* gave a mixture of three hydroxylated products. While hydroxylation at the tertiary carbon (C-2′) of substrate **14** furnished **16**, hydroxylation of the primary carbon (C-3′ or C-4′) of this starting material afforded two diastereoisomers **17** and **19** by virtue of the newly formed chiral centre at C-2′. Because the hydroxy ketone end product was expected to be in equilibrium with the corresponding hemiacetal, compounds **17** and **19** were benzylated to give **18** and **20**, respectively, prior to d/p group removal. Subsequently, cleavage of the d/p group from **18** and **20** gave rise to (*S*)-5-benzyloxy-4-methylpentan-2-one **23** and (*R*)-5-benzyloxy-4-methylpentan-2-one **24**, respectively.

In contrast, minor isomer **15** was diastereoselectively hydroxylated by *B. bassiana* at only one of the primary carbon atoms to afford product **21** in 60% isolated yield, this outcome being confirmed by X-ray crystal structure analysis. Indeed, this compound was furnished in a d.e. of 99%. To the best of our knowledge,[10] this is the highest d.e. ever reported for this fungus. After benzylation of product **21** to afford **22**, the d/p group was removed to give (*R*)-5-benzyloxy-4-methylpentan-2-one **24** in an e.e. of 99%.

## 3. Conclusion

In conclusion, we have shown that the concept of chiral docking/protecting groups can be successfully extended to acyclic and cyclic ketones other than cyclopentanone. In this manner, depending on the substrate employed, a hydroxyl moiety could be selectively introduced into the substrate to give the corresponding alcohol derivative. In addition, through 'fine tuning' of the fermentation conditions, hydroxylated product yields could be improved, if desired.[11]

## 4. Experimental

### 4.1. General methods

All chemicals were purchased from either Aldrich or Fluka. If required, chemicals and solvents were purified according to Perrin and Armarego.[12] Optical rotations were measured on a DIP-370 Digital Polarimeter (Japan Spectroscopic Company). Melting points (uncorrected) were determined in open capillaries using a Büchi 530. $^{1}H$ and $^{13}C$ NMR were recorded on either a Gemini 200 BB (Varian), INOVA 300 (Varian) or INOVA 500 (Varian). HETCOR, DEPT and COSY experiments were carried out as required. $CDCl_3$ was used as solvent and as internal standard unless otherwise stated. Before use, the $CDCl_3$ was filtered through a short plug of basic alumina to remove traces of acid. Mass spectra (HRMS, EI, 70 eV) were recorded on a Kratos Profile HV-4 double focussing magnetic sector instrument

equipped with direct insertion (DI) and GC (Shimadzu GC-14A, column HP-5MS). GC-MS was measured on a HP 6890 Series GC system equipped with a HP 5 column (25 m) and a HP 6890 series mass detector. Helium was used as carrier gas. Relative intensities are given in brackets for all mass spectral data. HPLC was determined with a JASCO system containing pump 880-PU, UV-detector 875-UV (detection at 238 nm) and AXXIOM Model 727 chromatography software. The chiral column used was a CHIRALCEL OD-H. LC was performed on Silica gel 60 (Merck, 70–230 mesh) using mixtures of ethyl acetate and petroleum ether unless otherwise stated. TLC was performed on Silica gel 60 F254 aluminium plates (Merck) and compounds detected with UV (254 nm) and spraying with either reagent A (5% vanillin in concentrated $H_2SO_4$) or reagent B (10% $H_2SO_4$, 10% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.8% $Ce(SO_4)_2\cdot 4H_2O$ in water). The TLC plates were then developed on a hot plate. Unless otherwise stated, mixtures of petroleum ether/ethyl acetate were used as eluent. Solvents needed for recrystallization were always filtered through basic alumina (ALDRICH, Basic Brockmann I, 150 mesh) prior to use. All crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. The respective CCDC numbers are given with the compound under consideration.

General procedures for substrate preparation and biohydroxylation as well as d/p removal have been published elsewhere.[4]

**4.1.1. (*R*)-4-Benzoyl-3-methyl-1-oxa-4-azaspiro[4.5]decane 5.** The title compound **5** was prepared as a white crystalline solid from cyclohexanone (3.40 g) and (*R*)-2-amino-1-propanol (2.00 g) in 70% isolated yield (4.83 g) after column chromatography; mp 108.0–109.0°C (from pet. ether/EtOAc); $[\alpha]_D^{20}=-58.3°$ (*c* 0.6, $CH_2Cl_2$); $^1$H NMR[13] 1.11 (3H, d, *J*=5.7 Hz, Me), 1.11–1.80, 2.49 and 2.72 (8H, 1H and 1H, bm and 2×bs, 6-H, 7-H, 8-H, 9-H, 10-H), 3.59 (1H, m, 2-H), 4.00 (2H, m, 2-H, 3-H), 7.34 (5H, s, benzoyl); $^{13}$C NMR 20.8 (Me), 23.4, 23.5, 24.8, 31.1, 35.1 (C-6, C-7, C-8, C-9, C-10), 54.7 (C-3), 69.5 (C-2), 97.2 (C-5), 126.3, 128.7, 129.4, 138.8, 168.3 (Bz); MS (70 eV): *m/z* (%) 259 (32) $[M]^+$, 216 (36) $[M-C_3H_7]^+$, 105 (100) $[Bz]^+$, 77 (26) $[Ph]^+$; HRMS ($C_{16}H_{21}NO_2$): calcd. 259.1572, found 259.1587.

