Tetrahedron 65 (2009) 5787–5798

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereocontrolled conjugate additions to dihydroindolizinone systems. Synthesis of enantiopure polysubstituted tetrahydropyrrolo[2,1-*a*]isoquinolones

Cristina Camarero, Inés González-Temprano, Asier Gómez-SanJuan, Sonia Arrasate, Esther Lete *, Nuria Sotomayor

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco, Euskal Herriko Unibertsitatea, Apdo. 644, 48080 Bilbao, Spain

ARTICLE INFO

Article history:
Received 30 March 2009
Received in revised form 5 May 2009
Accepted 6 May 2009
Available online 9 May 2009

ABSTRACT

Conjugate addition reactions of various types of nucleophiles to the γ-lactam unit of dihydroindolizinone systems have been studied. The addition of cuprates, amines or stabilized carbanions requires the activation of the unsaturated bicyclic lactam with a EWG at C-2, while sulfur-stabilized carbanions are reactive enough to add to the unsubstituted lactam. The stereochemical outcome of the conjugate addition reaction depends on the nature of the substituent at the angular position, and the incoming nucleophile. Thus 1,10b-cis or 1,10b-trans diastereomers could be obtained selectively with dr>95:5. The tandem conjugate addition–alkylation also takes place in good yields. These reactions have been applied to the synthesis of enantiopure tetrahydropyrrolo[2,1-*a*]isoquinolines.

1. Introduction

Pyrrolo[2,1-*a*]isoquinolines[1] have drawn a lot of interest in the last years due to their potential role in therapeutics for the central nervous system related disorders. This is attributed to their dual H_3 antagonist/serotonin transporters inhibitor activity.[2] Because of their biological activity, these alkaloids are also regarded as promising muscarinic agonist,[3] antiplatelet,[4] and antitumor[5] agents. The importance of these nitrogen heterocycles is further enhanced by their utility as advanced key intermediates for the synthesis of more complex alkaloids.[6] For several years we have dedicated part of our research program to the development of new methods for the synthesis of nitrogen heterocycles, based on diastereoselective Parham cyclization,[7] and intramolecular α-amidoalkylation reactions.[8] Through this effort we were able to achieve a stereodivergent approach for synthesis of the enantiopure C-10b substituted 5,6-dihydropyrroloisoquinolones.[9] The presence of the α,β-unsaturated lactam unit in benzo-fused indolizinones would allow for possible further functionalization to more complex targets via conjugate addition reactions. In fact, conjugate 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most useful methods to assemble carbon–carbon bonds in organic chemistry.[10]

It is known that α,β-unsaturated amides and lactams without an additional withdrawing group in the α-position possess an inherently low reactivity in 1,4-addition reactions,[11] except when sulfur-stabilized anions are used as nucleophiles.[12] Thus, in the case of α,β-unsaturated γ-lactams, we have recently described a stereocontrolled 1,4-addition of α-lithiodithioacetals to tetrahydrobenzo[*a*]quinolizines, which led to the synthesis of emetine-like derivatives.[13] On the other hand, the introduction of a carbomethoxy group in the α-position of α,β-unsaturated oxazolopiperidone lactams has allowed Amat et al.[14] to achieve the conjugate addition of hard nucleophiles to generate 3,4- and 2,4-disubstituted enantiopure piperidines, including the antidepressant drug (−)-paroxetine, cis-fused perhydrocycloalka[*c*]pyridines, and the indole alkaloid (+)-uleine.[15] The latter strategy has been proven to be effective for the conjugate addition of organocuprates to five-member α,β-unsaturated lactams, as it has been illustrated in the synthesis of erythrinanes.[16]

In our continued interest in the conjugate addition reactions on the α,β-unsaturated bicyclic lactams, we investigated the conjugate additions of different types of nucleophiles (organocuprates, amines, …) to dihydroindolizinones (Fig. 1), paying special attention to the effect of both the nucleophile and the substitution on C-10b (R^1=Me, *n*-Bu) on the stereoselectivity. To show the synthetic potential of these conjugate additions, the reactions were applied to the synthesis of enantiopure polyfunctionalized pyrrolo[2,1-*a*]isoquinolines.[17]

2. Results

Some years ago we reported the conjugate addition reactions of α-lithiodithioacetals (2-lithio-1,3-dithiane and bis(phenylthio)-methyllithium) to racemic unsaturated bicyclic γ-lactams **1a** and

* Corresponding author. Tel.: +34 94 6012576; fax: +34 94 6012748.
E-mail address: esther.lete@ehu.es (E. Lete).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.011

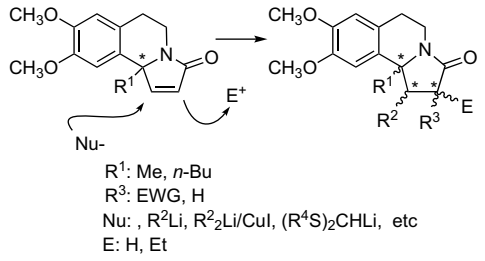


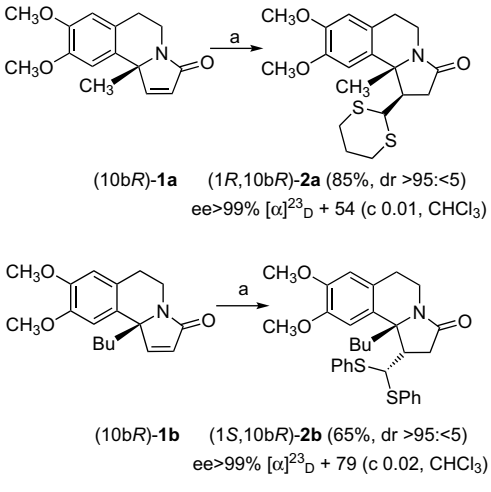
Figure 1.

1b. Thus, lactams **1a**,**b** underwent a clean 1,4-addition reaction of 2-lithio-1,3-dithiane with complete regio- and stereoselectivity in 1 h at room temperature to provide the corresponding 1,10b-cis isomers. Interestingly, a reversal of the stereoselectivity was observed when the C-10b butyl substituted lactam **1b** was reacted with bis(phenylthio)methyllithium, obtaining the trans adduct, as a single diastereomer in high yield.[18] It was necessary to show that these diastereoselective conjugate addition reactions could be used for the synthesis of enantiomerically pure compounds. In this context, we have previously described the synthesis of the enantiopure C-10b substituted 5,6-dihydropyrroloisoquinolones **1a**,**b**.[9b]

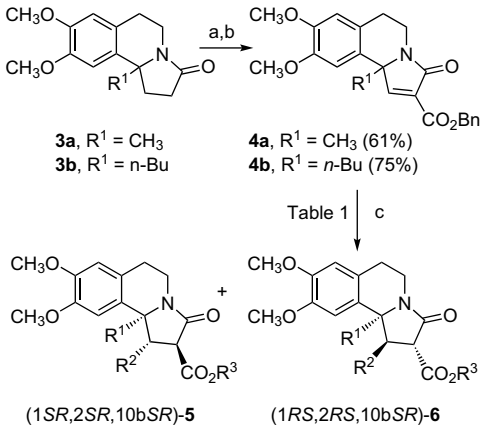
Thus, addition of 2-lithio-1,3-dithiane and bis(phenylthio) methyllithium prepared by treatment of the corresponding dithioacetals with *n*-BuLi at −78 °C, to these lactams (10b*R*)-**1a**,**b** afforded pyrroloisoquinolines (1*R*,10b*R*)-**2a** and (1*S*,10b*R*)-**2b**, respectively, with complete stereocontrol (Scheme 1). The enantiomeric purity (ee >99%) of adducts was established by comparison with the corresponding racemates by CSP HPLC.

Consistent with the low reactivity of unsaturated lactams and amides, we found that **1a**,**b** did not react with organocuprates, enolates, and nitrogen nucleophiles. For instance, conjugate addition reactions of organocuprates were tested on **1a**. Thus, several experiments were carried out varying temperature (from −78 °C to rt), reaction time (3–48 h) or using additives (HMPA or Lewis acids, such as TMSCl). However, unreacted lactam **1a** was always recovered. In the case of the addition of enolates to **1a**, no reaction occurred with preformed enolates derived from cyanoacetate, malonate, and acetoacetate, even working under reflux. In a similar way, screening of several experimental conditions for the addition of amines and lithium amides led to identical results.

