

Asymmetric Synthesis of 8-Aminoindolizidine from Chiral 2-Pyrroleimines

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 $Aux^* = (S)-CII(i-Pr)CII_2OII, (S)-CII(Ph)CII_2OII$

1-Allyl-2-pyrroleimines obtained from (S)-valinol and (S)-phenylglycinol underwent highly diastereoselective addition of allylmagnesium chloride, used in excess amounts, to give the corresponding secondary amines with concomitant allyl to (Z)-1-propenyl isomerization of the 1-pyrrole substituent. Transformation of the 2-amino alcohol moiety to an oxazolidinone, or its cleavage and subsequent N-protection, followed by ring-closing metathesis of the two alkene groups gave the unsaturated bicyclic compound. Full hydrogenation of the alkene function and the aromatic rings afforded the indolizidine derivative as a mixture of two or three diastereomers with a ratio which was dependent on the nature of both the N-substituent and the catalyst. The two prevalent diastereomers were isolated, and their configuration was determined by X-ray crystallographic analysis.

Introduction

7-Aminopyrrolizidine $1a^1$ and 8-aminoindolizidine $1b^1$ are relatively unexplored compounds, despite the presence in nature of these motifs and the potential activity of these compounds and their substituted derivatives as glycosidase inhibitors and anti-HIV drugs. 8-Aminoindolizidine 1b has been already prepared from L-proline 3 by a sequence of steps involving the reductive amination of indolizidin-8-one 2b (Scheme 1). This was described in a communication² where the experimental part was absent and the stereochemistry of both the starting material and the final product was not detailed, so we assume that the compound was obtained as a mixture of diastereomers in racemic form. This seems likely in view of the fact that the corresponding pyrrolizidin-7-one 2a, obtained from L-proline, was unstable and was converted to a mixture of optically inactive diastereomers 1b by reductive amination.³ Derivatives of 8-aminoindolizidin-3-one 2b were regarded as constrained analogues of bioactive peptides and substitutes of β -turns, so they were also prepared from L-ornithine by a synthetic sequence involving an intramolecular reductive amination step which, however, occurred with >28% racemisation of the pre-existing

SCHEME 1



stereocenter.⁴ 7-Alkyl-8-aminoindolizidines have been synthesized by intramolecular imino-ene reactions of L-1-(3-alkene-1-yl)prolinal imines, so forming the fused six-membered ring.⁵

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SCHEME 2



Pyrroles have been used as building blocks for the stereoselective synthesis of indolizidines, as the heteroaromatic ring can be hydrogenated to pyrrolidine and the six membered ring was formed by diverse cyclization strategies.⁶ Here, we report the synthesis of 8-aminoindolizidine **1b** by this general strategy, starting from the pyrroleimine 6 and constructing the sixmembered ring by the ring-closing metathesis (RCM) reaction of the crucial intermediate diene 5, so affording the unsaturated bicyclic compound 4. The two unsaturated alkyl substituents in the intermediate 5 can be introduced exploiting either the nucleophilic property of the pyrrolide anion and the electrophilic reactivity of the chiral imine 6. The asymmetric formation of the benzylic stereocenter in 4 is achieved exploiting the asymmetric induction of a chiral auxiliary (imine N-substituent) in 6, whereas in the final hydrogenation step a novel stereocenter is formed at the ring junction carbon.⁷

It should be observed that by this route any of the four possible stereoisomers of compounds 1 can be prepared by the proper choice of the chiral auxiliary and the other structural variances, i.e., the nature of the amino substituent or protective group, and the size of the newly formed ring. As a matter of fact, rings with different sizes can be obtained in the RCM step, depending on the values of "n" and "m" of the unsaturated substituents in the intermediate 5. Particularly, a five membered ring is formed by RCM when n = m = 0, thus leading ultimately to pyrrolizidines 1a, whereas to prepare indolizidines one has to build a six-membered ring in intermediate 2 by choosing n= 1, m = 0, or vice versa. All the routes appear viable at a first glance, as we have previously described the highly diastereoselective addition of various organometallic reagents to chiral 2-pyrrole imines derived from (S)-valinol and (S)-phenylglycinol, having either unprotected or trimethylsilyl-protected OH and NH functions.8

