Enantioselective Synthesis of (7*R*,8*R*,8a*R*)- and (7*S*,8*S*,8a*S*)-7-Hydroxy-8-indolizidinemethanol by 1,3-Dipolar Cycloaddition of 1-Pyrroline *N*-Oxide to Chiral Pentenoates

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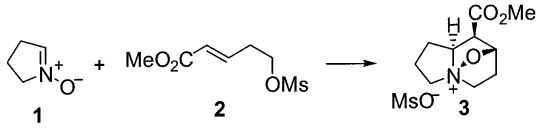
The 1,3-dipolar cycloadditions of pyrroline *N*-oxide (**1**) with (1*R*,2*S*)-*trans*-2-phenylcyclohexyl- and with (1*R*,2*S*,5*R*)-8-phenylmenthyl-pent-2-enoates (**9** and **10**) proceed with opposite diastereoselectivities. The two enantiomers of a new dihydroxyindolizidine, (+)-**6** and (–)-**6**, were synthesized using **4** and **5**, respectively, as the chiral auxiliary.

Introduction

The 1,3-dipolar cycloaddition reaction of nitrones to alkenes has been successfully applied to the synthesis of a wide variety of natural and unnatural target molecules.[1] One of the main outstanding features of this type of concerted process is its ability to generate up to three new, adjacent stereogenic centres in a stereospecific manner. Moreover, the isoxazolidine cycloadducts can be further elaborated to provide polyfunctionalized cyclic or acyclic chiral compounds with complete control of the relative stereochemistry.

Nitrones add to (*E*)-β-monosubstituted α,β-unsaturated esters (e.g. methylcrotonate) in a regioselective manner, affording almost exclusively isoxazolidines substituted with the ester group at C-4. Despite the abundant literature available on the subject[2,3] and the numerous studies of asymmetric induction in cycloadditions to optically pure acrylates,[4] the behaviour of nitrones towards chiral (*E*)-β-monosubstituted α,β-unsaturated esters or amides has received little attention.[4c–4d,5–7]

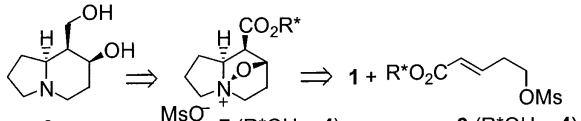


Scheme 1

Recently we have comprehensively revisited the 1,3-dipolar cycloaddition of the cyclic nitrone **1** with methyl (*E*)-5-[(methanesulfonyl)oxy]-2-pentenoate **2** (Scheme 1).[3] In connection with our project dealing with the synthesis of new enantiopure hydroxyindolizidines,[8] we carried out a study of the control of absolute stereochemistry in cycloadditions to chiral pentenoates for the synthesis of optically pure cycloadducts such as **3**. As a source of asymmetric induction, we chose two commercially available chiral auxiliaries: (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol[9] (**4**) and (–)-(1*R*,2*S*,5*R*)-8-phenylmenthol[10] (**5**), in view of their successful employment in asymmetric synthesis.[11]

4 **5**

In this paper we present the results of our study into the 1,3-dipolar cycloaddition reaction of 3,4-dihydro-2*H*-pyrrole 1-oxide (**1**) with the chiral pentenoates **9** and **10**, along with the transformation of the cycloadducts **7** and **8** into the new optically pure dihydroxyindolizidines **(+)-6** and **(–)-6** (Scheme 2).



6 **7** (R*OH = **4**) **8** (R*OH = **5**) **9** (R*OH = **4**) **10** (R*OH = **5**)

Scheme 2

Results and Discussion

The required chiral dipolarophiles **9** and **10** were prepared in good yields by condensation of the aldehyde **11**[12] either with the ylide generated in situ from the triphenylphosphonium bromide **12**, or with dimethylphosphonoacetate **13**, respectively (Scheme 3). The THP (tetrahydropyranyl) protecting group was replaced by the Ms (methanesulfonyl) group by treatment with Amberlyst®15 in methanol, followed by mesylation (Scheme 3).

Reaction of **9** with **1** in toluene at room temperature gave the two diastereomeric salts **7a** and **7b** (Scheme 4). Hydrogenation of this mixture with Pd/C catalyst afforded the indolizidines **18a** and **18b** in 2.3:1 ratio (39% *de*), with an overall yield of 60% relative to **9** (Scheme 4).

The cycloaddition of **10** and **1** gave a white precipitate (30% yield) that was found to be the salt **8b** in analytically pure form. This was quantitatively transformed into indolizidinol **19b** by hydrogenation (Scheme 4). Similar treatment

