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Asymmetric Synthesis of 8-Aminoindolizidine from Chiral 2-Pyrroleimines

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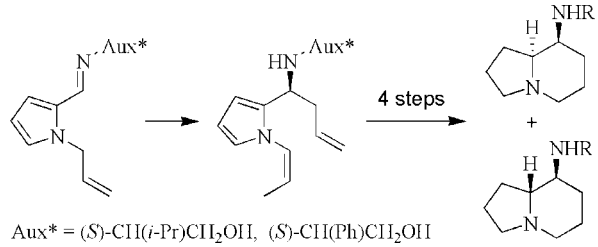

1-Allyl-2-pyrroleimines obtained from (*S*)-valinol and (*S*)-phenylglycinol underwent highly diastereoselective addition of allylmagnesium chloride, used in excess amounts, to give the corresponding secondary amines with concomitant allyl to (*Z*)-1-propenyl isomerization of the 1-pyrrole substituent. 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 communication[2] 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 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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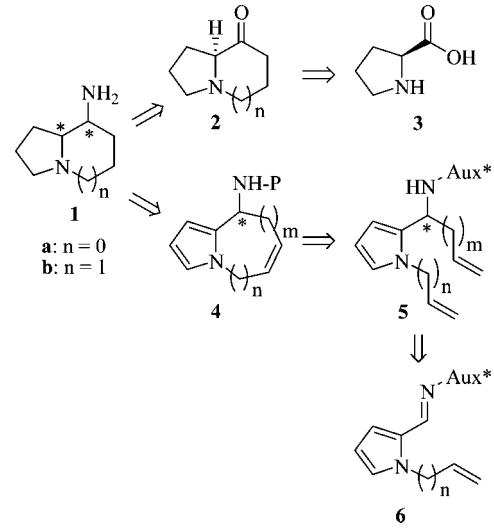

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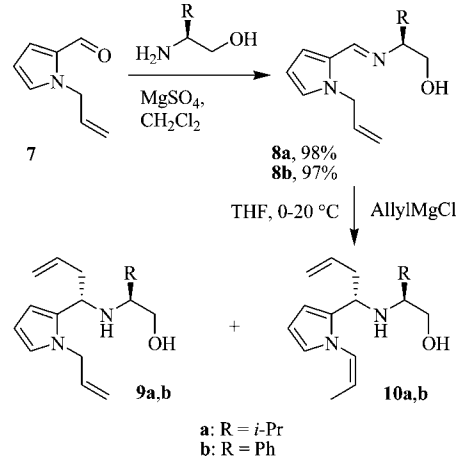

Pyrroles have been used as building blocks for the stereoselective synthesis of indolizidines, as the heteroaromatic ring can be hydrogenated to pyrrolidine and the six membered ring was formed by diverse cyclization strategies.[6] Here, we report the synthesis of 8-aminoindolizidine **1b** by this general strategy, starting from the pyrroleimine **6** and constructing the six-membered 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 exess of Grignard reagent (2.2 equiv), a 73:27 mixture of two isomeric amines were obtained, as evidenced by ^{1}H NMR analysis of the crude product. The major isomer was identified as the expected product **9a** on the basis of the ^{1}H 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.

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.

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 ^{1}H 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 *Z* on 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 SiO_2 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

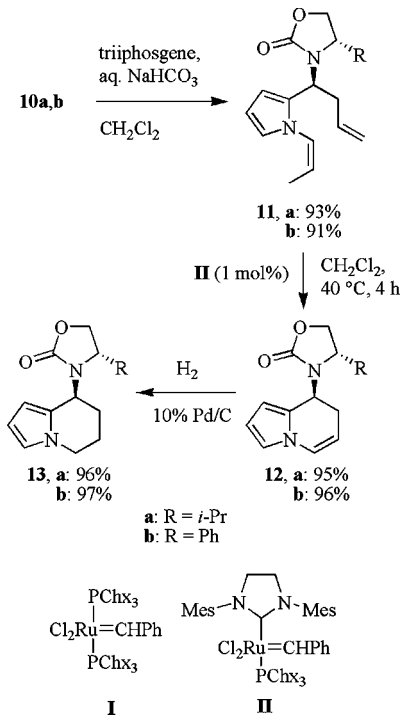

TABLE 2. Ring-Closing Metathesis of Compounds 11a,b[a]

entry	compd	Grubbs cat. (mol %)	solvent	*T* (°C)	time (h)	**12**, yield[b] (%)
1	**11a**	**I** (5)	CH_2Cl_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 corresponding pyrrolidines.[5,9] The results we have obtained using 10% Pd/C, 10% $Pd(OH)_2$/C, PtO_2, and 5% Rh/Al_2O_3 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 ^{1}H 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 H_2) 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 (PtO_2) proved to be ineffective, as only 10% conversion was observed after 24 h (entry 5).