Results and Discussion

We started the investigation by routinely preparing in high yields the 1-allyl-2-pyrroleimines **8a** and **8b** from 1-allyl-2-pyrrolealdehyde by reaction with either (*S*)-valinol and (*S*)-phenylglycinol in dry dichloromethane in the presence of anhydrous magnesium sulfate (Scheme 2). The OH-free imines **8a,b** were then treated with allylmagnesium chloride in excess amounts in anhydrous THF at 0 °C to give the known secondary homoallylic amines **9a,b**.⁸ Unexpectedly, in the first reaction run on the imine **8a**, using only a slight excess of Grignard

TABLE 1.Addition of Allylmagnesium Chloride to the Imines $8a,b^a$

| entry | imine | allylMgCl (equiv) | time (h) | ratio 9/10 | yield (%) of $9 + 10^{b}$ | yield (%) of 10 ^c |
|-------|-------|----------------------|----------|-------------------|---------------------------|-------------------------------------|
| 1 | 8a | 2.5 | 48 | 47:53 | 98 | |
| 2 | 8a | 3 | 24 | 24:76 | 97 | 66 |
| 3 | 8a | 4 | 24 | 0:100 | 98 | 92 |
| 4 | 8b | 4 | 24 | 0:100 | 98 | 96 |

^{*a*} The Grignard reagent was added to the imine (5.9 mmol) dissolved in THF (25 mL) at 0 °C, and the temperature was allowed to reach 20 °C during 24 h. ^{*b*} Yield of crude product. ^{*c*} Yield of isolated, pure product.

reagent (2.2 equiv), a 73:27 mixture of two isomeric amines were obtained, as evidenced by ¹H NMR analysis of the crude product. The major isomer was identified as the expected product **9a** on the basis of the ¹H NMR spectrum, whereas the minor one **10a** was supposed to have an isomerized propenyl substituent on the pyrrole nitrogen. The base-promoted isomerization was attributed to the action of the Grignard reagent in excess amount, hence the reaction was carried out with increased amounts of allylmagnesium chloride in order to optimize the yield of compound **10a**, since it has the required 1,7-octadiene moiety for the construction of a six-membered cycle by the RCM methodology. The results of these studies are reported in Table 1.

The results obtained showed that, by increasing the amount of the Grignard reagent, a corresponding increased conversion of 9a to 10a occurred (entries 2 and 3) and the complete conversion was achieved using four equivalents of allylmagnesium chloride (entry 4). The ¹H NMR spectrum of the crude product, obtained in 98% yield, showed the presence of a single diastereomer, concerning either the newly formed stereocenter and the double bond geometry, which was determined to be Zon the basis of the coupling constant of the vinylic protons. On the other hand, GC-MS and HPLC-MS analyses could not used to determine the purity and diastereomeric ratio, as the product was not eluted or underwent massive decomposition. The pure product 10a was then obtained with 92% yield by chromatography on a SiO₂ column. However, we found that the crude compound could be used without purification in the following step. Under the same conditions, the imine 8b was converted to the homoallylic amine 10b with complete selectivity and excellent yield.

Before performing the RCM step, it was necessary to protect the amino functionality. As acidic conditions are not suitable owing to the presence of the pyrrole ring, we chose to convert the β -amino alcohol moiety of **10a** into the oxazolidinone **11a** by routine reaction with triphosgene (Scheme 3). The RCM step was investigated on this compound, exploring the effectiveness of both first-generation and second-generation Grubbs catalysts (ruthenium benzylidene complexes I and II, respectively).