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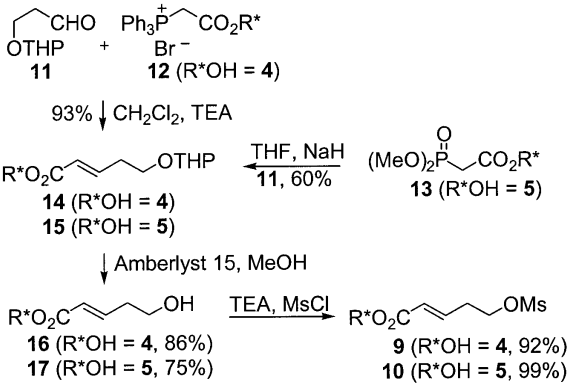
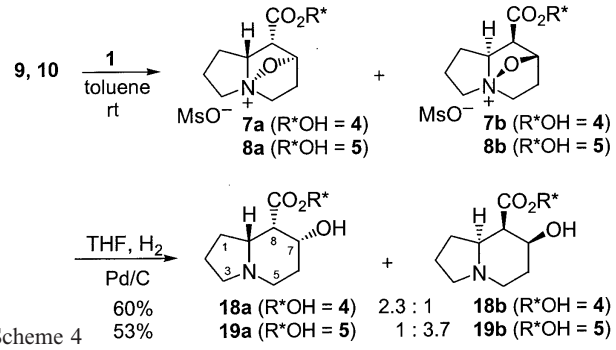


Scheme 3

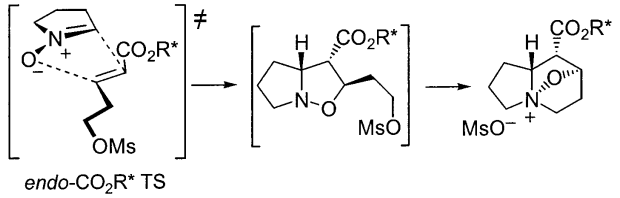


Scheme 4

of the mother liquor gave, after purification, the two indolizidines **19a** and **19b** in an overall molar ratio of 1:3.7 (57% *de*) and 53% yield relative to **10** (Scheme 4).

Only the salt **8b** could be completely analyzed by spectroscopic means. Its ^{1}H NMR spectrum was in agreement with the presence of a positive charge on the nitrogen, inducing a deshielding effect on the 8a-H and 7-H protons ($\delta_{8a\text{-}H}$ = 4.92 and $\delta_{7\text{-}H}$ = 5.17), in analogy with the data previously found for the methyl ester **3** (R = Me).[3] The relative configurations of the indolizidine moieties of **7a** and **b**, and **8a** and **b** were derived directly from those of the corresponding hydrogenated compounds **18a** and **b**, and **19a** and **b**, respectively. The indolizidine structures were assigned on the basis of the spectroscopic data and later confirmed by an X-ray analysis. The significant correlation between the IR and NMR spectra of **18a** and **b**, and **19a** and **b** with those of the hydrogenation product of **3**[3] suggested a correspondence of the relative stereochemistry of the three stereogenic centres on the indolizidine system. Particularly, the shape of the signal due to the resonance of 7-H in the ^{1}H NMR spectra of **18a**, **19a**, and **19b** (δ = 3.61, dt, J = 10.2; 5.1 Hz, δ = 3.49, br s, half-height width 21 Hz and δ = 3.61, br s, half-height width 22 Hz, respectively) was consistent with the assigned stereochemistry. Moreover, the presence of Bohlmann bands[13] in the IR spectrum of **18a**, **18b**, and **19b** (2795, 2736 cm^{-1}, 2795, 2740 cm^{-1} and 2790, 2736 cm^{-1}, respectively) showed that the ring systems were *trans*-fused.

The observed stereochemistry of the indolizidine moieties attested that the diastereoisomers **7a** and **b**, and **8a** and **b** had originated from an *endo*-CO_2R* approach of the two reagents **1** and either **9** or **10** in the cycloaddition reaction (Scheme 5).



Scheme 5

The absolute stereochemistry of the indolizidine moiety in the major product **18a**, deriving from (1*R*,2*S*)-2-phenylcyclohexanol (**4**), was assigned as (7*R*,8*S*,8a*R*) by X-ray analysis of a crystal obtained by slow evaporation of a CH_3CN solution of **18a** (Figure 1).

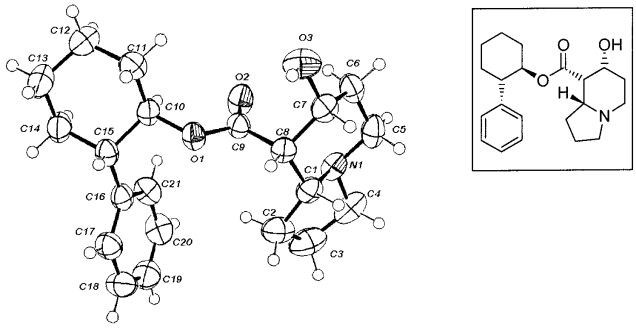
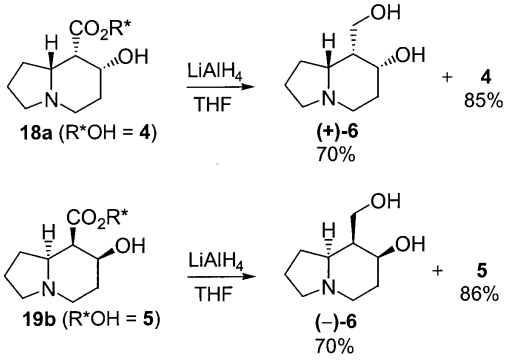


Figure 1. ORTEP drawing from the X-ray crystal structure of diastereoisomer **18a**

The assignment of absolute stereochemistry to the compounds **19a** and **19b** deriving from **5** could be assessed indirectly by further transformation of the esters **18** and **19**.