Therefore, we decided to introduce an electron withdrawing group (benzyloxycarbonyl) in the α-position to enhance the reactivity of these lactams. Thus, our first task was to prepare the activated unsaturated lactams **4a**,**b**. The pyrroloisoquinolone skeleton



Scheme 1. Reagents and conditions: (a) $(R^2S)_2CHLi$, −78 °C to rt, 1 h.



Scheme 2. Reagents and conditions: (a) LDA (2 equiv), −78 °C, 1 h, THF; $ClCO_2Bn$ (1 equiv), −78 °C, 1 h; PhSeBr (1 equiv), −78 °C, 1 h, (b) H_2O_2, pyridine, 0 °C to rt, CH_2Cl_2. (c) $(R^2)_2CuLi$, THF, −78 °C to rt, 16 h.

was assembled through α-amidoalkylation reactions of *N*-(3,4-dimethoxyphenethyl)-succinimide, a procedure that has been successfully used to access various types of isoquinoline skeletons.[19]

Thus, a double bond was introduced on **3a**,**b**[19a] in high yield by an oxidative elimination of a selenoxide. Subsequent sequential treatment with LDA, benzyl chloroformate, and phenylselenyl bromide, followed by elimination with H_2O_2 provided the dihydropyrroloisoquinolones **4a**,**b**, as described in Scheme 2.

We first studied the addition of Gilman's cuprates, prepared by addition of 2 equiv of methyllithium or *n*-butyllithium to a suspension of CuI (1 equiv) in THF at 0 °C. However, it was necessary to stir the reaction mixture at room temperature overnight, after adding the substrates **4a**,**b**, to have good conversions. In the 1,4-addition reaction of both organocuprates to lactam **4a** (R^1=Me) the cis adducts were obtained as single diastereomers, while the reactions took place with reasonable diastereoselectivities, also in favor of the cis diastereomer, when the lactam **4b** (R^1=*n*-Bu) was used as substrate (Table 1).

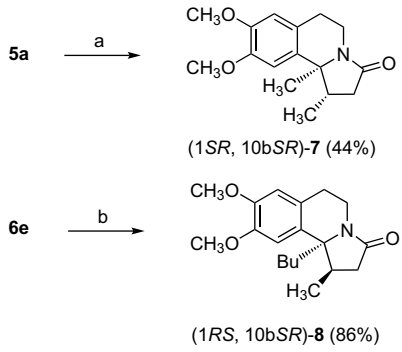
Since it is known that the use of low order cyanocuprates can improve the stereoselectivity of conjugate addition reactions,[20] we also tried the addition of MeCuCNLi (Table 1, entry 3) to lactam **4a**, but although the diastereoselectivity was still high in favor of the cis diastereomer **5a**, the yield dropped to 58%. The 1,4-addition of Bu_2CuLi to both lactams gave moderate yields, due to the simultaneous formation of the corresponding adducts with a CO_2Bu group, instead of the CO_2Bn. Therefore, we prepared the dihydro derivative **4c**, with the CO_2Bu group, and test on it the conjugate addition reaction as can be seen in Table 1, obtaining similar levels of diastereoselectivity.

Finally, the alkoxycarbonyl group necessary for the conjugate addition could be removed by hydrogenolysis or hydrolysis followed

Table 1
Conjugate additions of organocuprates to **4a**–**c**

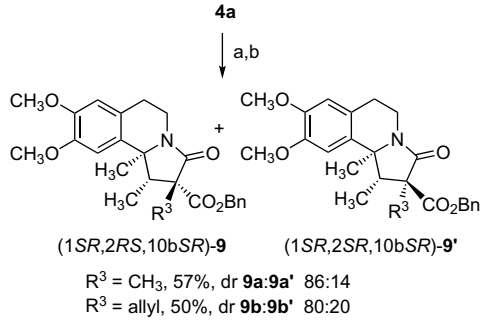
Entry	Subs	R^1	R^2	R^3	Prod	Yield (%)	dr **5**/**6**
1	**4a**	CH_3	CH_3	Bn	**5a**	85	>95:<5
2	**4b**	*n*-Bu	CH_3	Bn	**5b**:**6b**	89	67:33
3	**4a**	CH_3	CH_3[a]	Bn	**5a**	58	93:7
4	**4a**	CH_3	*n*-Bu	Bn	**5c**	51[b]	>95:<5
5	**4b**	*n*-Bu	*n*-Bu	Bn	**5d**:**6d**	57[c]	70:30
6	**4c**	*n*-Bu	CH_3	*n*-Bu	**5e**:**6e**	75	61:39
7	**4c**	*n*-Bu	*n*-Bu	*n*-Bu	**5f**:**6f**	78	66:34

[a] MeCuCNLi was used as nucleophile.
[b] The same pyrroloisoquinoline but with a butoxy-carbonyl group (**5c**′) was also isolated in a 24% yield.
[c] The same pyrroloisoquinoline but with a butoxy-carbonyl group (**5f**) was isolated in a 15% yield.



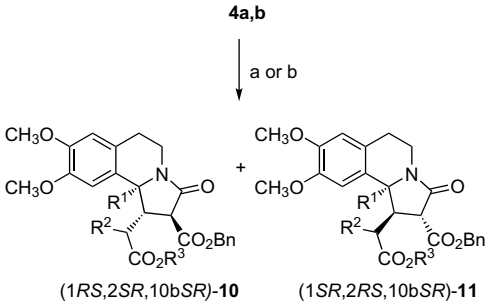
Scheme 3. Reagents and conditions: (a) Pd/C, H_2, MeOH, rt, 2 days; toluene, reflux, 12 h. (b) NaOH, THF/H_2O/MeOH, rt, 18 h; toluene, reflux, 12 h.

by decarboxylation (Scheme 3), obtaining the 1,2-disubstituted pyrroloisoquinolines **7** and **8**, and confirming the stereochemistry of the precursors **5** and **6**. On the other hand, tandem conjugate addition-α-alkylation reaction is an efficient method to build up more complex molecules. Thus, the intermediate lithium enolate derived from the conjugate addition of Gilman's methyl cuprate to unsaturated lactam **4a** could be trapped with methyl iodide to give the 1,2,2-trisubstituted tetrahydropyrroloisoquinolone as an inseparable epimeric mixture: **9a** and **9a′** in an 86:14 ratio. The same intermediate can also be trapped in one pot procedure by allyl iodide to give a mixture of **9b** and **9b′** in a similar ratio (80:20). The addition of $(CH_3)_2CuLi$ to **4a** was again *syn* selective, though enolate alkylation was not completely stereoselective (Scheme 4). Therefore, the sequential conjugate addition of organocuprates and in situ alkylation allowed us the construction of quaternary carbon centers.



Scheme 4. Reagents and conditions: (a) $(CH_3)_2CuLi$, THF, −78 °C to 0 °C, 24 h; (b) R^3I, rt, 24 h.

In order to expand the possibilities of functionalization on C-1 of the pyrroloisoquinolone skeleton, we studied the addition of various enolates to **4a**,**b**. Thus, **4a**,**b** underwent 1,4-additions of enolates derived from cyanoacetates, malonates, and acetoacetates in



Scheme 5. Reagents and conditions: (a) $NCCH_2CO_2Me$ (1 equiv) or $(MeO_2C)_2CH_2$ (1 equiv), $NaNH_2$ (1 equiv), DMPU, THF, rt to reflux. (b) $CH_3COCH_2CO_2Et$ (1 equiv), $Ba(OH)_2$ (1 equiv), EtOH, rt.

Table 2
Conjugate additions of enolates to **4a**,**b**

Entry	Subs	R^1	R^2	R^3	Prod	Yield (%)	dr **10**/**11**
1	**4a**	CH_3	CN	CH_3	**10a**	64	>95:<5
2	**4b**	*n*-Bu	CN	CH_3	**10b**	72[a]	>95:<5
3	**4a**	CH_3	CO_2CH_3	CH_3	**10c**:**11c**	61	20:80
4	**4b**	*n*-Bu	CO_2CH_3	CH_3	**11d**	51[b]	<5:>95
5	**4a**	CH_3	CH_3CO	Et	**10e**:**11e**	89	50:50[c]
6	**4b**	*n*-Bu	CH_3CO	Et	**10f**:**11f**	60	50:50

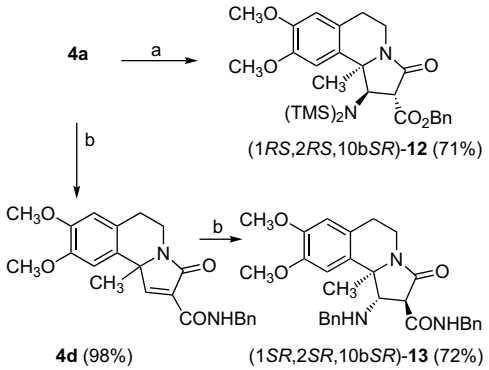
[a] Conversion: 72%.
[b] Conversion: 90%.
[c] dr was determined from ^1H NMR spectra of the mixture.

moderate to good yields. The best results were obtained by using preformed enolates, to which a solution of the substrate was added (Scheme 5). Conjugate addition of enolate of methyl cyanoacetate proceeded very cleanly in dry THF under reflux in 3–4 h to give the corresponding cis diastereomers **10a** and **10b** in good yields and with complete diastereoselectivity. When the reactions were carried out with enolate of dimethyl malonate reversal of stereoselectivity was observed and it was possible to obtain the trans diastereomers **11c** and **11d**. However, addition of the enolate of ethyl acetoacetate took place cleanly in ethanol at room temperature, but with complete lost of diastereoselectivity (Table 2).