The results obtained, reported in Table 2, showed that both catalysts can be used for that purpose, although II was more effective and allowed to obtain a complete reaction in less time with respect to I in the same experimental conditions (entries 1 and 2). Moreover, high yields of compound 12a were obtained using catalyst II in toluene at 111 °C for 0.5 h with 5 mol % loading (entry 3) and in dichloromethane at 40 °C for 1.5 h with 2.5 mol % loading (entry 4). Finally, by working with 1 mol % loading of catalyst II, a high yield of the product 12a was obtained in dichloromethane at the reflux temperature for 4 h (entry 5). Under the same conditions, the diene 11b in turn

SCHEME 3



TABLE 2. Ring-Closing Metathesis of Compounds 11a,b^a

| entry | compd | Grubbs cat. (mol %) | solvent | <i>T</i> (°C) | time (h) | 12, yield ^b (%) |
|-------|-------|------------------------|---------------------------------|---------------|-------------|-------------------------------|
| 1 | 11a | I (5) | CH ₂ Cl ₂ | 40 | 4 | 12a , 93 |
| 2 | 11a | II (5) | CH_2Cl_2 | 40 | 1 | 12a , 94 |
| 3 | 11a | II (5) | toluene | 111 | 0.5 | 12a, 95 |
| 4 | 11a | II (2.5) | CH_2Cl_2 | 40 | 1.5 | 12a , 94 |
| 5 | 11a | II (1) | CH_2Cl_2 | 40 | 4 | 12a, 95 |
| 6 | 11b | II (1) | CH_2Cl_2 | 40 | 4 | 12b , 96 |

^a The reactions were carried out on a 2-3 mmol scale. ^b Yield of isolated, pure product.

prepared with high yield from the phenylglycinol derivative 10b was converted to the bicyclic compound 12b with 96% yield (entry 6).

We then directed our efforts to the hydrogenation of the unsaturated bicyclic compounds 12a,b. The selective hydrogenation of the cyclohexene function of 12a,b to give 13a,b was easily achieved by stirring a solution of 12a,b in methanol under 1 atm of H_2 in the presence of 10% Pd/C (Scheme 3). As we were interested to obtain the fully saturated indolizidine derivatives, we checked the palladium, platinum and rhodium heterogeneous catalysts which were previously used for the hydrogenation of substituted pyrrole rings to give the corre-

sponding pyrrolidines.^{5,9} The results we have obtained using 10% Pd/C, 10% Pd(OH)₂/C, PtO₂, and 5% Rh/Al₂O₃ with the compounds 12a,b most frequently using methanol as the solvent are reported in Table 3.

In all cases, the hydrogenation occurred with poor diastereoselectivity. This is consistent with the outcomes of several reports on the hydrogenation of chiral pyrroles bearing stereocenters at the benzylic position. Since one stereocenter is formed under the asymmetric induction of the pre-existing stereocenter, two diastereomers are expected in this reaction, e.g., (S,S)- and (S,R)-14a,b. However, in several reactions mixtures a third diastereomer was observed. Amounts of sufficiently pure diastereomers (S,S)- and (S,R)-14a,b were obtained by chromatographic separation, but assignment of the configuration to each compounds was difficult by ¹H NMR spectroscopy, so that single crystal X-ray structure analysis of all four compounds was carried out for determination of their configuration. The molecular structures of diastereomers (S,R)- and (S,S)-14a,b are reported in the Supporting Information. Suitable crystals were not obtained for the minor diastereomers of 14a,b, and their (R,R)-configuration was assumed on the basis of the following mechanistic considerations. We assumed that after the partial saturation of the pyrrole ring to give the pyrrolines **15a**,**b** an alkene isomerization occurs, particularly using palladium catalysts, leading to the ene-1,2-diamines 16a,b. These intermediates, where the pre-existing stereocenter has been lost, can undergo hydrogen addition to both faces, so giving a mixture of diastereomers (S,S)- and (R,R)-14a,b, assuming the prevalent *syn*-addition of hydrogen to the double bond (Scheme 4).

It is noteworthy that (S,R)-14a was the minor diastereomer when the reaction was performed at 1 atm of H_2 in the presence of 10% Pd/C, even in the presence of acetic acid (Table 3, entries 1 and 2), but it was prevalently obtained when 10% Pd(OH)₂ was used, although with low conversion of 12a (entry 3). Hydrogenation at higher pressure (8 atm of H₂) in the presence of acetic acid gave a mixture of the three diastereomers with quantitative yield but low stereocontrol (entry 4). The Adam's catalyst (PtO₂) proved to be ineffective, as only 10% conversion was observed after 24 h (entry 5).