**4.1.2. *cis*-(3*R*)-4-Benzoyl-3-methyl-1-oxa-4-azaspiro[4.5]-decan-8-ol 6.** Treatment of substrate **5** (1.04 g) with *B. bassiana* furnished the title compound **6** (0.46 g, 44%) as the sole product, a white crystalline solid, after column chromatography; mp 212.0–213.0°C (from *n*-heptane/$CH_2Cl_2$); $[\alpha]_D^{20}=-55.0°$ (*c* 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 0.96 (3H, d, *J*=5.7 Hz, Me), 1.53–1.99 and 2.51–2.99 (7H and 2H, 2×bd, 6-H, 7-H, 9-H, 10-H, OH), 3.53–3.85 (2H, bm, 2-H, 8-H), 4.03 (2H, m, 2-H, 3-H), 7.35 (5H, s, Bz); $^{13}$C NMR $\delta$ 20.7 (Me), 29.1, 32.3, 32.4, 32.8 (C-6, C-7, C-9, C-10), 54.8 (C-3), 69.4, 69.6 (C-2, C-8), 96.0 (C-5), 126.2, 128.7, 129.6, 138.5, 168.7 (Bz); MS (70 eV): *m/z* (%) 275 (11) $[M]^+$, 216 (62) $[M-C_3H_7O]^+$, 202 (6), 105 (100) $[Bz]^+$, 77 (23) $[Ph]^+$; HRMS ($C_{16}H_{21}NO_3$): calcd 275.1521, found 275.1527; The absolute configuration of compound **6** was obtained by X-ray crystallographic analysis (CCDC 159175).

**4.1.3. 4-Hydroxycyclohexanone.** Removal of the d/p from **6** (55.9 mg) afforded the title compound as a clear syrup (13.6 mg, 59% yield) after column chromatography. $^1$H and $^{13}$C NMR data were in agreement with reported values.[6]

**4.1.4. (3*R*,5*S*,7*R*)-4-Benzoyl-3,7-dimethyl-1-oxa-4-azaspiro[4.5]decane 7.** Reacting (*R*)-3-methylcyclohexanone (1.40 g) with (*R*)-2-amino-1-propanol (0.78 g) afforded a syrupy mixture of diastereoisomers (3.4:1, HPLC, *n*-heptane/IPA; 95:5; flow=0.5 mL/min) in 94% yield (2.68 g) after column chromatography. The major isomer **7** was isolated as a single isomer (d.e. 93%, HPLC) by crystallisation to give white crystals in 67% isolated yield; mp 91.0–92.0°C (from pet. ether/$CH_2Cl_2$); $[\alpha]_D^{20}=-45.0°$ (*c* 1.4, $CH_2Cl_2$); $^1$H NMR $\delta$ 0.82–1.16 (6H, m, 2×Me), 1.43–1.87 and 2.46 (9H, m, 6-H, 7-H, 8-H, 9-H, 10-H), 3.61 (1H, m, 2-H), 4.01 (2H, m, 2-H, 3-H), 7.38 (5H, s, benzoyl); $^{13}$C NMR $\delta$ 20.9, 22.6 (2×Me), 23.0, 30.3, 33.5 (C-8, C-9, C-10), 30.0 (C-7), 43.5 (C-6), 54.7 (C-3), 69.6 (C-2), 97.6 (C-5), 126.3, 128.7, 129.4, 138.8, 168.4 (Bz); MS (70 eV): *m/z* (%) 273 (28) $[M]^+$, 258 (2) $[M-CH_3]^+$, 230 (36) $[M-C_3H_7]^+$, 216 (18) $[M-C_4H_9]^+$, 105 (100) $[Bz]^+$, 77 (25) $[Ph]^+$; HRMS ($C_{17}H_{23}NO_2$): calcd 273.1729, found 273.1745; The absolute configuration of compound **7** was obtained by X-ray crystallographic analysis (CCDC 159176).

**4.1.5. (3*R*,5*R*,7*S*,8*S*)-4-Benzoyl-3,7-dimethyl-1-oxa-4-azaspiro[4.5]decan-8-ol 8.** Treatment of substrate **7** (0.715 g) with *B. bassiana* furnished compound **8** as the sole product, a white crystalline solid, after column chromatography (0.325 g, 43% yield); mp 219.5–220.5°C (from pet. ether/$CH_2Cl_2$); $[\alpha]_D^{20}=-33.2°$ (*c* 0.5, $CH_2Cl_2$); $^1$H NMR $\delta$ 0.98 and 1.03 (6H, 2×d, *J*=6.7 and 6.4 Hz, 2×Me), 1.54–1.95 and 2.63 (6H and 2H, m and bm, 6-H, 7-H, 9-H, 10-H, OH), 3.31 (1H, ddd, $J_{8,9ax}=J_{8,7ax}=10.8$ Hz, $J_{8,9eq}=4.2$ Hz, 8-H), 3.63 (1H, m, 2-H), 4.02 (2H, m, 2-H, 3-H), 7.37 (5H, s, Bz); $^{13}$C NMR $\delta$ 18.5, 20.8 (2×Me), 29.4 (C-9), 31.9 (C-10), 36.9 (C-7), 41.3 (C-6), 54.8 (C-3), 69.6 (C-2), 75.0 (C-8), 96.5 (C-5), 126.2, 128.7, 129.5 138.5, 168.7 (Bz); MS (70 eV): *m/z* (%) 289 (8) $[M]^+$, 230 (37) $[M-C_3H_7O]^+$, 216 (31) $[M-C_4H_9O]^+$, 202 (6), 105 (100) $[Bz]^+$, 77 (24) $[Ph]^+$; HRMS ($C_{17}H_{23}NO_3$): calcd 289.1678, found 289.1692; The absolute configuration of compound **8** was determined by X-ray crystallographic analysis (CCDC 159177).