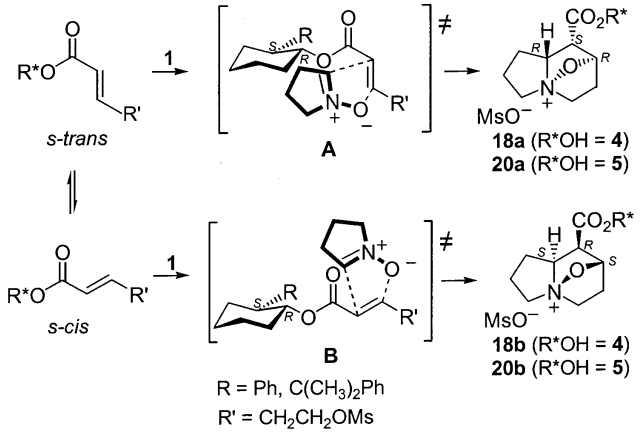
The two main products **18a** and **19b** were reduced with $LiAlH_4$ to dihydroxyindolizidine **6**. Unexpectedly, the two enantiomers **(+)-6** ($[\alpha]_D^{24}$ = +30.4) and **(−)-6** ($[\alpha]_D^{24}$ = −30.1) were obtained from **18a** and **19b**, respectively (Scheme 7), showing that the absolute configurations of the indolizidine moieties in the main cycloadducts **7a** and **8b** were opposite (Scheme 6). In both cases, the chiral auxiliaries **4** and **5** were recovered in good yield (Scheme 6).



Scheme 6

The observed stereochemical outcome of **18a** was consistent with a preferential attack of the nitrone **1** at the less sterically hindered π-face (2*Si*,3*Re* face) of the *s-trans* conformer[14] of **9** (**A**, Scheme 7). The moderate stereocontrol

(39% *de*) induced by *trans*-2-phenylcyclohexanol **4** can be ascribed to the "widening V" relative arrangement[15] of the phenyl and the enoate moieties, and to the occurrence of addition also on the *s-cis* conformer, having the opposite face (2*Re*,3*Si*) as the more accessible one (Scheme 7).



Scheme 7

The higher degree of diastereoselectivity (57% *de*) shown by 8-phenylmenthol **5**, (compared to **4**) is in agreement with other examples of uncatalyzed cycloaddition reactions of 8-phenylmenthol derivatives.[16] The efficiency of phenylmenthol has been ascribed to the prevalence of the stacked conformation in the corresponding crotonate.[11] Actually, the olefinic proton resonances in the pentenoate **10** proved to be very close to those in 8-phenylmenthol crotonate[11b] (δ = 6.33 and 5.32 and δ = 6.44 and 5.32, respectively) and shifted upfield compared to those in **9** (δ = 6.65 and 5.70), suggesting the presence of **10** in the stacked geometry. The opposite senses of diastereoselectivity showed by the two chiral auxiliaries **4** and **5** cannot easily be rationalised. In general, the two chiral auxiliaries afford the same absolute stereochemistry of products in the reaction studied.[11] However, at least one other example of this dichotomy has been reported, in a nucleophilic addition reaction to glyoxylate esters.[11a]

Assuming a high degree of π-face shielding in the cycloaddition of **1** and **10**, the experimental results proved that the preferred conformation of the pentenoate **10** in the transition state is *s-cis* (**B**, Scheme 7) and suggested that the moderate diastereoselectivity was determined by a low-level rotamer control.

Conclusion

We have proved that the 1,3-dipolar cycloadditions between the nitrone **1** and the pent-2-enoates **9** and **10** occur with a moderate degree of diastereoselectivity; higher when the chiral auxiliary is (−)-(1*R*,2*S*,5*R*)-8-phenylmenthol (**5**) than when it is (−)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol (**4**). The observation that the two chiral auxiliaries act in a complementary fashion is remarkable. The diastereoselectivity observed in the cycloaddition is much lower than the induction showed by the same auxiliaries in other types of reaction,[11] but is interesting in the context of the few data reported for chiral crotonates in nitrone cycloadditions. In fact, Murahashi et al.[5b] reported a lower diastereoselectivity in the 1,3-dipolar cycloaddition between cyclic nitrones and chiral crotonates in the absence of Lewis acid, while the introduction of greater than stoichiometric amounts of ZnI_2 increased the diastereoselectivity, but reduced the reaction yields. Finally, very fair diastereoselectivity and yield were recently obtained in metal-catalyzed cycloadditions of crotonyloxazolidinones,[5d,5e,17] but only acyclic and *C*,*N*-aromatic nitrones were investigated and therefore the data are less readily comparable.

The two diastereoisomer pairs **18** and **19** obtained by reduction of the primary cycloadducts **7** and **8**, respectively, are easily separated by column chromatography; therefore our strategy represents a convenient access to both enantiomeric new dihydroxyindolizidines (+)-**6** and (−)-**6** in optically pure form.