Rh/Al₂O₃ (1.2–1.4 mol equiv) gave more satisfactory results, and only two diastereomers (S,S)- and (S,R)-14a were quanti-

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TABLE 3. Hydrogenation of Compounds 12a,b^a

| entry | compd | catalyst (wt %; mol %) | H ₂ (atm) | solvent | time (h) | $\operatorname{conv}^{b}(\%)$ | 14a,b $(S,S)/(S,R)/(R,R)^b$ | yield ^c (%) |
|-------|-------|------------------------------------------------|----------------------|--------------------------------|----------|-------------------------------|------------------------------------|------------------------------------------|
| 1 | 12a | 10% Pd/C (20; 4.7) | 1 | MeOH | 24 | 100 | 14a , 43:15:42 | |
| 2 | 12a | 10% Pd/C (20; 4.7) | 1 | MeOH-AcOH (4:1) | 24 | 100 | 14a , 38:15:47 | |
| 3 | 12a | 10% Pd(OH) ₂ /C (20; 3.6) | 1 | MeOH | 24 | 30 | 14a , 16:73:11 | |
| 4 | 12a | 10% Pd(OH) ₂ /C (20; 3.6) | 8 | MeOH-AcOH (4:1) | 24 | 100 | 14a , 24:48:28 | |
| 5 | 12a | PtO ₂ (10; 11) | 1 | MeOH | 24 | 10 | 14a , 14:72:14 | (S,S)- 14a , 5 |
| | | | | | | | | (S,R)- 14a , 49 |
| 6 | 12a | 5% Rh/Al ₂ O ₃ (10; 1.2) | 1 | MeOH | 24 | 100 | 14a , 31:69:0 | (S,S)- 14a , 19 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14a , 57 |
| 7 | 12a | 5% Rh/Al ₂ O ₃ (10; 1.2) | 8 | MeOH | 24 | 100 | 14a , 26:74:0 | (S,S)- 14a , 11 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14a , 63 |
| 8 | 12a | 5% Rh/Al ₂ O ₃ (10; 1.2) | 8 | EtOAc | 24 | 96 | 14a , 40:60:0 | |
| 9 | 12b | 5% Rh/Al ₂ O ₃ (10; 1) | 1 | MeOH/AcOH (4:1) | 24 | 100 | 14b , 31:64:5 | (<i>S</i> , <i>S</i>)- 14b , 24 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14b , 56 |
| 10 | 12b | 5% Rh/Al ₂ O ₃ (10; 1.4) | 8 | MeOH/AcOH (4:1) | 24 | 100 | 14b , 28:69:3 | (<i>S</i> , <i>S</i>)- 14b , 20 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14b , 58 |
| 11 | 12a | 5% Rh/Al ₂ O ₃ (10; 1.2) | 1 | MeOH $-Et_3N$ (4:1) | 72 | 100 | 14a , 22:78 | (S,S)- 14a , 11 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14a , 65 |
| 12 | 12a | 26% Rh/Gr (1.5; 0.9) | 1 | MeOH/Et ₃ N $(4:1)$ | 48 | 100 | 14a , 24:76 | (S,S)- 14a , 11 |
| | | | | | | | | (<i>S</i> , <i>R</i>) -14a , 62 |
| 13 | 12a | 26% Rh/Gr (1.5; 0.9) | 8 | MeOH | 11 | 100 | 14a , 39:61 | (S,S)- 14a , 29 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14a , 48 |
| 14 | 12b | 26% Rh/Gr (1.5; 1.0) | 1 | MeOH | 48 | 100 | 14b , 26:67:7 | (<i>S</i> , <i>S</i>)- 14b , 18 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14b , 53 |
| 15 | 12b | 26% Rh/Gr (1.5; 1.0) | 1 | MeOH/AcOH (4:1) | 24 | 100 | 14b , 29:66:5 | (<i>S</i> , <i>S</i>)- 14b , 19 |
| | | | | | | | | (<i>S</i> , <i>R</i>)- 14b , 50 |