**4.1.6. (3*S*,4*S*)-4-Hydroxy-3-methylcyclohexanone.** Removal of the d/p from **8** (57 mg) afforded the title compound as a clear syrup (19 mg, 77% yield) after column chromatography; $[\alpha]_D^{20}=+22.0°$ (*c* 0.6, $CH_2Cl_2$); $^1$H NMR $\delta$ 1.05 (3H, d, *J*=6.1 Hz, Me), 1.68–2.59 (8H, m, 2-H, 3-H, 5-H, 6-H, OH), 3.69 (1H, ddd, $J_{4,5ax}=J_{4,3ax}=8.1$ Hz, $J_{4,5eq}=3.7$ Hz, 4-H); $^{13}$C NMR $\delta$ 18.6 (Me), 32.4, 38.4, 39.5 (C-2, C-5, C-6), 45.7 (C-3), 72.8 (C-4), 210.5 (C-1); MS (70 eV): *m/z* (%) 128 (100) $[M]^+$, 113 (18) $[M-CH_3]^+$, 110 (20) $[M-H_2O]^+$, 69 (90); HRMS ($C_7H_{12}O_2$): calcd 128.0837, found 128.0830.

**4.1.7. (*R*)-4-Benzoyl-3-methyl-1-oxa-4-azaspiro[4.6]-undecane 9.** Cycloheptanone (4.48 g) was reacted with (*R*)-2-amino-1-propanol (2.0 g) to afford the title compound **9** (2.0 g, 27% yield) as colourless crystals after column

chromatography; mp 86.0–89.0°C; $[\alpha]_D^{20}=-60.2°$ (*c* 1.5, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.96 (3H, d, $J$=5.9 Hz, Me), 1.50–1.98, 2.51 and 2.69 (10H, 1H and 1H, 3×m, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H), 3.60 (1H, dd, $J_{2,2}$=6.2 Hz, $J_{2,3}$= 0.9 Hz, 2-H), 4.03 (2H, m, 2-H, 3-H), 7.38 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.7 (Me), 23.0, 28.9, 29.2, 36.4, 39.6 (C-6, C-7, C-8, C-9, C-10, C-11), 54.5 (C-3), 69.6 (C-2), 100.8 (C-5), 126.3, 128.6, 129.4, 138.8, 168.4 (Bz); MS (70 eV): *m/z* (%) 273 (32) $[M]^+$, 216 (42) $[M-C_4H_9]^+$, 105 (100) $[Bz]^+$, 77 (22) $[Ph]^+$; HRMS ($C_{17}H_{23}NO_2$): calcd 273.1729, found 273.1747.

**4.1.8. (3*R*,5*R*,8*S*) and (3*R*,5*S*,8*R*)-4-Benzoyl-3-methyl-1-oxa-4-azaspiro[4.6]undecan-8-ol 10a and 10b.** Treatment of substrate **9** (0.720 g) with *B. bassiana* and column chromatography furnished an inseparable mixture of compounds **10a** and **10b** (0.2 g, 29% yield; 1:1, HPLC, *n*-heptane/IPA; 7:3; flow=0.5 mL/min), a white waxy solid, as well as the corresponding ketone derivative[14] as a waxy solid (0.050 g, 7%). Experimental data for **10a** and **10b**; $^1H$ NMR $\delta$ 0.96 (3H, m, Me), 1.50–2.08 and 2.20–2.80 (11H, 2×bm, 6-H, 7-H, 9-H, 10-H, 11-H, OH), 3.63 (1H, dd, $J_{2,2}$=6.1 Hz, $J_{2,3}$=2.5 Hz, 2-H), 3.82–4.13 (3H, m, 2-H, 3-H, 8-H), 7.38 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.4 (Me), 18.4, 31.1, 37.4, 37.9, 39.9 (C-6, C-7, C-9, C-10, C-11), 54.4 (C-3), 69.5 (C-2), 72.0 (C-8), 102.5 (C-5), 126.0, 128.5, 129.4, 138.1, 168.2 (Bz); MS (70 eV): *m/z* (%) 289 (32) $[M]^+$, 216 (54) $[M-C_4H_9O]^+$, 202 (8) $[M-C_5H_{11}O]^+$, 105 (100) $[Bz]^+$, 77 (23) $[Ph]^+$; HRMS ($C_{17}H_{23}NO_3$): calcd 289.1678, found 289.1685.