We next examined the conjugate addition reactions of nitrogen nucleophiles, which could allow us to synthesize the corresponding 1-aminopyrroloisoquinolone-2-carboxylate derivatives. These types of indolizinone-based amino acid derivatives have gained considerable attention due to their biological properties.[21]

Michael reaction of amines promoted by Lewis acids or base catalysts is one of the most important carbon–nitrogen bond-forming reactions in organic synthesis. Thus, the conjugate addition of homochiral secondary lithium amides to α,β-unsaturated esters and amides has been widely used for the asymmetric synthesis of amino acid derivatives.[22] On the other hand, although aza-Michael reactions of neutral amines often requires the use of Lewis acids in stoichiometric sub-stoichiometric amounts,[23] there are also examples of reactions carried out with the amines at room temperature[24] or even under 'green' reaction conditions, such as conjugate additions accelerated by water[25] or silica gel.[26]

Thus, we first tried the addition of bulky lithium bis-(trimethylsilyl)amide. The addition to lactam **4a** could be accomplished in good yield and complete stereoselectivity, isolating only the trans diastereomer **12** (*rd* >95:<5) as shown in Scheme 6. We next studied the possibility performing the addition of benzylamine without any added base. However, when lactam **4a** was treated with benzylamine under several experimental conditions, we observed that, prior to 1,4-addition, the carboxylic ester was transformed into the corresponding amide, and so lactam **4d**, with a CONHBn group, was isolated as the only reaction product when



Scheme 6. Reagents and conditions: (a) LiHMDS, 78 °C to rt. (b) $BnNH_2$, H_2O, rt, 18 h.

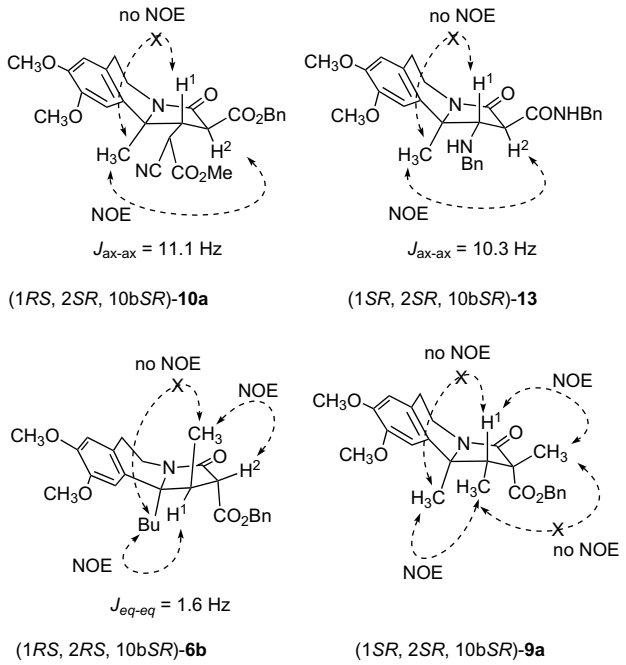


Figure 2. Selected NOE enhancements for **10a**, **13**, **6b**, and **9a**.

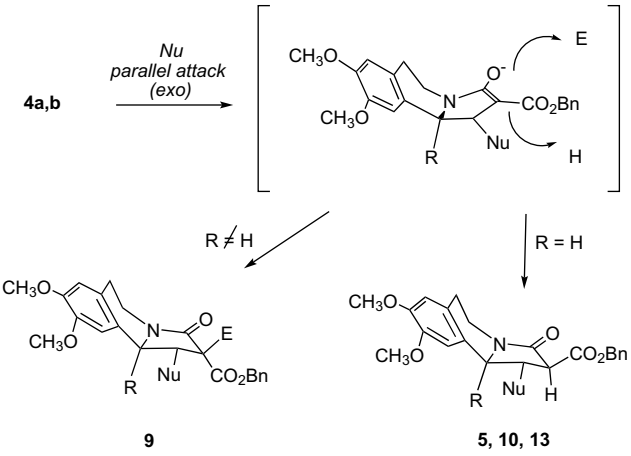
1 equiv of the amine was used. Therefore, we prepared the lactam **4d** and test on it the conjugate addition reaction as can be seen in Scheme 6. The best results were obtained by slowly adding benzylamine (1.8 equiv) to a mixture of the lactam (1 equiv) and water (5 equiv) without solvent at room temperature and then stirring the reaction mixture for 18 h, affording the cis adduct **13** in good yield as a single diastereomer (*dr* >95:<5).

NOESY and COSY experiments confirmed the stereochemistry of all the tetrahydropyrroloisoquinoline derivatives. As an example, the most significant results for pyrroloisoquinolines **6b**, **9a**, **10a**, and **13** are shown in Figure 2. Thus, in the 1,10b-cis substituted derivatives **10a** or **13**, the *J* value of the spin system formed by H-1 and H-2 protons indicates that both are in a *pseudo*-axial position (10–12 Hz). Besides, NOE difference spectroscopy showed an enhancement between the methyl group in C-10b and H-2. In the case of the alkylated system **9a**, a clear NOE enhancement was observed between H-1 and the methyl group on C-2, and between both methyl groups on C-10b and C-1.

On the other hand, for the 1,10b-trans diastereomers as **6b**, the *J* value of the system formed by H-2 and H-1 protons (1.6 Hz) indicate that both are in a *pseudo*-equatorial position. In this case, the absence of NOE enhancement between methyl group on C-1 and the butyl group on C-10b, confirms that they are in a relative trans disposition. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry in each case.

We can now propose a general model to rationalize the facial selectivity (Scheme 7). Thus, attack of the nucleophile to the conformationally rigid lactams **4** occurs under stereoelectronic control, parallel with respect to the substituent at C-10b (exo attack, from the convex face). This leads to a *syn* disposition of both substituents in the resulting enolate intermediate. However, when the size of the substituent at the angular position increases and/or bulky nucleophiles are used, this interaction in the resulting intermediate or in the transition state leading to it would favor an antiparallel attack thus leading to the formation of the trans diastereomers in a larger ratio.

Thus, as shown on Scheme 7, attack of the nucleophiles to substituted lactams **4** occurs mainly parallel to the substituent at C-10b to afford 1,-10b-cis pyrroloisoquinolines **5**, **10**, and **13**. Only

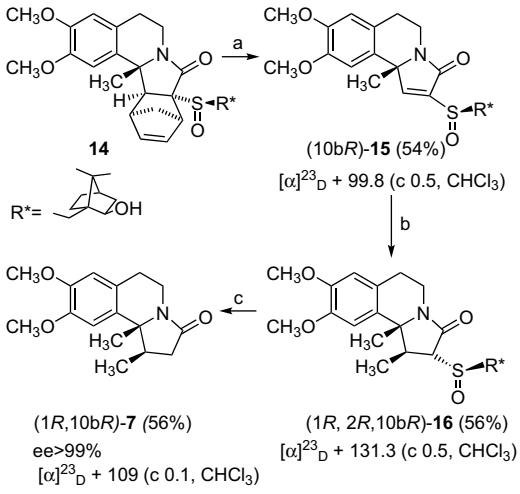


Scheme 7. Stereochemical outcome of the addition reactions.

when a bulky bis(trimethylsilyl)amide or malonate derived enolates are used as nucleophiles, the trans adducts **12** and **11c**,**d**, respectively, were obtained preferentially. It is also noteworthy that protonation of the enolate intermediate occurs from the same face of incoming nucleophile to afford the more stable 1,2-trans adducts. On the contrary, approach of bulkier electrophiles (E) takes place opposite to the *pseudo*-axial R group on C-10b and the nucleophile on C-1, leading mainly to cis adducts **9**. Although there are relatively few examples of conjugate addition reactions to bicyclic γ-lactams,[20,27] our results are in agreement with Meyers,[20,27a,b] who has studied the effect of the angular substituent in the facial selectivity observed in the conjugate addition of nucleophiles to bicyclic γ-lactams derived from pyroglutamic acid. These results are also in agreement with previous results of our group on bicyclic δ-lactams.[13] When stabilized anions are used, the sterochemical outcome of the conjugate addition could also be attributed to the thermodynamic stability of the resulting stereomers, although this possibility is unclear, as the adducts, once formed, do not appear to undergo reversal to the unsaturated lactam.