^{*a*} The reactions were carried out on a 2–3 mmol scale. ^{*b*} The conversion degree of compounds **12a**,**b** and the dr of the products **14a**,**b** were determined by GC–MS analysis; the ratio is reported according to the increasing retention times of the diastereomers. ^{*c*} Yield of isolated, pure diastereomers



tatively formed with a moderate prevalence of the latter, especially under 8 atm of H₂ pressure (entries 6 and 7), whereas substitution of methanol by ethyl acetate gave slightly minor conversion and diastereoselectivity (entry 8). A slightly greater ratio ((S,R)/(S,S)-**14a** = 74:26) was obtained in MeOH at a pressure of 8 atm of H₂ (entry 8). The hydrogenation of the

phenylglycinol derivative **12b** with the same rhodium catalyst in methanol under 1 and 8 atm of H₂ pressure gave complex mixtures of products after comparable times, as the hydrogenation of the Ph substituents was incomplete. However, the addition of acetic acid increased the reaction rate, although the formation of a third diastereomer was observed (entries 9 and 10). It was then found that when hydrogenation was carried out with Rh/Al₂O₃ in methanol in the presence of triethylamine only the (*S*,*R*)- and (*S*,*S*)-diastereomers were formed with a slightly better diastereoselectivity, although at the expense of the rate, as the reaction was complete after 72 h (entry 11).

Finally, we checked 24% rhodium on graphite (Rh/Gr) as a novel catalyst for the hydrogenation of the pyrrole as well as arene rings.¹⁰ This catalyst proved to be more effective than previously tested heterogeneous catalysts. As a matter of fact, using a slightly lower catalyst loading (0.9–1.0 molar equiv) the complete reduction of **12a**,**b** occurred in shorter times, other reaction conditions being the same (compare entries 12/11 and 13/7). The reduction of **12b** was positively affected by the presence of acetic acid, although the diastereoselectivity remained low (entries 14 and 15).

We reasoned that the diastereoselectivity of the hydrogenation step could be affected by the amino substituent, so the preparation of differently *N*-substituted derivatives was then addressed. The removal of the chiral auxiliary from the β -aminoalcohols **10a,b** was routinely accomplished by treatment with periodic acid—methylamine system, then the obtained crude primary amines were benzoylated under Schotten—Baumann conditions to obtain the benzamide **17a** from the valinol derivative **10a** and the *N*-Boc amine **17b** from the phenylglycinol derivative **10b** with high overall yields (Scheme 5).

The RCM reactions on these products were then carried out in the optimized reaction conditions to give the unsaturated

⁽¹⁰⁾ The preparation of Rh/Gr and its use in hydrogenation of aromatic ring will be reported in a forthcoming paper.



bicyclic compounds 18a,b, which were finally submitted to hydrogenation using Rh/Al₂O₃ as the catalyst in methanol under 1 atm H₂. In both cases, after complete reduction of the aromatic rings, two diastereomers of the products 19a,b were observed. They were isolated by column chromatography, then GC analyses of both diastereomers on a chiral column showed that the prevalent diastereomers were mixtures of enantiomers, although with high e.e.'s (89 and 91%), whereas the minor diastereomers were enantiomerically pure. The incomplete optical purity of the prevalent diastereomers is certainly due to the alkene isomerization occurring during hydrogenation, similarly to the step described in Scheme 4 (15a,b to 16a,b), the only difference is that an achiral intermediate (enediamine) is formed from 18a,b.

Aiming to determine the relative configuration of the stereocenters in the products, we transformed the oxazolidinone (*S*,*R*)-**14a** into the *N*-Boc derivative (*S*,*R*)-**19b** through a sequence of steps which involves the hydrolytic cleavage of the oxazolidinone ring, oxidative cleavage of the β -amino alcohol and *N*-Boc protection of the free amine. This correlation demonstrated that the hydrogenation of the pyrrole rings in the differently substituted unsaturated bicyclic compounds **12** and **18** occurred with opposite diastereoselectivity, probably owing to a different steric bulkiness and orientation of the functionalized amino substituent of the bicyclic skeleton.