Experimental data for the ketone by-product[14]. $[\alpha]_D^{20}=-65.7°$ (*c* 1.8, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.98 (3H, $J$=6.3 Hz, Me), 1.70–2.20 and 2.30–3.20 (10H, 2×bm, 6-H, 7-H, 9-H, 10-H, 11-H), 3.65 (1H, d, $J_{2,2}$=6.1 Hz, 2-H), 4.08 (2H, m, 2-H, 3-H), 7.38 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.5 (Me), 19.0, 31.1, 37.2, 38.9, 37.9, 43.4 (C-6, C-7, C-9, C-10, C-11), 54.6 (C-3), 69.8 (C-2), 97.7 (C-5), 126.0, 128.6, 129.5, 138.0, 168.2 (Bz), 213.9 (C-8); GC-MS, *m/z* (%) 287 ($M^+$, 11), 216 (8), 182 (9), 154 (23), 105 (100), 77 (43).

**4.1.9. (3*R*,5*S*,8*R*)- and (3*R*,5*R*,8*S*)-4-Benzoyl-3-methyl-8-phenylcarbamoyloxy-1-oxa-4-azaspiro[4.6]undecane 25a and 25b.**[14] Alcohols **10a** and **10b** (0.330 g), an inseparable mixture, were derivatised with phenylisocyanate (0.160 g) according to a known procedure[15] to give the title compounds **25a** and **25b**, also an inseparable mixture, as colourless crystals (0.47 g, 28% yield): mp 70.0–70.5°C (from *n*-hexane/$CH_2Cl_2$); $^1H$ NMR $\delta$ 0.97 (3H, d, $J$= 6.5 Hz, Me), 1.60–2.34 and 2.40–2.83 (10H, 2×bm, 6-H, 7-H, 9-H, 10-H, 11-H), 3.64 (1H, d, $J_{2,2}$=6.4 Hz, 2-H), 4.18 (2H, m, 2-H, 3-H), 5.01 (1H, bs, 8-H), 7.03 (1H, t, $J$= 7.1 Hz, OCONH*Ph*), 7.28 (2H, t, $J$=8.3 Hz, OCONH*Ph*), 7.39 (7H, m, Bz, OCONH*Ph*); $^{13}C$ NMR $\delta$ 20.6 (Me), 18.5, 27.4, 34.4, 37.2, 39.7 (C-6, C-7, C-9, C-10, C-11), 54.4 (C-3), 69.5 (C-2), 75.5 (C-8), 99.7 (C-5), 118.6, 123.2, 126.1, 128.6, 129.0, 129.4, 138.2, 138.3, 153.2, 168.4 (O*C*ONH*Ph*; Bz); MS (70 eV): *m/z* (%) 408 (6) $[M]^+$, 289 (9) $[M-PhNCO]^+$, 271 (17) $[M-C_7H_7NO_2]^+$, 216 (24) $[M-C_{11}H_{14}NO_2]^+$, 162 (20), 119 (35) $[PhNCO]^+$, 105 (100) $[Bz]^+$, 91 (15), 77 (25) $[Ph]^+$; HRMS ($C_{24}H_{28}N_2O_4$): calcd 408.2049, found 408.2042; The absolute configurations of compounds **25a** and **25b** (mixed crystals) were obtained by X-ray crystallographic analysis (CCDC 159784).

**4.1.10. (2Ξ,4*R*)-3-Benzoyl-2,4-dimethyl-2-(3′-methylbutyl)oxazolidine 11.** Reacting 5-methyl-2-hexanone (2.28 g) with (*R*)-2-amino-1-propanol (1.00 g) produced a mixture of diastereoisomers which were separated by column chromatography (major isomer **11**: 0.86 g, 24%, colourless oil; minor isomer: 0.35 g, 10%, white crystalline solid). Experimental data for **11**: $[\alpha]_D^{20}=-27.3°$ (*c* 1.2, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.92 (9H, m, 4′-H, 5′-H, 7′-H), 1.24 (3H, m, 2′-H, 3′-H), 1.58 (3H, s, 6′-H), 2.10 (2H, m, 1′-H), 3.59 (1H, d, $J_{5,4}$ =6.5 Hz, 5-H), 4.09 (2H, m, 4-H, 5-H), 7.40 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.1, 22.0, 22.7, 22.8 (C-4′, C-5′, C-6′, C-7′), 28.2 (C-3′), 33.1, 35.9 (C-1′, C-2′), 54.1 (C-4), 69.4 (C-5), 97.9 (C-2), 125.9, 128.4, 129.1, 138.4, 168.1 (Bz); MS (70 eV): *m/z* (%) 260 (7) $[M-CH_3]^+$, 204 (97) $[M-C_5H_{11}]^+$, 105 (100) $[Bz]^+$, 77 (16) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{16}H_{22}NO_2$): calcd 260.1651, found 260.1671. Experimental data for the minor isomer: mp 63.5–66.0°C; $[\alpha]_D^{20}=-87.3°$ (*c* 1.2, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.88 (9H, m, 4′-H, 5′-H, 7′-H), 1.27 (2H, m, 2′-H), 1.51 (1H, m, 3′-H), 1.69 (3H, s, 6′-H), 2.10 (2H, m, 1′-H), 3.62 (1H, dd, $J_{5,4}$=3.6 Hz, $J_{5,5}$=7.9 Hz, 5-H), 4.10 (2H, m, 4-H, 5-H), 7.40 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.4, 22.7, 24.9 (C-4′, C-5′, C-6′, C-7′), 28.2 (C-3′), 32.6, 34.5 (C-1′, C-2′), 54.6 (C-4), 70.4 (C-5), 97.8 (C-2), 126.4, 128.5, 129.6, 138.2, 164.2 (Bz); GC-MS, *m/z* (%) 274 ($M^+$, 1), 260 (2), 204 (33), 162 (2), 105 (100), 77 (30).