As shown above, the conjugate addition of cuprates or enolates required the presence of an electron withdrawing group on C-2 to proceed efficiently. Our previously described strategy for the synthesis of enantiomerically pure 5,6-dihydropyrroloisoquinolones as **1a**,**b**[9b] was based on the stereoselective inter- or intramolecular α-amidoalkylation reactions of norborn-5-ene-2,3-dicarboxyimides that incorporate a 2-*exo*-hydroxybornylsulfinyl as a chiral auxiliary. At this point we thought that the sulfinyl group used as a chiral auxiliary could also act as an electron withdrawing group. In fact, α,β-unsaturated sulfoxides have been extensively used in asymmetric synthesis as versatile chiral reagents with the sulfinyl group playing the role of chiral auxiliary.[28] Thus, it has been demonstrated that the conjugate addition of several types of nucleophiles to chiral α,β-unsaturated α-arylsulfinyl carbonyl compounds took place in a completely stereoselective manner.[29]

First, methaneisoindolin[2,3-*a*]isoquinolin-8-one **14** was prepared according to our described procedure.[9b] Then, as shown on Scheme 8, the double bond was unmasked by a thermal retro-Diels–Alder reaction. Thus, using a FVP technique (500 °C, 1 mmHg) the α,β-unsaturated pyrroloisoquinoline (10b*R*)-**15** was obtained without racemization, although in low yield (20%). This yield could be significantly improved to 54% performing the extrusion of cyclopentene in refluxing *o*-DCB to afford enantiomerically pure (10b*R*)-**15**. The enantiomeric purity of (10b*R*)-**15** was established by removal of the sulfinyl group with SmI_2 and *t*-BuOH/HMPA to afford **7**. The sulfinyl group incorporated on C-2 turned out to be able to activate the lactam toward conjugate addition reactions.



Scheme 8. Reagents and conditions: (a) *o*-DCB, reflux, 24 h. (b) MeMgCl, CuI, TMSCl, 0 °C, 16 h. (c) SmI_2, HMPA, t-BuOH, rt, 2 h.

After some experimentation, we found that best results were obtained using the cuprates, generated by treatment of MeMgCl with CuI, in the presence of TMSCl. Thus, (1*R*,10b*R*)-**16** was obtained in moderate yield as a single diastereomer. The addition of Gilman's cuprates under the conditions described on Table 1 led to slightly lower yields. Therefore, the sulfinyl group plays a dual role, both as chiral auxiliary in the synthesis of **14** and as activating group for the conjugate addition. The stereochemical outcome is the same that has been observed with **4a**, so it seems that in this case it should be controlled by the axial substituent on C-10b, and not by the sulfinyl group. Finally, reductive removal of the sulfinyl group with SmI_2 provided (1*R*,10b*R*)-pyrroloisoquinoline **7** in enantiomerically pure form. The enantiomeric purity (ee>99%) of adducts was established by comparison with the corresponding racemates by CSP HPLC.

3. Conclusion

In conclusion, conjugate addition reactions of various types of nucleophiles to the γ-lactam unit of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines allows the stereocontrolled formation of carbon–carbon bonds at the C-1 position. While sulfur-stabilized anions react with non-activated lactams, the addition of other nucleophiles as cuprates, amines or π-stabilized carbanions requires the presence of an electron withdrawing group on C-2. The attack of the nucleophile occurs preferentially parallel to the substituent on C-10b, although the steric interaction between the angular substituent on C-10b and the incoming nucleophile may cause a reversal of the stereochemical course of the addition. Thus 1,10b-cis or 1,10b-trans diastereomers could be selectively obtained. These reactions proceed with complete stereocontrol on chiral non-racemic substrates, allowing the synthesis of enantiomerically pure 1,10b-disubstituted tetrahydropyrrolo[2,1-*a*]isoquinolines. Thus, the 2-*exo*-hydroxybornylsulfinyl group plays a dual role, as a chiral auxiliary on the asymmetric synthesis of 5,6-dihydroisoquinolines and as an efficient electron withdrawing group to activate the lactam toward the 1,4-addition.

4. Experimental section

4.1. (1*R*,10b*R*)-(+)-1-[1,3-Dithian-2-yl]-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (2a)

To a solution of 1,3-dithiane (0.24 mg, 0.2 mmol) in dry THF (3 mL), *n*-BuLi (0.15 mL of a 1.04 M solution in hexanes, 0.15 mmol) was added at −78 °C. The resulting mixture was stirred at this temperature for 1 h, and allowed to warm up to rt. A solution of pyrroloisoquinolone (10b*R*)-**1a**[9b] (27 mg, 0.1 mmol) in THF (3 mL) was added, and the resulting solution was stirred for 24 h. The reaction was quenched by the addition of saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with 10% aq NaOH (2×10 mL), brine (2×10 mL), and H_2O (2×10 mL), then dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 80% hexane/AcOEt) afforded pyrroloisoquinolone (1*R*,10b*R*)-**2a**, (34 mg, 85%) as an oil: mp (Et_2O) 155–156 °C. IR (KBr) ν=1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.67 (s, 3H), 1.67–1.94 (m, 1H), 2.09–2.25 (m, 1H), 2.48–2.62 (m, 2H), 2.71 (dtd, *J*=8.5, 8.3, 3.5 Hz, 1H), 2.82–3.06 (m, 7H), 3.84 (s, 3H), 3.89 (s, 3H), 4.25 (dd, *J*=12.3, 5.5 Hz, 1H), 4.62 (d, *J*=3.5 Hz, 1H), 6.54 (s, 1H), 6.93 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=23.6, 25.2, 28.0, 30.4, 31.7, 33.9, 34.8, 48.6, 49.3, 55.8, 56.2, 64.2, 108.5, 111.8, 125.5, 134.1, 147.5, 147.8, 171.5. LRMS (EI, 70 eV): *m*/*z* (%)=380 (M^++1, 5), 379 (M^+, 15), 364 (27), 272 (8), 258 (12), 207 (10), 206 (64), 205 (17), 204 (13), 190 (12), 121 (11), 120 (10), 119 (100), 85 (10), 83 (10), 71 (12), 57 (14), 55 (11). $C_{19}H_{25}NO_3S_2$: calcd C 60.12, H 6.64, N 3.69; found: C 59.91; H 6.76; N 3.48. $[\alpha]_D^{23}$ +54.0 (*c* 0.01, $CHCl_3$). The enantiomeric excess determined by CSP HPLC was >99% by comparison with the racemic mixture. Chiralcel OD, 5% hexane/2-propanol, 0.4 mL/min; *t* [(1*R*,10b*R*)-**2a**]=25 min (>99%); t_R[(1*S*,10b*S*)-**2a**]=19.9 min (<1%).