Conclusions

N-Protected 8-aminoindolizidines have been synthesized by an efficient route that involves organometallic allylation of 2-pyrroleimines derived from (*S*)-valinol and (*S*)-phenylglycinol, RCM reaction, and pyrrole ring hydrogenation as the key steps. Further optimization of the effectiveness and stereoselectivity of the hydrogenation step should be in principle accomplished by modifying the nitrogen substituent. Moreover, the configuration and the chiral auxiliary can be changed, and different chiral auxiliaries can be tested as well. Moreover, the unsaturated substituent introduced by the organometallic addition can be varied in length, so that either a five- or a seven-membered ring can be constructed in the RCM step. In conclusion, the auxiliary based methodology starting from 2-pyrrolealdehyde can be effectively used to prepare all the possible stereoisomers of amino-substituted fused bicyclic compounds containing the pyrrolidine nucleus.

Experimental Section

N-Alkylation of Pyrrole- and Indolealdehydes. General Procedure. To a solution of 2-pyrrolecarbaldehyde (2.42 g, 25.4 mmol) in dioxane (40 mL) were added allyl bromide (6.6 mL, 9.22 g, 76.2 mmol) and K_2CO_3 (12.30 g, 89.0 mmol), and the mixture was stirred at the reflux temperature during 8 h. Then the mixture was cooled at room temperature, and cyclohexane (40 mL) was added. The solid was filtered off through a pad of Celite, and the organic phase was concentrated at reduced pressure. Flash column chromatography (SiO₂) eluting with cyclohexane/ethyl acetate 9:1 mixture gave the aldehyde 7^{11} as a red oil: 3.05 g (89%).

Preparation of Imines. General Procedure. To a solution of (*S*)-phenylglycinol (1.50 g, 11.1 mmol) or (*S*)-valinol (1.14 g, 11.1 mmol) in dry CH₂Cl₂ (40 mL) were added anhydrous MgSO₄ (5 g) and the aldehyde 7 (1.5 g, 11.1 mmol), and the mixture was stirred overnight. The solid was filtered off through a pad of Celite, and the organic phase was concentrated at reduced pressure to leave the crude imine **8a** as a red oil, which was used as obtained avoiding purification: 2.39 g (98%). Compound **8b** was similarly obtained as a red oil: 2.73 g (97%).

Organometallic Addition to Imines. Typical Procedure. Allylmagnesium chloride (1.0 M in THF, 23.6 mL, 23.6 mmol) was added to a magnetically stirred solution of the imine 8b (1.50 g, 5.9 mmol) in THF (25 mL) cooled at 0 °C. After 30 min, the reaction mixture was slowly warmed until room temperature was reached, and stirring was continued for 24 h. The mixture was quenched with a saturated aqueous solution of NaHCO₃ (30 mL) at 0 °C, and then the organic material was extracted with diethyl ether (3 \times 20 mL). The collected ethereal layers were dried over Na₂SO₄ and concentrated to leave the crude product. ¹H NMR analysis showed the presence of a single compound. Flash column chromatography (SiO₂) eluting with cyclohexane/ethyl acetate 9:1 mixture gave the product 10b as a yellow oil: 1.69 g, (96%). The compound decomposed during GC-MS and HPLC-MS analyses. Compound 10a was similarly obtained as a yellow oil starting from the imine 8a (1.32 g, 6.0 mmol): 1.45 g (92%).

Preparation of Oxazolidinonones. Typical Procedure. To a solution of the β -amino alcohol **10b** (1.30 g, 4.4 mmol) in CH₂Cl₂ (20 mL) cooled at 0 °C were added a saturated aqueous solution of NaHCO₃ (10 mL) and triphosgene (0.65 g, 2.2 mmol) dissolved in CH₂Cl₂ (5 mL), and the mixture was stirred overnight. The mixture was extracted with CH₂Cl₂ (3 × 20 mL). The collected organic layers were dried over Na₂SO₄ and concentrated to leave the crude product. Flash column chromatography (SiO₂) eluting with cyclohexane/ethyl acetate (8:2) mixtures gave the product **11b** as a yellowish oil: 1.29 g, 4 mmol, 91%. Compound **11a** was similarly obtained as a white solid from **10a** (0.79 g, 3.0 mmol): 0.785 g (93%).