**4.1.11. (2Ξ,4*R*)-3-Benzoyl-2,4-dimethyl-2-(3′-hydroxy-3′-methylbutyl)oxazolidine 12.** Treating substrate **11** (0.869 g) with *B. bassiana* furnished compound **12** (0.619 g, 67%) as a colourless oil after chromatography: $[\alpha]_D^{20}=-17.4°$ (*c* 1.7, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.93 (3H, d, $J$=8.6 Hz, 7′-H), 1.22 (6H, s, 4′-H, 5′-H), 1.60 (5H, m, 2′-H, 6′-H), 2.21 (2H, m, 1′-H), 3.60 (1H, d, $J_{5,4}$=7.9 Hz, 5-H), 4.07 (2H, m, 4-H, 5-H), 7.35 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.5 (C-7′), 22.2 (C-6′), 29.1, 29.8 (C-4′, C-5′), 32.7, 38.0 (C-1′, C-2′), 54.0 (C-4), 69.4 (C-3′), 70.3 (C-5), 97.8 (C-2), 125.8, 128.2, 129.3, 138.1, 168.1 (Bz); MS (70 eV): *m/z* (%) 276 (3) $[M-CH_3]^+$, 204 (73) $[M-C_5H_{11}O]^+$, 162 (18), 105 (100) $[Bz]^+$, 77 (19) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{16}H_{22}NO_3$): calcd 276.1600, found 276.1604.

**4.1.12. (2*R*,4*R*)-3-Benzoyl-2,4-dimethyl-2-(2′-methylpropyl)oxazolidine 14 and (2*S*, 4*R*)-3-Benzoyl-2,4-dimethyl-2-(2′-methylpropyl)oxazolidine 15.** Reacting 4-methyl-2-pentanone **13** (7.22 g) with (*R*)-2-amino-1-propanol (3.60 g) afforded a mixture (1.8:1, HPLC, *n*-heptane/IPA; 95:5; $T$=10°C; flow=0.5 mL/min) of diastereoisomers **14** and **15** (4.03 g, 32% combined yield). These were separated with careful column chromatography to give major isomer **14** as a clear syrup and the minor isomer **15** as a white crystalline solid. Experimental data for the major isomer **14**: $[\alpha]_D^{20}=-42.2°$ (*c* 1.5, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.96 (9H, 3′-H, 4′-H, 6′-H), 1.65 (3H, s, 5′-H), 1.87 and 2.21 (3H, 2×m, 2′-H, 1′-H), 3.62 (1H, bd, 5-H), 4.06 (2H, m, 4-H, 5-H), 7.36 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.7, 24.0, 24.6, 24.9, 46.2 (C-1′, C-2′, C-3′, C-4′, C-5′, C-6′), 54.2 (C-4), 69.7 (C-5), 98.4 (C-2), 126.1, 128.6, 129.4, 138.6, 163.0 (Bz); MS (70 eV): *m/z* (%) 261 (<0.1) $[M]^+$, 246 (5) $[M-CH_3]^+$, 204 (64) $[M-C_4H_9]^+$, 105 (100) $[Bz]^+$, 77

(19) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{15}H_{20}NO_2$): calcd 246.1494, found 246.1511; HRMS ($[M]^+$; $C_{16}H_{23}NO_2$): calcd 261.1729, found 261.1708. (very low intensity). Experimental data for **15**; mp 56.0–57.0°C; $[\alpha]_D^{20}=-77.5°$ (*c* 1.1, $CH_2Cl_2$); $^1H$ NMR[12] $\delta$ 0.95 (9H, m, 3′-H, 4′-H, 6′-H), 1.73 (3H, s, 5′-H), 1.77–2.15 (3H, m, 2′-H, 1′-H), 3.62 (1H, bd, 5-H), 4.08 (2H, m, 4-H, 5-H), 7.38 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.7, 24.0, 24.7, 25.3, 44.1 (C-1′, C-2′, C-3′, C-4′, C-5′, C-6′), 54.6 (C-4), 70.1 (C-5), 98.3 (C-2), 126.5, 128.7, 129.7, 138.5, 169.0 (Bz); MS (70 eV): *m/z* (%) 261 (0.1) $[M]^+$, 246 (7) $[M-CH_3]^+$, 204 (59) $[M-C_4H_9]^+$, 105 (100) $[Bz]^+$, 77 (18) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{15}H_{20}NO_2$): calcd 246.1494, found 246.1506.