Experimental Section

General Remarks: All reactions that required dry conditions were performed under a nitrogen atmosphere using anhydrous solvents. − Melting points (mp) are uncorrected. − R_f values refer to TLC on 0.25 mm silica gel plates (Merck F254) using the same eluent used for the chromatographic separation of the compound unless otherwise stated. − ^{1}H and ^{13}C NMR spectra (in $CDCl_3$, unless otherwise stated) were recorded on a Varian Gemini (^{1}H 200 MHz) or Bruker DRX 500 (^{1}H 500 MHz). Chemical shifts are given in ppm. Notation s, d, t, q, m, and br indicate singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively. − IR spectra (in $CDCl_3$, unless otherwise stated) were recorded with a Perkin−Elmer 881 spectrophotometer. − Mass spectra (MS) were recorded on 5792A Hewlett-Packard and QMD 1000 Carlo Erba instruments. − Microanalyses were measured with a Perkin−Elmer 240 C instrument.

(1*R*,2*S*)-*trans*-2-Phenyl-1-cyclohexyl (*E*)-5-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2-pentenoate (14): Triethylamine (TEA, 6.8 mmol, 691 mg) was added to a solution of **12** ($[\alpha]_D^{20}$ = +6.8 (*c* = 1.25, $CHCl_3$), 5.7 mmol, 3.20 g) in CH_2Cl_2 (10 mL). The solution was stirred at room temp. for 2.5 h and then a solution of **11** (11.4 mmol, 1.80 g) in CH_2Cl_2 (5 mL) was added. The mixture was heated at reflux temperature for 3 h, kept at room temp. for 60 h, filtered through a short pad of Celite and concentrated to obtain a yellow oil (2.5 g). The crude oil was purified by column chromatography on silica gel (eluent $CHCl_3$/MeOH, 50:1) to obtain **14** (1.90 g, 93%) as an inseparable mixture of the two diastereoisomers.

Compound 14: R_f = 0.64. − ^{1}H NMR (diastereomeric mixture): δ = 7.30−7.16 (m, 5 H), 6.75 (dt, *J* = 15.5; 7.6 Hz, 1 H), 5.65 (d, 15.5 Hz, 1 H), 5.15−4.95 (m, 1 H), 4.55 (br s, 1 H), 3.82−3.65 (m, 2 H), 3.50−3.38 (m, 2 H), 2.80−2.60 (m, 1 H), 2.42−2.30 (m, 2 H), 2.20−1.25 (m, 14 H). − ^{13}C NMR (major diastereoisomer): δ = 165.6 s, 145.1 d, 143.1 s, 128.2 d (2 C), 127.4 d (2 C), 126.2 d, 122.9 d, 98.6 d, 75.7 d, 65.4 t, 62.9 t, 49.6 d, 34.0 t, 32.4 t, 32.3 t, 30.5 t, 25.8 t, 25.4 t, 24.7 t, 19.4 t. − MS *m*/*z* (rel intensity): 244 (4), 158 (100), 129 (15), 99 (18), 91 (41), 85 (88). − IR: $\tilde{\nu}$ [cm^{-1}] = 3031, 2939, 1708, 1656, 1601, 1280, 1176.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (*E*)-5-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2-pentenoate (15): A solution of **13** ($[\alpha]_D^{23}$ = +9.6 (*c* = 1.1,

MeOH), 3 mmol, 1.160 g) in THF (10 mL) was added dropwise to NaH (3.45 mmol, 78 mg) at 0 °C. The mixture was stirred at room temp. for 1 h, then cooled at 0 °C, and a solution of **11** (545 mg, 3.45 mmol) in THF (3 mL) was added dropwise. The mixture was kept at room temp. for 15 h, warmed at 40 °C for 3 h and then diluted with diethyl ether and washed with H_2O. The aqueous phase was extracted 3 times with diethyl ether and the combined extracts were washed with sat. aq. $NaHCO_3$, dried with Na_2SO_4, and concentrated under reduced pressure. The crude yellow oil (1.5 g) was purified by column chromatography (eluent: petroleum ether/AcOEt 6:1) to obtain **15** (726 mg, 60%) as an inseparable mixture of the two diastereoisomers, in addition to some unchanged **13** (200 mg).

Compound 15: R_f = 0.47. − ^{1}H NMR (diastereomeric mixture): δ = 7.30−7.20 (m, 4 H), 7.18−7.05 (m, 1 H), 6.53 (m, 1 H), 5.23 (m, 2 H), 4.82 (m, 1 H), 4.58 (m, 1 H), 3.86−3.72 (m, 2 H), 3.58−3.38 (m, 2 H), 2.38 (m, 2 H), 2.10−1.65 (m, 4 H), 1.62−1.38 (m, 6 H), 1.36−1.18 (m, 1 H), 1.31 (s, 3 H), 1.21 (s, 3 H), 1.15−0.80 (m, 5 H).

(1*R*,2*S*)-*trans*-2-Phenyl-1-cyclohexyl (*E*)-5-Hydroxy-2-pentenoate (16): A solution of the diastereomeric mixture of **14** (5.3 mmol, 1.90 g) in MeOH (10 mL) was warmed to 40 °C for 6.5 h in the presence of Amberlyst® 15 (160 mg). The mixture was filtered through a short pad of Celite, concentrated under reduced pressure, and the crude product was purified by column chromatography (eluent: $CHCl_3$/MeOH 50:1) to obtain **16** (1.27 g, 86%) in analytically pure form.