4.2. (1*S*,10b*R*)-(+)-1-Butyl-2-[bis(thiophenyl)methyl]-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (2b)

To a solution of bis(thiophenyl)methane (134 mg, 0.56 mmol) in dry THF (5 mL), *n*-BuLi (0.3 mL of a 1.4 M solution in hexanes, 0.42 mmol) was added at −78 °C. The resulting mixture was stirred at this temperature for 1 h, and allowed to warm up to rt. A solution of pyrroloisoquinolone (10b*R*)-**1b** (84 mg, 0.28 mmol)[4] in THF (5 mL) was added, and the resulting solution was stirred for 24 h. The reaction was quenched by the addition of saturated NH_4Cl (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic extracts were washed with 10% aq NaOH (2×15 mL), brine (2×15 mL), and H_2O (2×15 mL), then dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 80% hexane/AcOEt) afforded pyrroloisoquinolone (1*S*,10b*R*)-**2b**, (97 mg, 65%) as an oil: mp (Et_2O) 118–119 °C; IR (KBr) ν=1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.79 (t, *J*=7.0 Hz, 3H), 1.08–1.47 (m, 4H), 1.67–1.83 (m, 2H), 2.51–2.56 (m, 1H), 2.81–2.90 (m, 3H), 3.01–3.15 (m, 2H), 3.66 (s, 3H), 3.82 (s, 3H), 4.28 (d, *J*=2.1 Hz, 1H), 4.42–4.48 (m, 1H), 6.19 (s, 1H), 6.51 (s, 1H), 6.68–6.72 (m, 2H), 7.06–7.29 (m, 8H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.8, 23.0, 26.9, 27.8, 33.9, 36.3, 44.2, 47.7, 55.8, 55.9, 62.9, 66.7, 108.4, 111.7, 127.4, 127.5, 128.2, 128.4, 128.6, 129.1, 131.5, 133.1, 133.6, 134.5, 147.4, 147.8, 171.9. LRMS (EI, 70 eV): *m*/*z* (%)=533 (M^+, <1), 477 (16), 424 (12), 366 (11), 258 (17), 249 (15), 248 (78), 233 (14), 232 (30), 231 (100), 153 (15), 149 (22), 147 (10), 121 (18), 116 (22), 115 (15), 77 (16), 65 (16). $C_{31}H_{35}NO_3S_2$: calcd C 69.76, H 6.61, N 2.62; found: C 69.70, H 6.61, N 2.72. $[\alpha]_D^{23}$ +79.0 (*c* 0.02, $CHCl_3$). The enantiomeric excess determined by CSP HPLC was >99% by comparison with the racemic mixture. Chiralcel OD, 5% hexane/2-propanol, 0.4 mL/min; t_R[(1*S*,10b*R*)-**2b**]=35 min (>99%); t_R[(1*R*,10b*S*)-**2b**]=31.6 min (<1%). The spectroscopic data were identical to those of racemate.

4.3. 2-Benzyloxycarbonyl-8,9-dimethoxy-10b-methyl-5,6-dihydropyrrolo-[2,1-*a*]isoquinolin-3-one (4a)

A solution of pyrroloisoquinoline **3a**[19a] (520 mg, 1.99 mmol) in dry THF (5 mL) was added over a solution of LDA (0.73 M,

4.38 mmol) [obtained from $^{i}Pr_2NH$ (0.61 mL, 4.38 mmol) and *n*-BuLi (3.5 mL of a 1.24 M solution, 4.38 mmol)] at −78 °C. The reaction mixture was stirred for 1 h and benzyl chloroformate (0.3 mL, 1.99 mmol) was added. After stirring the mixture for 45 min, a solution of phenylselenyl bromide (672 mg, 0.7 M) in THF (4 mL) was added, and the reaction was stirred at −78 °C for 1 h. The reaction was quenched by addition of HCl (1 M, 10 mL) and allowed to reach rt. The organic layer was separated, and the aqueous phase was extracted with Et_2O (15 mL) and CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a diastereomeric mixture of selenides. To carry out the oxidative elimination, pyridine (0.65 mL, 7.97 mol) and 30% H_2O_2 (0.34 mL, 11.9 mmol) were added sequentially to a solution of the diastereomeric mixture of selenides in dry CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was allowed to reach rt, and stirred for 12 h. The reaction was quenched by addition of HCl (5% aq, 25 mL), the organic layer was separated, and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silicagel, 60% hexane/AcOEt) afforded pyrroloisoquinoline **4a** (479 mg, 61%) as a white solid: mp (Et_2O): 128–130 °C. IR (KBr) ν=1740, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.59 (s, 3H), 262 (dd, *J*=16.0, 3.8 Hz, 1H), 2.91 (td, *J*=11.9, 6.3 Hz, 1H), 3.18 (ddd, *J*=13.1, 11.9, 4.4 Hz, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.43 (dd, *J*=13.1, 6.3 Hz, 1H), 5.23 (s, 2H), 6.60 (s, 1H), 6.70 (s, 1H), 7.27–7.40 (m, 5H), 8.10 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=26.1, 28.7, 34.7, 55.6, 55.8, 62.9, 66.4, 108.7, 111.8, 125.3, 127.2, 127.7, 128.0, 128.3, 135.2, 147.5, 148.1, 159.8, 161.2, 164.8. LRMS (EI, 70 eV): *m*/*z* (%)=394 (M^++1, 3), 393 (M^+, 11), 379 (20), 378 (71), 284 (6), 259 (8), 244 (39), 242 (9), 107 (12), 91 (100), 79 (27), 77 (25), 65 (26), 57 (15). $C_{23}H_{23}NO_5$: calcd C 70.21, H 5.89, N 3.56; found: C 69.85, H 5.84, N 3.53.

4.4. 2-Benzyloxycarbonyl-10b-butyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-one (4b)

A solution of pyrroloisoquinoline **3b**[19a] (465 mg, 1.53 mmol) in dry THF (8 mL) was added over a solution of LDA (0.7 M, 3.4 mmol) [obtained from $^{i}Pr_2NH$ (0.47 mL, 3.4 mmol) and *n*-BuLi (2.7 mL of a 1.24 M solution, 3.4 mmol)] at −78 °C. The reaction mixture was stirred for 1 h and benzyl chloroformate (0.28 mL, 1.53 mmol) was added. After stirring the mixture for 45 min, a solution of phenylselenyl bromide (507 mg, 0.7 M) in THF (3 mL) was added, and the reaction was stirred at −78 °C for 1 h. The reaction was quenched by addition of HCl (1 M, 10 mL) and allowed to reach rt. The organic layer was separated, and the aqueous phase was extracted with Et_2O (15 mL) and CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a diastereomeric mixture of selenides. To carry out the oxidative elimination, pyridine (0.5 mL, 6.14 mol) and 30% H_2O_2 (0.3 mL, 9.21 mmol) were added sequentially to a solution of the diastereomeric mixture of selenides in dry CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was allowed to reach rt, and stirred for 16 h. The reaction was quenched by addition of HCl (5% aq, 25 mL), the organic layer was separated, and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silicagel, 70% hexane/AcOEt) afforded pyrroloisoquinoline **4b** (501 mg, 75%) as an oil: IR (KBr) ν=1795, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.83 (t, *J*=7.1 Hz, 3H), 1.05–1.14 (m, 4H), 1.98 (t, *J*=6.7 Hz, 2H), 2.64 (dd, *J*=15.8, 3.5 Hz, 1H), 2.93 (ddd, *J*=15.8, 11.8, 6.3 Hz, 1H), 3.15 (ddd, *J*=13.1, 11.8, 4.3 Hz, 1H), 3.82 (s, 3H), 3.88 (s, 3H), 4.46 (dd, *J*=13.1, 6.3 Hz, 1H), 5.21 (s, 2H), 6.59 (s, 1H), 6.68 (s, 1H), 7.26–7.45 (m, 5H), 7.99 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 22.5, 25.2, 28.7, 34.8, 38.7, 55.7, 56.0, 66.1, 66.5, 108.9, 111.9, 125.3, 127.7, 128.1, 128.4, 128.9, 135.3, 147.5, 148.2, 159.4, 161.3, 165.6. LRMS (EI, 70 eV): *m*/*z* (%)=435 (M^+, 2), 380 (4), 379 (25), 378 (100), 328 (2), 327 (4), 284 (8), 245 (4), 244 (20), 242 (3), 91 (21), 79 (4), 65 (3). $C_{26}H_{29}NO_5$: calcd C 71.70, H 6.71, N 3.22; found: C 71.55, H 6.69, N 3.10.