**4.1.13. (2*R*,4*R*)-3-Benzoyl-2,4-dimethyl-2-(2′-hydroxy-2′-methylpropyl)oxazolidine 16.** Subjecting major isomer **14** (0.917 g) to *B. bassiana* afforded three hydroxylated products **16** (0.103 g), **17** (0.126 g) and **19** (0.047 g) after chromatography. Experimental data for **16**: a colourless syrup; 12% yield; $^1H$ NMR $\delta$ 1.06 (3H, d, *J*=6.0 Hz, 6′-H), 1.32 and 1.40 (2×3H, 2×s, 3′-H, 4′-H), 1.61 (1H, bs, OH), 1.80 (3H, s, 5′H), 2.25 and 2.70 (2×1H, 2×d, *J*=14.9 Hz, 1′-H), 3.77 (1H, d, *J*=8.4 Hz, 5-H), 4.13 (2H, m, 4-H, 5-H), 7.40 (5H, s, Bz); $^{13}C$ NMR $\delta$ 20.6 (C-6′), 24.1 (C-5′), 30.5 and 31.6 (C-3′, C-4′), 50.7 (C-1′), 54.3 (C-4), 70.1 (C-5), 70.9 (C-2′), 98.2 (C-2), 126.1, 128.8, 129.6, 138.1, 168.4 (Bz); MS (70 eV): *m/z* (%) 262 (7) $[M-CH_3]^+$, 204 (69) $[M-C_4H_9O]^+$, 162 (14), 140 (12), 105 (100) $[Bz]^+$, 77 (17) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{15}H_{20}NO_3$): calcd 262.1443, found 262.1437.

**4.1.14. (2*R*,4*R*, 2′*S*)-3-Benzoyl-2,4-dimethyl-2-(3′-hydroxy-2′-methylpropyl)oxazolidine 17.** Subjecting major isomer **14** (0.917 g) to *B. bassiana* afforded three hydroxylated products **16** (0.103 g), **17** (0.126 g) and **19** (0.047 g) after chromatography. Experimental data for **17**: a colourless syrup; 14% yield; d.e. 99% (HPLC, *n*-heptane/IPA; 90:10; *T*=10°C, flow=0.5 mL/min); $[\alpha]_D^{20}=-23.9°$ (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR $\delta$ 1.01 (6H, m, 4′-H, 6′-H), 1.64 (3H, s, 5′-H), 1.88 (1H, m, 2′-H), 2.19 (2H, d, *J*=5.4 Hz, 1′-H), 2.53 (H, bs, OH), 3.47 (2H, d, *J*=6.6 Hz, 3′-H), 3.65 (1H, d, *J*=8.8 Hz, 5-H), 4.09 (2H, m, 4-H, 5-H), 7.38 (5H, s, Bz); $^{13}C$ NMR $\delta$ 18.5, 20.6, 22.7, 32.0, 41.6 (C-1′, C-2′, C-4′, C-5′, C-6′), 54.0 (C-4), 69.3, 69.6 (C-5, C-3′), 98.1 (C-2), 126.0, 128.6, 129.3, 138.3, 168.3 (Bz); MS (70 eV): *m/z* (%) 262 (8) $[M-CH_3]^+$, 204 (72) $[M-C_4H_9O]^+$, 162 (6), 105 (100) $[Bz]^+$, 77 (20) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{15}H_{20}NO_3$): calcd 262.1443, found 262.1443.

**4.1.15. (2*R*,4*R*, 2′*S*)-3-Benzoyl-2,4-dimethyl-2-(3′-benzyloxy-2′-methylpropyl)oxazolidine 18.** Benzylation of **17** (0.071 g) under standard conditions[16] afforded the title compound (0.073 g) as a colourless syrup: 78% yield; $[\alpha]_D^{20}=-19.5°$ (*c* 1.1, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.97 and 1.09 (2×3H, 2×d, *J*=5.7 and 6.2 Hz, 4′-H, 6′-H), 1.64 (3H, s, 5′-H), 1.95 and 2.31 (2H and 1H, 2×m, 1′-H, 2′-H), 3.24 and 3.47 (2×1H, 2×dd, *J*=5.3, 7.0 and 8.8 Hz, 3′-H), 3.62 (1H, dd, *J*=2.0 and 8.1 Hz, 5-H), 4.06 (2H, m, 4-H, 5-H), 4.52 (2H, s, C*H*$_2$Ph), 7.35 (10H, m, $CH_2$*Ph*, Bz); $^{13}C$ NMR $\delta$ 18.8, 20.5, 22.8, 30.0, 41.0 (C-1′, C-2′, C-4′, C-5′, C-6′), 54.1 (C-4), 69.6, 73.1, 76.5 (C-5, C-3′, *C*H$_2$Ph), 98.1 (C-2), 126.1, 127.5, 127.8, 128.4, 128.6, 129.3, 138.4, 138.9, 168.3 ($CH_2$*Ph*, Bz); MS (70 eV): *m/z* (%) 367 (2) $[M]^+$, 352 (7) $[M-CH_3]^+$, 204 (96) $[M-C_{11}H_{15}O]^+$, 162 (8), 105 (100) $[Bz]^+$, 91 (19) $[C_7H_7]^+$, 77 (17) $[Ph]^+$; HRMS ($C_{23}H_{29}NO_3$): calcd. 367.2147, found 367.2152.