^{(11) (}a) Settambolo, R.; Savi, S.; Caiazzo, A.; Lazzaroni, R. J. Organomet. Chem. 2001, 619, 241–244. (b) Broggini, G.; La Rosa, C.; Pilati, T.; Terraneo, A.; Zecchi, G. Tetrahedron 2001, 57, 8323–8332.

Cleavage of the Chiral Auxiliary and N-Benzoylation of the Secondary Amines. General Procedure. The valinol derivative 10a (0.445 g, 1.7 mmol) was dissolved in MeOH (5 mL), and then a 40% solution of MeNH₂ in H₂O (4.0 mL, 5.2 mmol) and successively a solution of H_5IO_6 (1.40 g, 6.0 mmol) in H_2O (5 mL) were added dropwise. The mixture was stirred for 2 h at room temperature, and the organic materials were extracted with Et₂O $(3 \times 20 \text{ mL})$. The collected ethereal layers were washed with brine, dried over Na₂SO₄, and concentrated to leave the primary amine as a yellow oil. This was dissolved in acetone (5 mL), and then H₂O (5 mL), K₂CO₃ (0.47 g, 3.4 mmol), and benzoyl chloride (300 μ L, 2.6 mmol) were added with magnetic stirring. After 12 h, most of the solvent was evaporated at reduced pressure and the organic materials were extracted with Et₂O (3 \times 20 mL). The collected ethereal layers were dried over Na2SO4 and concentrated to leave a white solid, which was crystallized from pentane/Et₂O (9:1) to give pure **17a** (0.42 g, 89%).

Cleavage of the Chiral Auxiliary and N-Boc Protection of the Secondary Amines. General Procedure. The compound 10b (0.50 g, 1.7 mmol) and a 40% solution of MeNH₂ in H₂O (4.4 mL, 5.8 mmol) were dissolved in MeOH (5 mL), a solution of H₅IO₆ (1.35 g, 5.7 mmol) in H₂O (5 mL) was added dropwise, and the mixture was stirred for 2 h at room temperature. The organic materials were extracted with Et₂O (3 \times 20 mL), and the collected ethereal layers were washed with brine, dried over Na₂SO₄, and concentrated to leave the primary amine as a yellow oil. This was dissolved in THF (5 mL), and then a saturated aqueous solution of NaHCO₃ (5 mL) and (Boc)₂O (0.75 g, 3.4 mmol) were added while the mixture was magnetically stirred. After 2 h, Et₂O (10 mL) was added, and the organic materials were extracted with $\mathrm{Et_2O}~(3\times20$ mL). The collected ethereal layers were dried over Na₂SO₄ and concentrated to leave a white solid, which was washed with pentane $(2 \times 5 \text{ mL})$ to give pure **17b** as white powder: 0.415 g (91%).

Ring-Closing Metathesis Reactions. General Procedure. The oxazolidinone **11b** (1.29 g, 4.4 mmol) was dissolved in anhydrous CH₂Cl₂ (20 mL), and the solution was deaerated by bubbling a stream of Ar through it during 2 min. The Grubbs catalyst **II** (0.044 g, 0.01 mmol) was added, and the solution was again deaerated for 2 min further. The mixture was stirred at the reflux temperature, and the progress of the reaction was monitored by TLC. Disappearance of the starting material was observed within 4 h. The solvent was removed at reduced pressure to leave the crude product. Flash column chromatography (SiO₂) eluting with cyclohexane/ethyl acetate 9:1 mixture gave the product **12b** as a white solid: 1.18 g (96%). Colorless crystals were obtained by crystallization from pentane/Et₂O (7:3).

12a was prepared as a white solid from **11a** (0.98 g, 3.4 mmol): 0.795 g (95%). Colorless crystals were obtained by crystallization from pentane/Et₂O (7:3).