Compound 16: R_f = 0.2. − ^{1}H NMR: δ = 7.31−7.11 (m, 5 H), 6.70 (dt, *J* = 15.7; 7.1 Hz, 1 H), 5.68 (dt, *J* = 15.6; 1.5, 1 H), 5.03 (dt, *J* = 4.8; 10.6 Hz, 1 H), 3.72−3.60 (m, 2 H), 2.71 (dt, *J* = 3.7; 11.7 Hz 1 H), 2.35 (dq, *J* = 1.5; 6.5 Hz, 2 H) 2.23−2.10 (m, 1 H), 2.02−1.26 (m, 8 H). − ^{13}C NMR: δ = 165.6 s, 144.6 d, 143.2 s, 128.2 d (2 C), 127.5 d (2 C), 126.3 d, 123.7 d, 75.9 d, 60.9 t, 49.7 d, 35.3 t, 34.0 t, 32.3 t, 25.8 t, 24.7 t. MS *m*/*z* (rel intensity): 177 (3), 158 (88), 143 (10), 130 (14), 117 (7), 99 (27), 91 (56), 81 (100). − IR: ṽ [cm^{-1}] = 3626, 3033, 2939, 1707, 1654, 1448, 1272, 1190, 1021. − $[\alpha]_D^{26}$ = −55.6 (*c* = 1.36, MeOH). − $C_{17}H_{22}O_3$ (274.4): calcd. C 74.42, H 8.08; found C 74.61, H 8.09.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (*E*)-5-Hydroxy-2-pentenoate (17): Following the procedure described above, the diastereomeric mixture of **15** (1.65 mmol, 685 mg) gave **17**[18] (400 mg, 75%).

Compound 17: ^{1}H NMR: δ = 7.29−7.20 (m, 4 H), 7.15−7.06 (m, 1 H), 6.44 (dt, *J* = 15.6; 7.0 Hz, 1 H), 5.37−5.28 (m, 1 H). 4.48 (td, *J* = 10.8; 4.4 Hz, 1 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 2.38−2.26 (m, 2 H). 2.12−1.99 (m, 1 H), 1.96−1.84 (m, 1 H), 1.78−1.59 (m, 3 H), 1.52−1.40 (m, 1 H), 1.30 (s, 3 H), 1.29−1.20 (m, 1 H), 1.20 (s, 3 H), 1.18−0.92 (m, 2 H), 0.86 (d, *J* = 6.6 Hz, 3 H). − ^{13}C NMR: δ = 165.3 s, 151.8 s, 144.1 d, 127.9 d (2 C), 125.4 d (2 C), 124.7 d, 124.0 d, 74.2 d, 60.8 t, 50.4 d, 41.7 t, 39.6 s, 35.3 t, 34.6 t, 31.3 d, 28.2 q, 26.5 t, 24.6 q, 21.8 q. − MS; *m*/*z* (rel. intensity): 330 [M$^+$] (1), 214 (21), 211 (11), 199 (5), 119 (98), 118 (100), 99 (64), 91 (88). − $[\alpha]_D^{23}$ = −6.4 (*c* = 0.96, MeOH). − $C_{21}H_{30}O_3$ (330.5): calcd. C 76.33, H 9.15; found C 76.44, H 9.50.

(1*R*,2*S*)-*trans*-2-Phenyl-1-cyclohexyl (*E*)-5-[(Methylsulfonyl)oxy]-2-pentenoate (9): MsCl (82 mg, 0.71 mmol) was added dropwise to a solution of **16** (150 mg, 0.55 mmol) and TEA (71 mg 0.71 mmol) in CH_2Cl_2 (3 mL), with cooling in an ice/water bath. The mixture was allowed to stand at room temp. for 1.5 h and then treated with ice. The separated organic phase was washed sequentially with 1 M HCl, sat. aq. $NaHCO_3$ and H_2O, and dried with Na_2SO_4. The solvent was removed under reduced pressure to give **9** (184 mg, 96%), which was used in the next step without further purification.

Compound 9: ^{1}H NMR: δ = 7.79−7.13 (m, 5 H), 6.65 (dt, *J* = 15.7; 7.0 Hz, 1 H), 5.70 (dt, *J* = 15.7; 1.5 Hz, 1 H), 5.04 (dt, *J* = 4.7; 10.3 Hz, 1 H), 4.24 (t, *J* = 6.4 Hz, 2 H), 2.93 (s, 3 H), 2.71 (dt, *J* = 3.4; 11.2 Hz, 1 H); 2.54 (dq, *J* = 1.5; 6.6 Hz, 2 H), 2.21−216 (m, 1 H), 2.05−1.22 (m, 7 H). − ^{13}C NMR: δ = 165.0 s, 143.1 s, 141.5 d, 128.2 d (2 C), 127.4 d (2 C), 126.3 d, 124.7 d, 76.1 d, 67.2 t, 49.6 d, 37.5 q, 34.0 t, 32.3 t, 31.6 t, 25.8 t, 24.7 t. − MS *m*/*z* (rel intensity): 176 (67), 158 (11), 143 (15), 130 (56), 117 (30), 104 (40), 91 (100), 77 (20). − IR: ṽ [cm^{-1}] = 2940, 2865, 1711, 1449, 1358, 1174.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (*E*)-5-[(Methylsulfonyl)oxy]-2-pentenoate (10): Following the procedure described above, the alcohol **17** (340 mg, 1.0 mmol) gave **10** (415 mg, 99%) as an oil, which was used in the next step without further purification.