Rh/Al_2O_3 (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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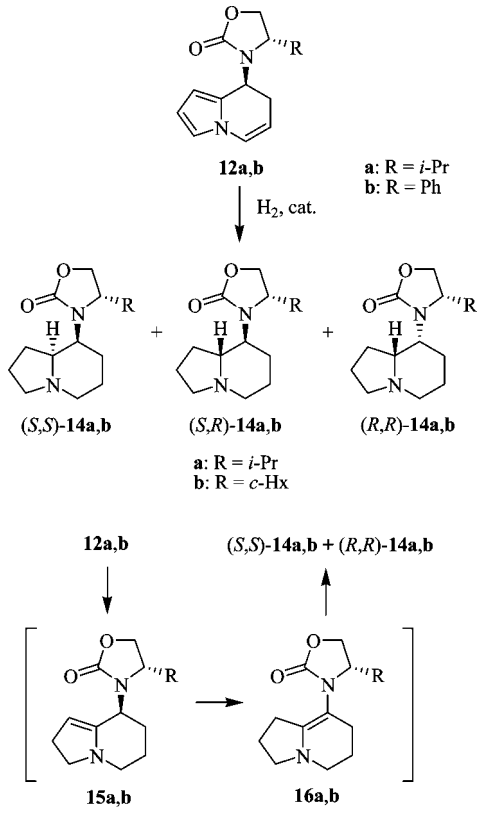
TABLE 3. Hydrogenation of Compounds 12a,b[a]

entry	compd	catalyst (wt %; mol %)	H_2 (atm)	solvent	time (h)	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_2O_3 (10; 1.2)	1	MeOH	24	100	**14a**, 31:69:0	(*S*,*S*)-**14a**, 19 (*S*,*R*)-**14a**, 57
7	**12a**	5% Rh/Al_2O_3 (10; 1.2)	8	MeOH	24	100	**14a**, 26:74:0	(*S*,*S*)-**14a**, 11 (*S*,*R*)-**14a**, 63
8	**12a**	5% Rh/Al_2O_3 (10; 1.2)	8	EtOAc	24	96	**14a**, 40:60:0	
9	**12b**	5% Rh/Al_2O_3 (10; 1)	1	MeOH/AcOH (4:1)	24	100	**14b**, 31:64:5	(*S*,*S*)-**14b**, 24 (*S*,*R*)-**14b**, 56
10	**12b**	5% Rh/Al_2O_3 (10; 1.4)	8	MeOH/AcOH (4:1)	24	100	**14b**, 28:69:3	(*S*,*S*)-**14b**, 20 (*S*,*R*)-**14b**, 58
11	**12a**	5% Rh/Al_2O_3 (10; 1.2)	1	MeOH−Et_3N (4:1)	72	100	**14a**, 22:78	(*S*,*S*)-**14a**, 11 (*S*,*R*)-**14a**, 65
12	**12a**	26% Rh/Gr (1.5; 0.9)	1	MeOH/Et_3N (4:1)	48	100	**14a**, 24:76	(*S*,*S*)-**14a**, 11 (*S*,*R*)-**14a**, 62
13	**12a**	26% Rh/Gr (1.5; 0.9)	8	MeOH	11	100	**14a**, 39:61	(*S*,*S*)-**14a**, 29 (*S*,*R*)-**14a**, 48
14	**12b**	26% Rh/Gr (1.5; 1.0)	1	MeOH	48	100	**14b**, 26:67:7	(*S*,*S*)-**14b**, 18 (*S*,*R*)-**14b**, 53
15	**12b**	26% Rh/Gr (1.5; 1.0)	1	MeOH/AcOH (4:1)	24	100	**14b**, 29:66:5	(*S*,*S*)-**14b**, 19 (*S*,*R*)-**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.

SCHEME 4



tatively formed with a moderate prevalence of the latter, especially under 8 atm of H_2 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 H_2 (entry 8). The hydrogenation of the phenylglycinol derivative **12b** with the same rhodium catalyst in methanol under 1 and 8 atm of H_2 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/Al_2O_3 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).