4.5. 2-Butoxycarbonyl-10b-butyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-one (4c)

A solution of pyrroloisoquinoline **3b**[19a] (532 mg, 1.75 mmol) in dry THF (10 mL) was added over a solution of LDA (0.7 M, 3.9 mmol) [obtained from $^{i}Pr_2NH$ (0.54 mL, 3.9 mmol) and *n*-BuLi (3.71 mL of a 1.05 M solution, 3.9 mmol)] at −78 °C. The reaction mixture was stirred for 1 h and butyl chloroformate (0.32 mL, 1.75 mmol) was added. After stirring the mixture for 45 min, a solution of phenylselenyl bromide (580 mg, 0.7 M) in THF (5 mL) was added, and the reaction was stirred at −78 °C for 1 h. The reaction was quenched by addition of HCl (1 M, 10 mL) and allowed to reach rt. The organic layer was separated, and the aqueous phase was extracted with Et_2O (15 mL) and CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a diastereomeric mixture of selenides. To carry out the oxidative elimination, pyridine (0.6 mL, 7.02 mol) and 30% H_2O_2 (0.35 mL, 10.5 mmol) were added sequentially to a solution of the diastereomeric mixture of selenides in dry CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was allowed to reach rt, and stirred for 16 h. The reaction was quenched by addition of HCl (5% aq, 25 mL), the organic layer was separated, and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silicagel, 60% hexane/AcOEt) afforded pyrroloisoquinoline **4c** (477 mg, 68%) as an oil; IR (KBr) ν=1740, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.68–0.86 (m, 6H), 0.97–1.28 (m, 4H), 1.31–1.40 (m, 2H), 1.54–1.66 (m, 2H), 1.85–2.00 (m, 2H), 2.58 (dd, *J*=15.8, 3.5 Hz, 1H), 2.85 (ddd, *J*=15.8, 11.5, 6.3 Hz, 1H), 3.08 (ddd, *J*=12.7, 11.9, 4.4 Hz, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 4.15 (t, *J*=6.7 Hz, 2H), 4.37 (dd, *J*=12.7, 5.5 Hz, 1H), 6.53 (s, 1H), 6.68 (s, 1H), 7.94 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.8, 13.4, 18.8, 22.3, 25.0, 28.5, 30.2, 34.6, 38.4, 55.5, 55.8, 64.6, 65.8, 108.8, 111.8, 125.1, 127.7, 129.0, 147.3, 148.0, 158.9, 161.4, 165.5. LRMS (EI, 70 eV): *m*/*z* (%)=401 (M^+, 1), 345 (23), 344 (100), 288 (33), 258 (7), 244 (14), 242 (10), 200 (9), 115 (5), 91 (8), 57 (16), 56 (10), 55 (14). $C_{23}H_{31}NO_5$: calcd C 68.80, H 7.78, N 3.49; found C 68.64, H 7.69, N 3.54.

4.6. 2-*N*-Benzylcarbamoyl-8,9-dimethoxy-10b-methyl-5,6,-dihydropyrrolo[2,1-*a*]isoquinolin-3-one (4d)

Benzylamine (0.08 mL, 0.7 mmol) and water (0.04 mL, 1.9 mmol) were added drop wise over lactam **4a** (154 mg, 0.4 mmol) at rt and the reaction mixture was stirred for 18 h. Flash column chromatography (silicagel, 70% hexane/AcOEt) afforded pyrroloisoquinoline **4d** (90 mg, 60%) as a white solid: mp (Et_2O) 167–168 °C. IR (KBr) ν=3280, 3060, 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.62 (s, 3H), 2.69 (dd, *J*=16.2, 3.9 Hz, 1H), 2.93 (ddd, *J*=16.2, 11.9, 6.7 Hz, 1H), 3.27 (td, *J*=13.2, 4.7 Hz, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 4.38 (dd, *J*=13.2, 6.1 Hz, 1H), 4.48–4.64 (m, 2H), 6.58 (s, 1H), 6.73 (s, 1H), 7.21–7.29 (m, 5H), 8.18 (s, 1H), 8.93 (t, *J*=11.5, 5.7 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=26.2, 28.9, 34.9, 42.8, 55.8, 56.0, 63.4, 108.8, 111.8, 124.7, 127.2, 127.5, 127.7, 127.9, 128.5, 137.8, 147.7, 148.3, 157.0, 160.6, 167.5. LRMS (EI, 70 eV): *m*/*z* (%)=393 (M^++1, 14), 392 (M^+, 44), 378 (15), 377 (M^+−15, 58), 286 (29), 272 (22), 259 (7), 245 (20), 244 (25), 228 (6), 207 (6), 206 (29), 200 (10), 115 (6), 107 (9), 106 (100), 91 (27), 79 (11), 77 (9), 65 (9). $C_{23}H_{24}N_2O_4$: calcd C 70.39, H 6.16, N 7.14; found: C 70.11, H 6.02, N 7.28.

4.7. Conjugate addition reactions of organocuprates to pyrrolo[2,1-*a*]isoquinolones 4a,b. General procedure

Methyllithium or *n*-butyllithium (10 mmol) was added drop wise over a suspension of CuI (5 mmol) in dry THF (10 mL) at 0 °C.

After 30 min, the mixture was cooled to −78 °C, and a solution of lactams **4a**,**b** (1 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 3 h, allowed to warm up to 0 °C, and stirred at this temperature for 12 h. The reaction was quenched by sequential addition of NH_4OH (12% aq) (20 mL) and NH_4Cl (satd) (10 mL) at 0 °C. After allowing the mixture to warm up to rt, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silicagel, 70% hexane/AcOEt) afforded pyrroloisoquinolones **5** and/or **6**.

*4.7.1. (1SR,2SR,10bSR)-2-Benzyloxycarbonyl-8,9-dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5a**)*

According to the general procedure, a solution of **4a** (157 mg, 0.4 mmol) in dry THF (10 mL) was treated with the organocuprate, prepared from CuI (228 mg, 2.0 mmol) and MeLi (2.5 mL of a 1.6 M solution in hexanes, 4.0 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded **5a** (140 mg, 85%) as a single diastereomer, white solid: mp (Et_2O) 104–105 °C. IR (KBr) ν=1736, 1692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.36 (t, J=6.7 Hz, 3H), 1.41 (s, 3H), 2.61–3.04 (m, 4H), 3.36 (d, J=11.9 Hz, 1H), 3.84 (s, 6H), 4.29–4.32 (m, 1H), 5.21 (s, 2H), 6.57 (s, 1H), 6.69 (s, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.9, 21.9, 28.8, 34.8, 44.2, 55.6, 55.7, 55.9, 61.5, 66.9, 107.6, 11.7, 124.9, 127.8, 128.0, 128.4, 133.2, 135.4, 147.6, 147.7, 166.3, 169.2. LRMS (EI, 70 eV): m/z (%)=409 (M^+, 8), 395 (26), 394 (100), 259 (32), 258 (14), 244 (20), 206 (10), 204 (10), 91(52). $C_{24}H_{27}NO_5$: calcd C 70.40, H 6.65, N 3.42; found C 70.35, H 6.43, N 3.16.

*4.7.2. (1SR,2SR,10bSR)-2-Benzyloxycarbonyl-10b-butyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5b**) and (1RS,2RS,10bSR)-2-benzyloxycarbonyl-10b-butyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**6b**)*

According to the general procedure, a solution of **4b** (159 mg, 0.36 mmol) in dry THF (10 mL) was treated with the organocuprate, prepared from CuI (348 mg, 1.8 mmol) and MeLi (2.8 mL of a 1.3 M solution in hexanes, 3.6 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **5b** and **6b** in a 67:33 diastereomeric ratio (97 mg, 59%). Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **5b**, oil (68 mg, 41%): IR (KBr) ν=1745, 1700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.85 (t, J=6.5 Hz, 3H), 1.08–1.25 (m, 4H), 1.36 (d, J=7.1 Hz, 3H), 1.82–1.85 (m, 2H), 2.64–2.70 (m, 1H), 2.74 (dd, J=12.3, 7.1 Hz, 1H), 2.81–3.05 (m, 2H), 3.47 (d, J=12.3 Hz, 1H), 3.85 (s, 6H), 4.37–4.42 (m, 1H), 5.21 (s, 2H), 6.58 (s, 1H), 6.70 (s, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 13.9, 23.2, 27.0, 29.0, 36.5, 36.8, 45.0, 55.8, 56.0, 56.2, 64.3, 67.1, 107.4, 111.9, 125.3, 132.7, 135.6, 128.0, 128.1, 128.5, 147.8, 167.7, 169.6; LRMS (EI, 70 eV): m/z (%)=451 (M^+, 2), 395 (26), 394 (100), 286 (13), 259 (39), 258 (16), 244 (23), 91 (75), 57 (7). $C_{27}H_{33}NO_5$: calcd C 71.83, H 7.37, N 3.10; found C 71.62, H 7.15, N 3.05. Minor diastereomer **6b**, oil (29 mg, 18%): IR (KBr) ν=1745, 1700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.66 (d, J=7.1 Hz, 3H), 0.70 (t, J=6.5 Hz, 3H), 0.90–1.23 (m, 4H), 1.71–2.0 (m, 2H), 2.57–2.74 (m, 2H), 2.79–2.88 (m, 1H), 3.00–3.12 (m, 1H), 3.09 (d, J=1.6 Hz, 1H), 3.80 (s, 6H), 4.38–4.45 (m, 1H), 5.23 (d, J=1.6 Hz, 2H), 6.49 (s, 1H), 6.55 (s, 1H), 7.29–7.43 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 19.1, 23.0, 27.4, 28.9, 37.4, 43.6, 42.9, 55.7, 56.1, 57.4, 67.2, 67.5, 109.0, 111.4, 125.3, 127.9, 135.4, 128.3, 128.4, 128.5, 147.6, 147.7, 167.9, 169.9. LRMS (EI, 70 eV): m/z (%)=451 (M^+, 2), 395 (26), 394 (100), 286 (9), 259 (23), 258 (9), 244 (14), 91 (28). $C_{27}H_{33}NO_5$: calcd C 71.83, H 7.37, N 3.10; found: C 71.48, H 7.09, N 2.99.