Compound 10: ^{1}H NMR: δ = 7.26−7.10 (m, 4 H), 7.16−7.11 (m, 1 H), 6.33 (dt, *J* = 15.9; 6.8 Hz, 1 H), 5.32 (dt, *J* = 15.9, 1.4 Hz, 1 H), 4.84 (dt, *J* = 4.2; 10.7 Hz, 1 H), 4.24 (t, *J* = 6.6 Hz, 2 H), 3.01 (s, 3 H), 2.50 (qd, *J* = 1.4; 6.6 Hz, 2 H), 2.14−2.01 (m, 1 H), 1.96−0.90 (m, 7 H), 1.29 (s, 3 H), 1.20 (s, 3 H), 0.87 (d, *J* = 6.2 Hz, 3 H). − ^{13}C NMR: δ = 164.9 s, 151.8 s, 141.0 d, 128.0 d (2 C), 125.4 d (2 C), 124.8 d, 124.7 d, 74.4 d, 67.1 t, 50.4 d, 41.6 t, 39.6 s, 37.6 q, 34.6 t, 31.6 t, 31.2 q, 28.3 q, 26.5 t, 24.5 d, 21.8 q. − MS *m*/*z* (rel intensity): 243 (2), 214 (6), 177 (4), 158 (23), 119 (100), 91 (37). − IR: ṽ [cm^{-1}] = 2927, 1704, 1651, 1517, 1448, 1357, 1173.

(7*R*,8*S*,8a*R*)-7-Hydroxy-8-[(1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexyloxycarbonyl]octahydroindolizine (18a)[19] **and (7*S*,8*R*,8a*S*)-7-Hydroxy-8-[(1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexyloxycarbonyl]-octahydroindolizine (18b):** A solution of **1** (391 mg, 4.6 mmol) in toluene (11 mL) was added dropwise to **9** (810 mg, 2.3 mmol), with cooling in an ice/water bath. The reaction mixture was stirred at 0 °C for 1 h and then at room temp. for 4 days. The solvent was removed under reduced pressure to give a dark viscous oil. The crude mixture was diluted with THF (10 mL) and hydrogenated over 10% Pd-C (49 mg, 46 μmol) at atmospheric pressure for 3 days. The catalyst was removed by filtration through a short pad of Celite. The filtrate was concentrated, diluted with CH_2Cl_2, treated with Amberlyst® A26 for 5 min and filtered through a short pad of Celite. The concentrated crude mixture of the two diastereoisomers **18a** and **18b** in 2.3:1 ratio was purified by column chromatography on silica gel (eluent: initially CH_2Cl_2/MeOH, 15:1, then the polarity was gradually increased) to afford analytically pure **18a** (213 mg) and **18b** (93 mg) with a total yield of 60% relative to the mesylate **9**.

Compound 18a: R_f = 0.20 (CH_2Cl_2/MeOH 5:1). m.p. 168 °C (benzene). − ^{1}H NMR: δ = 7.30−7.16 (m, 5 H), 5.07 (dt, *J* = 4.2; 10.5 Hz, 1 H), 3.61 (dt, *J* = 10.2; 5.1 Hz,1 H), 2.99 (dt, *J* = 11.3, 4.2 Hz, 1 H), 2.86 (m, 2 H), 2.70 (dt, *J* = 3.5; 11.3 Hz, 1 H), 2.19−0.70 (m, 18 H). − ^{13}C NMR: δ = 171.1 s, 143.4 s, 128.5 d (2 C), 127.5 d (2 C), 126.5 d, 76.7 d, 69.6 d, 63.5 d, 53.7 t, 49.7 d, 49.4 t, 49.0 d, 34.6 t, 32.4 t, 30.7 t, 25.8 t (2 C), 24.6 t, 21.5 t. − MS; *m*/*z* (rel. intensity): 343 [M$^+$] (7), 184 (100), 166 (12), 140 (28), 122 (41), 96 (54), 91 (42). − IR: ṽ [cm^{-1}] = 3562, 2939, 2860, 2795, and 2736 (Bohlmann bands),[13] 1710, 1447, 1326, 1258, 1180. − $C_{21}H_{29}NO_3$ (343.5): calcd. C 73.44, H 8.51, N 4.08; found C 73.00, H 8.30, N 4.30. − $[\alpha]_D^{27}$ = +29.0 (*c* = 0.5, MeOH).