**4.1.16. (2*R*,4*R*,2′*R*)-3-Benzoyl-2,4-dimethyl-2-(3′-hydroxy-2′-methylpropyl)oxazolidine 19.** Subjecting major isomer **14** (0.917 g) to *B. bassiana* afforded three hydroxylated products **16** (0.103 g), **17** (0.126 g) and **19** (0.047 g, HPLC indicated that **19** was contaminated with both **16** and **17**) after chromatography. Experimental data for **19**: a colourless syrup; 5% yield; d.e. 23%; HPLC, *n*-heptane/IPA; 90:10; *T*=10°C, flow=0.5 mL/min; $[\alpha]_D^{20}=-22.9°$ (*c* 0.9, $CH_2Cl_2$); $^1H$ NMR $\delta$ 1.00 (6H, m, 4′-H, 6′-H), 1.68 (3H, s, 5′-H), 1.73–2.43 (3H, m, 1′-H, 2′-H), 2.90 (1H, bs, OH), 3.35–3.80 (3H, bm, 5-H, 3′-H), 4.10 (2H, m, 4-H, 5-H), 7.39 (5H, s, Bz); $^{13}C$ NMR $\delta$ 19.5, 20.7, 22.2, 32.4, 42.6 (C-1′, C-2′, C-4′, C-5′, C-6′), 54.2 (C-4), 68.6, 69.6 (C-5, C-3′), 98.3 (C-2), 126.1, 128.7, 129.5, 138.0, 168.7 (Bz); MS (70 eV): *m/z* (%) 262 (6) $[M-CH_3]^+$, 204 (68) $[M-C_4H_9O]^+$, 162 (8), 105 (100) $[Bz]^+$, 77 (19) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{15}H_{20}NO_3$): calcd 262.1443, found 262.1425.

**4.1.17. (2*R*,4*R*,2′*R*)-3-Benzoyl-2,4-dimethyl-2-(3′-benzyloxy-2′-methylpropyl)oxazolidine 20.** Benzylation of **19** (0.061 g) under standard conditions[16] afforded the title compound (0.067 g) as a colourless syrup: 83% yield; $[\alpha]_D^{20}=-22.7°$ (*c* 1.2, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.95 and 1.10 (2×3H, 2×m, 4′-H, 6′-H), 1.66 (3H, s, 5′-H), 2.06 (3H, m, 1′-H, 2′H), 3.28 (1H, m, 3′H), 3.40–3.72 (2H, m, 5-H, 3′-H), 4.06 (2H, m, 4-H, 5-H), 4.53 (2H, s, C*H*$_2$Ph), 7.35 (10H, m, $CH_2$*Ph*, Bz); $^{13}C$ NMR $\delta$ 19.7, 20.5, 22.8, 30.0, 41.2 (C-1′, C-2′, C-4′, C-5′, C-6′), 54.1 (C-4), 69.6, 73.1, 76.1 (C-5, C-3′, *C*H$_2$Ph), 98.2 (C-2), 126.1, 127.5, 127.7, 128.4, 128.6, 129.4, 138.4, 139.1, 168.3 ($CH_2$*Ph*, Bz); MS (70 eV): *m/z* (%) 367 (2) $[M]^+$, 352 (6) $[M-CH_3]^+$, 204 (92) $[M-C_{11}H_{15}O]^+$, 162 (20), 105 (100) $[Bz]^+$, 91 (22) $[C_7H_7]^+$, 77 (19) $[Ph]^+$; HRMS ($C_{23}H_{29}NO_3$): calcd 367.2147, found 367.2165.

**4.1.18. (2*S*,4*R*,2′*R*)-3-Benzoyl-2,4-dimethyl-2-(3′-hydroxy-2′-methylpropyl)oxazolidine 21.** Treatment of substrate **15** (0.927 g) with *B. bassiana* furnished the title compound **21**. After column chromatography, compound **21** was afforded as a clear syrup which later solidified (0.529 g, 60% yield, d.e. 99%, HPLC, *n*-heptane/IPA; 90:10; *T*=10°C, flow=0.5 mL/min). Recrystallisation furnished white needles ($CH_2Cl_2$/pet. ether); mp 66.5–67.0°C; $[\alpha]_D^{20}=-87.4°$ (*c* 1.4, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.84 and 0.96 (6H, 2×d, *J*=4.4 and 6.6 Hz, 4′H, 6′-H), 1.70 (3H, s, 5′H), 1.74–2.06 and 2.39 (2H and 1H, m and bd, 1′H, 2′-H), 2.62 (1H, bs, OH), 3.53 (3H, bm, 3′H, 5-H), 4.16 (2H, m, 4-H, 5-H), 7.44 (5H, s, Bz); $^{13}C$ NMR $\delta$ 18.8, 20.2, 24.8, 32.2, 40.6 (C-1′ C-2′, C-4′, C-5′ C-6′ 54.7 (C-4), 69.0, 70.5 (C-5, C-3′), 98.1 (C-2), 126.7, 128.9, 130.2, 138.1, 169.1 (Bz); MS (70 eV): *m/z* (%) 262 (12) $[M-CH_3]^+$, 204 (68) $[M-C_4H_9O]^+$, 162 (9), 140 (6), 105 (100) $[Bz]^+$, 77 (25) $[Ph]^+$; HRMS ($[M-CH_3]^+$; $C_{15}H_{20}NO_3$): calcd 262.1443, found 262.1452. The absolute configuration of compound **21** was obtained by X-ray crystallographic analysis (CCDC 164173).