*4.7.3. (1SR,2SR,10bSR)-2-Benzyloxycarbonyl-1-butyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5c**) and (1SR,2SR,10bSR)-1-butyl-2-butoxycarbonyl-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5c′**)*

According to the general procedure, a solution of **4a** (95 mg, 0.24 mmol) in dry THF (10 mL) was treated with the organocuprate, prepared from CuI (231 mg, 1.2 mmol) and *n*-BuLi (1.5 mL of a 1.6 M solution in hexanes, 2.4 mmol). Flash column chromatography (silica gel, 50% hexane/AcOEt) afforded **5c** and **5c′**. Major product **5c** (56 mg, 51%) as an oil: IR (KBr) ν=1740, 1690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.79 (t, J=7.1 Hz, 3H), 1.05–1.27 (m, 4H), 1.41 (s, 3H), 1.66–2.04 (m, 2H), 2.61–2.70 (m, 1H), 2.77 (dd, J=11.5, 2.8 Hz, 1H), 2.86–3.08 (m, 2H), 3.37 (d, J=11.1 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.28–4.35 (m, 1H), 5.21 (d, J=5.5 Hz, 2H), 6.58 (s, 1H), 6.74 (s, 1H), 7.31–7.37 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.8, 23.1, 22.7, 28.9, 29.8, 30.5, 35.1, 49.2, 55.6, 55.8, 56.0, 62.0, 67.2, 107.7, 111.8, 125.2, 128.2, 128.4, 128.5, 133.8, 135.4, 147.7, 147.9, 166.9, 170.4. LRMS (EI, 70 eV): m/z (%)=452 (M^++1, 8), 451 (M^+, 23), 437 (30), 436 (100), 328 (10), 301 (21), 258 (11), 206 (11), 205 (12), 91 (33). $C_{27}H_{33}NO_5$: calcd C 71.82, H 7.37, N 3.10; found C 71.60; H 7.54; N 3.28. Minor product **5c′** (24 mg, 24%) as an oil: IR (KBr) ν=1745, 1669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.86–0.95 (m, 6H), 1.23–1.42 (m, 11H), 1.61–2.04 (m, 2H), 2.60–2.70 (m, 1H), 2.77 (dd, J=11.1, 3.0 Hz, 1H), 2.86–3.06 (m, 2H), 3.31 (d, J=11.1 Hz, 1H), 3.86 (s, 6H), 4.17 (t, J=6.7 Hz, 2H), 4.27–4.34 (m, 1H), 6.59 (s, 1H), 6.77 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.6, 13.9, 19.0, 22.8, 23.1, 29.0, 29.9, 30.4, 30.5, 35.1, 49.1, 55.7, 55.8, 56.1, 62.0, 65.4, 107.8, 111.8, 125.3, 133.9, 147.7, 147.9, 167.1, 170.7. LRMS (EI, 70 eV): m/z (%)=418 (M^++1, 5), 417 (M^+, 15), 403 (25), 402 (M^+−15, 100), 328 (26), 300 (7), 206 (9), 205 (11), 55 (3). $C_{24}H_{32}NO_5$: calcd C 69.04, H 8.45, N 3.35; found C 68.79; H 8.56; N 3.47.

*4.7.4. (1SR,2SR,10bSR)-2-Benzyloxycarbonyl-1,10b-dibutyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5d**), (1RS,2RS,10bSR)-2-benzyloxycarbonyl-1,10b-dibutyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**6d**), and (1SR,2SR,10bSR)-1,10b-dibutyl-2-butoxycarbonyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5f**)*

According to the general procedure, a solution of **4b** (167 mg, 0.27 mmol) in dry THF (10 mL) was treated with the organocuprate, prepared from CuI (255 mg, 1.3 mmol) and *n*-BuLi (2.2 mL of a 1.24 M solution in hexanes, 2.73 mmol). Flash column chromatography (silica gel, 50% hexane/AcOEt) afforded as major product a diastereomeric mixture of **5d** and **6d** in a 70:30 diastereomeric ratio (76 mg, 57%), together with **5f** (18.5 mg, 15%) as minor product. Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **5d**, oil (59 mg, 44%): IR (KBr) ν=1745, 1700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.76–0.94 (m, 6H), 1.01–1.40 (m, 8H), 1.60–1.98 (m, 4H), 2.61–2.66 (m, 1H), 2.73–2.78 (m, 1H), 2.83–3.04 (m, 2H), 3.45 (d, J=11.1 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.35–4.39 (m, 1H), 5.21 (d, J=5.5 Hz, 2H), 6.58 (s, 1H), 6.73 (s, 1H), 7.30–7.36 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.8, 13.9, 22.8, 23.1, 27.2, 29.0, 30.0, 30.1, 36.4, 37.5, 49.8, 55.8, 56.0, 56.1, 64.8, 67.3, 107.4, 111.9, 125.3, 133.4, 135.4, 128.3, 128.5, 128.6, 147.8, 168.1, 170.7; LRMS (EI, 70 eV): m/z (%)=493 (M^+, 1), 437 (27), 436 (M^+−57, 100), 328 (10), 301 (16), 258 (10), 244 (7), 91 (23), 55 (5). $C_{30}H_{39}NO_5$: calcd C 72.99, H 7.96, N 2.84; found C 72.62, H 8.11, N 3.03. Minor diastereomer **6d**, oil (18 mg, 13%): IR (KBr) ν=1745, 1700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.69–1.28 (m, 16H), 1.73–1.86 (m, 2H), 2.58–2.80 (m, 3H), 3.08 (td, J=12.3, 4.4 Hz, 1H), 3.27 (d, J=1.2 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.43 (dd, J=12.7, 5.5 Hz, 1H), 5.26 (d, J=2.4 Hz, 2H), 6.49 (s, 1H), 6.57 (s, 1H), 7.19–7.43 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.8, 14.2, 22.1, 23.0, 27.4, 28.3, 28.9, 29.1, 29.7, 36.8, 46.6, 55.7, 56.1, 56.1, 67.2, 67.6,

103.0, 111.4, 127.4, 128.2, 128.3, 128.5, 132.7, 135.6, 147.6, 147.8, 168.1, 170.4. LRMS (EI, 70 eV): *m*/*z* (%)=493 (M^+, <1), 437 (29), 436 (M^+-57, 100), 347 (19), 345 (15), 344 (46), 343 (23), 329 (35), 328 (14), 301 (22), 258 (15), 244 (18), 91 (51), 57 (16), 55 (16). $C_{30}H_{39}NO_5$: calcd C 72.99, H 7.96, N 2.84; found C 72.60, H 8.13, N 3.06. Minor product **5f**, oil (18.5 mg, 15%): IR (KBr) ν=1737, 1692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.83–0.94 (m, 9H), 1.08–1.46 (m, 10H), 1.57–2.14 (m, 6H), 2.59–3.05 (m, 4H), 3.4 (d, *J*=11.5 Hz, 1H), 3.86 (s, 6H), 4.20 (t, *J*=6.7 Hz, 2H), 4.36 (dd, *J*=11.9, 3.6 Hz, 1H), 6.58 (s, 1H), 6.74 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.6, 13.8, 13.9, 19.0, 22.8, 23.1, 27.1, 28.9, 29.9, 30.1, 30.4, 36.3, 37.4, 49.6, 55.6, 55.7, 56.0, 64.7, 65.3, 107.3, 111.8, 125.2, 133.4, 147.7, 168.2, 170.9. LRMS (EI, 70 eV): *m*/*z* (%)=459 (M^+, <1), 403 (26), 402 (100), 328 (22), 300 (9), 258 (10), 244 (6), 57 (10), 55 (6). $C_{27}H_{41}NO_5$: calcd C 70.56, H 8.99, N 3.05; found C 70.39, H 9.04, N 3.12.