X-ray Structural Analysis: Orthorhombic, space group $P2_12_12_1$, *a* = 5.398(5), *b* = 12.223(5), *c* = 28.801(5) Å, *V* = 1900.0(2) Å^3, *Z* = 4, D_c = 1.200, μ = 0.630 mm^{-1}, *F*(000) = 744. Analysis on a

prismatic transparent single crystal was carried out with a Siemens P4 X-ray diffractometer at room temperature. Graphite-monochromated Cu-*Kα* radiation was used for cell parameter determination and data collection. The intensities of two standard reflections were monitored during data collection to check the stability of the crystal: no loss of intensity was recognized. The integrated intensities, measured using the θ/2θ scan mode, were corrected for Lorentz and polarization effects.[20] The number of reflections collected was 2017 with a $3.07<\theta<55.00$ range; 1829 were independent and the final R index was 0.0404 for reflections having $I > 2\sigma I$, and 0.0423 for all data. The non-hydrogen atoms were refined anisotropically; aromatic and methylene hydrogens were assigned in calculated positions, the others were found by Fourier difference synthesis; all of them were refined as isotropic. This structure was solved by SIR92[21] direct methods and refined using the full-matrix, least-squares method on F^2 provided by SHELXL97.[22]

Compound 18b: R_f = 0.32 (CH_2Cl_2/MeOH, 5:1). m.p. 52−53 °C. − ^{1}H NMR (500 MHz): δ = 7.30−7.18 (m, 5 H), 5.12 (dt, J = 4.4; 10.6 Hz, 1 H), 3.49 (br s, 1 H), 3.03−2.98 (m, 2 H), 2.78 (br s, 1 H), 2.69 (dt, J = 3.3; 11.6 Hz, 1 H), 2.22−0.90 (m, 18 H). − ^{13}C NMR: δ = 170.6 s, 142.9 s, 128.4 d (2 C), 127.6 d (2 C), 126.6 d, 76.0 d, 10.0 d, 63.9 d, 53.9 t, 50.0 d, 49.6 t, 48.4 d, 34.0 t, 32.6 t, 30.6 t, 26.6 t, 25.7 t, 24.7 t, 21.7 t. − MS; *m*/*z* (rel. intensity): 343 [M$^+$] (3), 184 (100), 166 (9), 140 (13), 122 (28), 96 (25), 91 (19). − IR: ṽ [cm^{-1}] = 3562, 2930, 2857, 2795 and 2740 (Bohlmann bands), 1708, 1359, 1221. − $C_{21}H_{29}NO_3$ (343.5): calcd. C 73.44, H 8.51, N 4.08; found C 73.09, H 8.75, N 4.11. − $[\alpha]_D^{26}$ = −39.1 (c = 0.3, MeOH).

(7*R*,8*R*,8a*R*)-7-Hydroxyindolizidin-8-ylmethanol [(+)-6]: A suspension of $LiAlH_4$ (7.6 mg, 0.20 mmol) in THF (3 mL) was cooled in an ice/water bath and treated dropwise with a solution of **18a** (34 mg, 0.10 mmol) in THF (3 mL). The mixture was maintained at 40 °C for 4 h, then at room temp. for 14 h and finally cooled to 0 °C and treated sequentially with H_2O (25 μL), 10% aq. NaOH (50 μL), and H_2O (70 μL). The heterogeneous system was vigorously stirred at room temp. overnight, filtered through a short pad of Celite, concentrated and purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH/conc. NH_4OH, 75: 24.5: 5) to afford pure **(+)-6** (12 mg, 70%) and the chiral auxiliary **4** (15 mg, 85%).

Compound (+)-6: R_f = 0.12. − ^{1}H NMR (500 MHz, D_2O): δ = 3.92 (dt, J = 10.5; 4.8 Hz, 1 H), 3.84 (A part of an ABX system, J = 10.0; 5.0 Hz, 1 H,), 3.76 (B part of an ABX system; J = 10.0; 5.0 Hz, 1 H,), 3.04 (dt, J = 11.7; 4.3 Hz, 1 H), 2.99−2.95 (m, 1 H), 2.49 (b, 1 H), 2.31−2.16 (m, 2 H), 2.13 (m, 1 H), 1.88−1.73 (m, 5 H), 1.67−1.56 (m, 1 H). − ^{13}C NMR (CD_3OD): δ = 73.3 d, 67.0 d, 59.0 t, 54.7 t, 51.3 t, 44.4 d, 31.8 t, 26.8 t, 22.8 t. − MS; *m*/*z* (rel. intensity): 171 [M$^+$] (15), 170 (15), 154 (35), 140 (15), 122 (34), 112 (30), 96 (100), 84 (94), 83 (79). − $[\alpha]_D^{24}$ = +30.4 (c = 1.0, MeOH). − $C_9H_{17}NO_2$ (171.2): calcd. C 63.13, H 10.01, N 8.18; found C 62.86, H 10.04, N 8.33.

(7*S*,8*S*,8a*R*)-4,7-Epoxy-8-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl]octahydroindolizinium Methanesulfonate (8a) and (7*R*,8*R*,8a*S*)-8-[(1*R*,2*S*,5*R*)-4,7-Epoxy-8-phenylmenthyloxycarbonyl]octahydroindolizinium Methanesulfonate (8b): A solution of **1** (170 mg, 2 mmol) in toluene (5 mL) was cooled in an ice/water bath and treated dropwise with a solution of **10** (408 mg, 1 mmol) in toluene (7 mL). The mixture was then stirred at room temp. for 15 days. The precipitate was filtered, washed with light petroleum ether and dried to give analytically pure **8b** (144 mg, 30%) as a white powder. A mixture of **8a** and **8b** (318 mg) of lower purity, was obtained from the mother liquor.