**4.1.19. (2*R*,4*S*,2′*R*)-3-Benzoyl-2,4-dimethyl-2-(3′-benzyloxy-2′-methylpropyl)oxazolidine 22.** Benzylation of **21**

(0.152 g) under standard conditions[16] afforded the title compound (0.131 g) as a colourless syrup: 65% yield; $[\alpha]_D^{20}=-92.6°$ (*c* 1.1, $CH_2Cl_2$); $^1H$ NMR $\delta$ 0.92 and 1.07 (2×3H, 2 × d, *J*=5.3 and 6.2 Hz, 4′H, 6′-H), 1.74 (3H, s, 5′H), 2.05 (3H, m, 1′-H, 2′-H), 3.23 (1H, m, 3′-H), 3.49 and 3.61 (2×1H, 2×m, 5-H, 3′H), 4.06 (2H, m, 4-H, 5-H), 4.53 (2H, s, C*H*$_2$Ph), 7.35 (10H, m, $CH_2$*Ph*, Bz); $^{13}C$ NMR $\delta$ 18.9, 20.5, 25.1, 30.1, 39.3 (C-1′, C-2′, C-4′, C-5′, C-6′), 54.5 (C-4), 70.1, 73.1, 76.5 (C-5, C-3′, *C*H$_2$Ph), 98.0 (C-2), 126.4, 127.5, 127.8, 128.4, 128.6, 129.7, 138.3, 138.9, 168.3 ($CH_2$*Ph*, Bz); MS (70 eV): *m*/*z* (%) 367 (2) $[M]^+$, 352 (18) $[M-CH_3]^+$, 204 (96) $[M-C_{11}H_{15}O]^+$, 162 (16), 105 (100) $[Bz]^+$, 91 (24) $[C_7H_7]^+$, 77 (21) $[Ph]^+$; HRMS ($C_{23}H_{29}NO_3$): calcd 367.2147, found 367.2145.

**4.1.20. (*S*)-5-Benzyloxy-4-methylpentan-2-one 23.**[17] Removal of d/p group[4] from **18** (0.059 g) afforded the title compound (0.030 g) as a colourless syrup; 91% yield; e.e. 99% (GC); $[\alpha]_D^{20}=-3.2$ (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR data was in agreement with the values published for the corresponding racemate.[17]

**4.1.21. (*R*)-5-benzyloxy-4-methylpentan-2-one 24.**[17] Removal of d/p group[4] from either **20** (0.054 g) or **22** (0.077 g) provided the title compound in 67% (0.020 g, 23% e.e.) and 73% (0.031 g, 99% e.e.) yield, respectively. Experimental data for **24** (99% e.e.): $[\alpha]_D^{20}=+3.1$ (*c* 1.5, $CH_2Cl_2$); $^1H$ NMR (500 MHz) $\delta$ 0.96 (3H, d, *J*=6.8 Hz, 6-H), 2.13 (3H, s, 1-H), 2.27 (1H, dd, *J*=7.9 and 16.2 Hz, 3-H), 2.37 (1H, m, 4-H), 2.62 (1H, dd, *J*=5.8 and 16.2 Hz, 3-H), 3.27 (1H, dd, *J*=7.1 and 9.4 Hz, 5-$H_a$) 3.37 (1H, dd, *J*=5.2 and 7.1 Hz, 5-$H_b$), 4.49 (2H, s, 7-H), 7.33 (5H, m, Ph); $^{13}C$ NMR $\delta$ 17.2 (C-6), 30.0 (C-4), 30.5 (C-1), 48.1 (C-3), 73.1 (C-7), 75.1 (C-5), 127.7, 128.5, 138.6 (Ph), 208.8 (C-2); MS (70 eV): *m*/*z* (%) 206 (1) $[M]^+$, 164 (18) $[M-C_2H_2O]^+$, 148 (8), 115(10), 107 (22) $[C_7H_7O]^+$, 99 (16), 91 (100) $[C_7H_7]^+$, 43 (13); HRMS ($C_{13}H_{18}O_2$): calcd 206.1307, found 206.1282.

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7. This structure determination showed that the *N*-phenylurethane derivatives **25a** and **25b** of diastereomers **10a** and **10b** enter a single crystal lattice of monoclinic symmetry, space group *P*21, with two independent molecules in the asymmetric unit. In context with the pseudo-enantiomeric nature of the two diastereomers **25a** and **25b**, they are able to mimic, in the crystalline state, a lattice with pseudo-inversions and pseudo-symmetry *P*21/*n* thus forming a crystalline pseudo-racemate.
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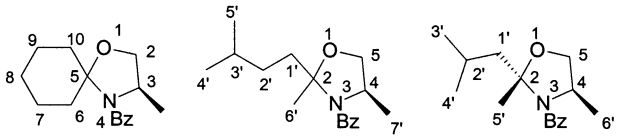
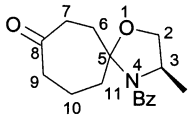
13. The numbering of the cyclic and acyclic derivatives is depicted below for substrates **5**, **11** and **15**:

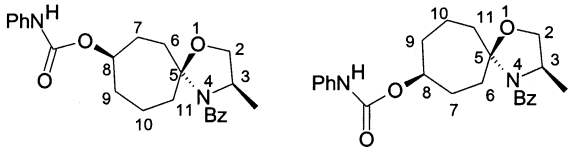


**5** **11** **15**

14. The structures of the ketone by-product as well as of derivatives **25a** and **25b** are shown below:



ketone by-product



**25a** and **25b**

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