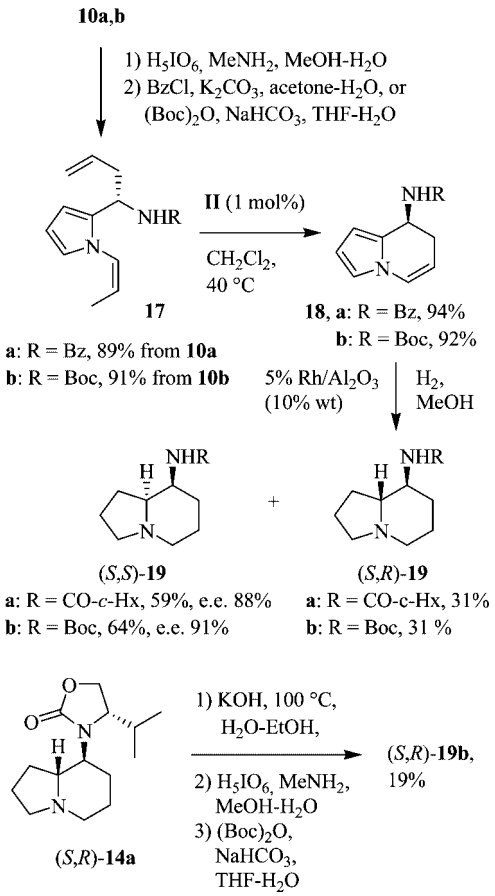
Finally, we checked 24% rhodium on graphite (Rh/Gr) as a novel catalyst for the hydrogenation of the pyrrole as well as arene rings.[10] This catalyst proved to be more effective than previously tested heterogeneous catalysts. As a matter of fact, using a slightly lower catalyst loading (0.9−1.0 molar 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.

SCHEME 5



bicyclic compounds **18a**,**b**, which were finally submitted to hydrogenation using Rh/Al_2O_3 as the catalyst in methanol under 1 atm H_2. 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 (SiO_2) 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 CH_2Cl_2 (40 mL) were added anhydrous $MgSO_4$ (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 $NaHCO_3$ (30 mL) at 0 °C, and then the organic material was extracted with diethyl ether (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the crude product. ^1H NMR analysis showed the presence of a single compound. Flash column chromatography (SiO_2) 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 Oxazolidinononones. Typical Procedure. To a solution of the β-amino alcohol **10b** (1.30 g, 4.4 mmol) in CH_2Cl_2 (20 mL) cooled at 0 °C were added a saturated aqueous solution of $NaHCO_3$ (10 mL) and triphosgene (0.65 g, 2.2 mmol) dissolved in CH_2Cl_2 (5 mL), and the mixture was stirred overnight. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to leave the crude product. Flash column chromatography (SiO_2) 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 $MeNH_2$ in H_2O (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 Et_2O (3 × 20 mL). The collected ethereal layers were washed with brine, dried over Na_2SO_4, and concentrated to leave the primary amine as a yellow oil. This was dissolved in acetone (5 mL), and then H_2O (5 mL), K_2CO_3 (0.47 g, 3.4 mmol), and benzoyl chloride (300 μL, 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 Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a white solid, which was crystallized from pentane/Et_2O (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 $MeNH_2$ in H_2O (4.4 mL, 5.8 mmol) were dissolved in MeOH (5 mL), a solution of H_5IO_6 (1.35 g, 5.7 mmol) in H_2O (5 mL) was added dropwise, and the mixture was stirred for 2 h at room temperature. The organic materials were extracted with Et_2O (3 × 20 mL), and the collected ethereal layers were washed with brine, dried over Na_2SO_4, 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 $NaHCO_3$ (5 mL) and $(Boc)_2O$ (0.75 g, 3.4 mmol) were added while the mixture was magnetically stirred. After 2 h, Et_2O (10 mL) was added, and the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a white solid, which was washed with pentane (2 × 5 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 CH_2Cl_2 (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 (SiO_2) 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/Et_2O (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/Et_2O (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/Al_2O_3 (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 (SiO_2) eluting with ethyl acetate/methanol/30% NH_4OH (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 Et_2O/CH_2Cl_2 (10:1).

(*S*,*R*)-**14a** was a white solid, 0.287 g (57%). Colorless crystals were obtained by crystallization from Et_2O/CH_2Cl_2 (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 Et_2O/CH_2Cl_2 (8:2). (*S*,*R*)-**14b**: 0.293 g (56%). Colorless crystals were obtained by crystallization from Et_2O/CH_2Cl_2 (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 Et_2O/CH_2Cl_2 (9:1). Compound (*S*,*R*)-**19a**: white solid, 0.059 g (31%). Colorless crystals were obtained by crystallization from Et_2O/CH_2Cl_2 (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 Et_2O/CH_2Cl_2 (9:1). Compound (*S*,*R*)-**19b**: white solid; 0.064 g (31%). Colorless crystals were obtained by crystallization from Et_2O/CH_2Cl_2 (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 ^{13}C 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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