Compound 8b: ^{1}H NMR: δ = 7.35−7.20 (m, 4 H), 7.10−7.05 (m, 1 H), 5.20−5.05 (m, 1 H), 5.17 (d, J = 4.0 Hz, 1 H), 5.00−4.85 (m, 2 H), 4.75−4.58 (m, 1 H), 3.85−3.70 (m, 1 H), 3.63−3.45 (m, 1 H), 2.77 (m, 3 H), 2.70−1.95 (m, 5 H), 1.93−0.90 (m, 10 H), 1.28 (s, 3 H), 1.20 (s, 3 H), 0.86 (d, J = 6.3 Hz, 3 H). − ^{13}C NMR: δ = 166.7 s, 152.0 s, 128.0 d (2 C); 125.6 d (2 C), 125.0 d, 83.7 d, 79.1 d, 75.1 d, 59.8 t, 57.7 t, 52.1 d, 49.9 d, 41.6 t, 39.4 q, 39.3 s, 34.1 t, 31.4 q, 31.3 q, 29.8 t, 26.9 t, 25.9 t, 24.6 t, 21.8 d, 20.9 q. − $C_{26}H_{39}NO_6S$ (493.7): calcd. C 63.26, H 7.96, N 2.84; found C 63.09, H 8.05, N 2.85.

(7*R*,8*S*,8a*R*)-7-Hydroxy-8-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl]octahydroindolizine (19a) and (7*S*,8*R*,8a*S*)-7-Hydroxy-8-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl]octahydroindolizine (19b): Salt **8b** (120 mg, 0.24 mmol) in THF (4 mL) was hydrogenated over 10% Pd-C (5.2 mg) at atmospheric pressure overnight. The catalyst was removed by filtration on a short pad of Celite, and the filtrate was concentrated, diluted with CH_2Cl_2 and treated with Amberlyst® A26 for 15 min. The mixture was filtered through a short pad of Celite, dried with Na_2SO_4, filtered and concentrated to give analytically pure **19b** as a white solid (95 mg, 99%).

The crude mixture of **8a** and **8b** (318 mg) was hydrogenated separately to give a mixture of **19a** and **19b** as described above. The resulting crude solid was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH/conc. NH_4OH, 150:10:1) to afford pure **19a** (45 mg) and **19b** (35 mg). Overall, the two diastereoisomers **19a** and **19b** were obtained in 3.7:1 ratio with a total yield of 53% relative to the mesylate **10**.

Compound 19a: R_f = 0.10. − ^{1}H NMR: δ = 7.32−7.20 (m, 4 H), 7.18−7.10 (m, 1 H), 4.89 (dt, J = 4.0; 11.0 Hz, 1 H), 3.49 (br s, half-height width 21 Hz, 1 H), 3.10−2.98 (m, 2 H), 2.52−0.83 (m, 19 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 0.87 (d, J = 6.6 Hz, 3 H).

Compound 19b: R_f = 0.33. m.p. 106−108 °C. − ^{1}H NMR (300 MHz): δ = 7.35−7.21 (m, 4 H), 7.18−7.11 (m, 1 H), 4.83 (dt, J = 4.1; 10.8 Hz, 1 H), 3.61 (br s, half-height width 22 Hz, 1 H), 3.09−2.96 (m, 2 H), 2.64 (br s, 1 H), 2.29−0.80 (m, 18 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 0.88 (d, J = 6.5 Hz, 3 H). − ^{13}C NMR (75 MHz): δ = 171.8 s, 151.6 s, 128.0 d (2 C), 125.5 d (2 C), 125.1 d, 74.9 d, 69.9 d, 64.0 d, 54.2 t, 50.4 d, 50.0 t, 48.1 d, 42.0 t, 39.6 s, 34.6 t, 31.4 q, 30.9 t, 29.7 t, 27.8 q, 26.6 t, 26.4 t, 25.3 d, 21.8 q. − MS; *m*/*z* (rel. intensity): 399 [M$^+$] (4), 184 (100), 166 (9), 152 (6), 140 (6), 122 (15), 97 (24), 84 (36). − IR: ṽ [cm^{-1}] = 3568, 2960, 2790 and 2736 (Bohlmann bands),[13] 1699, 1597, 1492, 1455, 1441, 1371, 1324, 1172, 1084. − $[\alpha]_D^{20}$ = −33.9 (c = 0.92; MeOH), − $C_{25}H_{37}NO_3$ (399.6): calcd. C 75.15, H 9.33, N 3.51; found C 75.09, H, 9.43, N, 3.15.

(7*S*,8*S*,8a*S*)-7-Hydroxyindolizidin-8-ylmethanol ((−)-6): Reduction of **19b** (80 mg, 0.20 mmol) following the procedure described above afforded pure **(−)-6** (24 mg, 70%) and the chiral auxiliary **5** (40 mg, 86%).

Compound (−)-6: $[\alpha]_D^{24}$ = −30.1 (c = 0.87, MeOH). The ^{1}H NMR, ^{13}C NMR, and MS spectra were identical with those recorded for (+)-**6**.

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