18a was similarly obtained as a white solid from **17a** (0.260 g, 0.90 mmol) and was purified by washing with pentane: 0.237 g (94%).

18b was similarly obtained as a white solid from **17b** (0.25 g, 0.91 mmol) and purified by washing with pentane: 0.195 g (92%).

General Procedure for the Hydrogenation Reactions. To **12a** (0.50 g, 2.0 mmol) dissolved in anhydrous MeOH (20 mL) was added 5% Rh/Al₂O₃ (10%, 0.050 g), and the mixture was kept under hydrogen (1 atm). The progress of the reaction was monitored by GC–MS analysis, and the disappearance of the starting material was observed within 24 h. The solid was filtered off through a pad of Celite, and the organic phase was concentrated at reduced

pressure. Flash column chromatography (SiO₂) eluting with ethyl acetate/methanol/30% NH₄OH (9:1:0.1) mixture gave the diastereomers of **14a**, which were eluted in the order (R,R), (S,S), (S,R). The order of elution in GC-MS analysis was found: (S,S), (R,R), (S,R).

(S,S)-**14a** was a white solid, 0.096 g (19%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (10:1).

(S,R)-**14a** was a white solid, 0.287 g (57%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (10:1).

(R,R)-14a could not be obtained in a pure state, being contaminated by (S,S)-14a. It had the same molecular weight of previous diastereomers by GC-MS analysis.

Compound **13a** was obtained as a yellowish oil from **12a** (0.10 g, 0.40 mmol) after a 2 h reaction time: 0.095 g (96%). Compound **13b** was similarly obtained as a white solid from **12b** (0.10 g, 0.36 mmol) after a 2 h reaction time: 0.098 g (97%).

Full hydrogenation of compound **12b** (0.5 g, 1.79 mmol) gave the following diastereomers:

(S,S)-14b: 0.100 g (19%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (8:2). (S,R)-14b: 0.293 g (56%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (8:2). (R,R)-14b could not be obtained in a pure state, being contaminated by (S,S)-14b.

Full hydrogenation of compound **18a** (0.20 g, 0.84 mmol) gave two diastereomers. Compound (*S*,*S*)-**19a**: white solid, 0.129 g, (60%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (9:1). Compound (*S*,*R*)-**19a**: white solid, 0.059 g (31%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (9:1). The ee of (*S*,*S*)-**19a** was determined by chiral GC on a Megadex chiral column (25 m, flow rate: 15 mL/min, isotherm 150 °C for 2 min then 2 °C/min to 220 °C, FID detection). Retention times: (*S*,*S*)-**19a** (major enantiomer), 28.2 min; (*R*,*R*)-**19a**, 28.6 min. Under the same analytical conditions, (*S*,*R*)-**19a** was found to be enantiomerically pure with a retention time 21.2 min,

Full hydrogenation of compound **18b** (0.200 g, 0.86 mmol) gave two diastereomers. Compound (*S*,*S*)-**19b**: white solid; 0.132 g (64%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (9:1). Compound (*S*,*R*)-**19b**: white solid; 0.064 g (31%). Colorless crystals were obtained by crystallization from Et₂O/CH₂Cl₂ (9:1). The ee of (*S*,*S*)-**19b** was determined by chiral GC on a Megadex chiral column (25 m, flow rate 15 mL/min, isotherm at 100 °C for 2 min, then 5 °C/min to 220 °C, FID detection). Retention times: (*S*,*S*)-**19b** (major enantiomer), 17.6 min; (*R*,*R*)-**19b**, 18.3 min; ee 91%. Under the same analytical conditions, (*S*,*R*)-**19b** resulted enantiomerically pure: retention time 15.8 min.

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Supporting Information Available: General methods, analytical data, and copies of ¹H NMR and ¹³C NMR spectra for all of the new compounds prepared. ORTEP drawing and CIF files of compounds (*S*,*R*)- and (*S*,*S*)-**14a** and (*S*,*R*)- and (*S*,*S*)-**14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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