*4.7.5. (1SR,2SR,10bSR)-10b-Butyl-2-butoxycarbonyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5e**) and (1RS,2RS,10bSR)-10b-butyl-2-butoxycarbonyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**6e**)*

According to the general procedure, a solution of **4c** (106 mg, 0.26 mmol) in dry THF (4 mL) was treated with the organocuprate, prepared from CuI (252 mg, 1.32 mmol) and MeLi (1.65 mL of a 1.6 M solution in hexanes, 2.64 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **5e** and **6e** in a 61:39 diastereomeric ratio (80 mg, 75%). Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **5e**, oil (49 mg, 47%): IR (KBr) ν=1734, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.82–0.94 (m, 6H), 1.08–1.34 (m, 6H), 1.37 (d, *J*=6.7 Hz, 3H), 1.58–1.69 (m, 2H), 1.79–1.88 (m, 2H), 2.60–2.95 (m, 3H), 3.03 (dd, *J*=12.3, 3.4 Hz, 1H), 3.39 (d, *J*=12.3 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 4.11–4.25 (m, 2H), 4.36–4.43 (m, 1H), 6.58 (s, 1H), 6.71 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 13.9, 18.9, 23.2, 27.0, 29.0, 30.5, 36.5, 36.8, 44.9, 55.7, 56.0, 56.2, 64.3, 65.3, 107.4, 111.8, 125.3, 132.8, 147.7, 167.9, 169.7. LRMS (EI, 70 eV): *m*/*z* (%)=417 (M^+, 2), 361 (24), 360 (100), 286 (37), 260 (8), 259 (10), 258 (19), 244 (11), 200 (3), 91 (3), 57 (8). $C_{24}H_{35}NO_5$: calcd C 69.04, H 8.45, N 3.35; found C 68.99, H 8.37, N 3.41. Minor diastereomer **6e**, oil (31 mg, 31%): IR (KBr) ν=1735, 1691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.68 (d, *J*=7.1 Hz, 3H), 0.78 (t, *J*=6.7 Hz, 3H), 0.93 (t, *J*=7.3 Hz, 3H), 1.04–1.47 (m, 5H), 1.55–2.01 (m, 5H), 2.58–2.89 (m, 3H), 3.04 (d, *J*=1.6 Hz, 1H), 3.10 (dd, *J*=12.3, 4.4 Hz, 1H), 3.89 (s, 6H), 4.20 (td, *J*=6.7, 2.3 Hz, 2H), 4.4 (dd, *J*=13.1, 4.4 Hz, 1H), 6.53 (s, 1H), 6.58 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 13.8, 19.1, 23.2, 27.5, 28.9, 30.5, 37.4, 43.6, 43.0, 55.7, 56.1, 57.5, 65.6, 67.4, 108.9, 111.3, 127.3, 127.9, 147.6, 147.7, 168.1, 170.2. LRMS (EI, 70 eV): *m*/*z* (%)=417 (M^+, 2), 361 (24), 360 (100), 286 (32), 258 (16), 244 (11), 230 (4), 214 (3), 200 (3), 57 (6). $C_{24}H_{35}NO_5$: calcd C 69.04, H 8.45, N 3.35; found C 68.85, H 8.28, N 3.48.

*4.7.6. (1SR,2SR,10bSR)-1,10b-Dibutyl-2-butoxycarbonyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**5f**) and (1RS,2RS,10bSR)-1,10b-dibutyl-2-butoxycarbonyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**6f**)*

According to the general procedure, a solution of **4c** (98 mg, 0.24 mmol) in dry THF (5 mL) was treated with the organocuprate, prepared from CuI (233 mg, 1.32 mmol) and *n*-BuLi (1.5 mL of a 1.6 M solution in hexanes, 2.44 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **5f** and **6f** in a 66:34 diastereomeric ratio (87 mg, 78%). Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **5f**, oil (55 mg, 52%) (spectroscopic data are described above). Minor diastereomer **6f**, oil (30 mg, 26%). IR (KBr) ν=1730, 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.66–0.87 (m, 6H), 0.94 (t, *J*=7.3 Hz, 3H), 1.00–1.50 (m, 10H), 1.60–2.04 (m, 6H), 2.58–2.66 (m, 2H), 2.75 (dd, *J*=15.5, 5.5 Hz, 1H), 3.08 (td, *J*=12.3, 4.4 Hz, 1H), 3.21 (s, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.21 (t, *J*=6.7 Hz, 2H), 4.43 (dd, *J*=12.3, 5.5 Hz, 1H), 6.52 (s, 1H), 6.57 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 13.8, 13.9, 19.1, 22.1, 23.2, 27.5, 28.3, 29.1, 30.4, 30.5, 37.6, 44.3, 48.5, 54.4, 55.7, 56.1, 65.6, 67.6, 109.1, 111.3, 127.4, 128.1, 147.6, 147.7, 168.3, 170.7. LRMS (EI, 70 eV): *m*/*z* (%)=459 (M^+, <1), 431 (1), 375 (22), 374 (100), 328 (27), 302 (31), 300 (7), 258 (5), 244 (2), 57 (10), 55 (1). $C_{27}H_{41}NO_5$: calcd C 70.56, H 8.99, N 3.05; found C 70.38, H 9.11, N 3.12.

4.8. (1*SR*,10b*SR*)-8,9-Dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (7)

A solution of (1*SR*,2*SR*,10b*SR*)-**5a** (163 mg, 0.4 mmol) in MeOH (30 mL) was treated with hydrogenated (H_2, 20 psi) in the presence of Pd/C (0.2 mmol) at rt for 2 days. The crude reaction mixture was filtered through Celite and the solvent evaporated. The residue was dissolved in toluene (5 mL) and the solution heated under reflux for 12 h. Flash column chromatography (silica gel, AcOEt) afforded the pyrroloisoquinolone **7** (10 mg, 44%): IR (KBr) ν=1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.37 (d, *J*=5.9 Hz, 3H), 1.40 (s, 3H), 2.20–2.40 (m, 2H), 2.49 (dd, *J*=13.5, 6.3 Hz, 1H), 2.59–2.66 (m, 1H), 2.80–3.02 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.28–4.35 (m, 1H), 6.58 (s, 1H), 6.75 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=15.1, 21.5, 29.0, 34.4, 39.2, 40.3, 55.8, 56.0, 62.9, 107.8, 111.8, 125.1, 134.6, 147.7, 171.4. LRMS (EI, 70 eV): *m*/*z* (%)=276 (M^++1, 4), 275 (M^+, 17), 261 (17), 260 (M^+-15, 100), 245 (3), 244 (6), 216 (3), 205 (4), 204 (4), 190 (3), 130 (3), 57 (2). $C_{16}H_{21}NO_3$: calcd C 69.79, H 7.69, N 5.09; found: C 69.89, H 7.86, N 4.77.

4.9. (1*RS*,10b*SR*)-10b-Butyl-8,9-dimethoxy-1-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (8)

NaOH (70 mg, 1.7 mmol) was added to a solution of (1*RS*,2*RS*,10b*SR*)-**6e** (26 mg, 0.07 mmol) in THF:H_2O:MeOH (3:2:1) (2 mL) at rt, and the resulting mixture was stirred for 12 h. H_2O (5 mL) was added and the reaction mixture was extracted with AcOEt (10 mL). The aqueous phase was treated with 1 M HCl till pH=1 and was extracted with AcOEt (3×10 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in toluene (3 mL) and the solution heated under reflux for 12 h. Flash column chromatography (silica gel, AcOEt) afforded **8** (17 mg, 86%) as a white solid: mp (AcOEt) 120–122 °C; IR (KBr) ν=1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.56 (d, *J*=6.7 Hz, 3H), 0.81 (t, *J*=7.1 Hz, 3H), 1.10–1.37 (m, 4H), 1.74–2.04 (m, 3H), 2.30–3.07 (m, 5H), 3.86 (s, 6H), 4.40 (dd, *J*=12.3, 4.8 Hz, 1H), 6.5 (s, 1H), 6.60 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.9, 18.4, 23.3, 28.9, 36.2, 38.9, 40.0, 42.5, 38.9, 55.7, 56.1, 67.7, 108.8, 111.3, 127.0, 129.0, 147.4, 147.7, 172.9. LRMS (EI, 70 eV): *m*/*z* (%)=317 (M^+, 1), 262 (2), 261 (16), 260 (100), 244 (4), 216 (2), 130 (4), 83 (2). $C_{19}H_{27}NO_3$: calcd C 71.89, H 8.57, N 4.41; found: C 71.84, H 8.53, N 4.28.

4.10. Tandem conjugate addition of organocuprates/α-alkylation reactions on pyrrolo[2,1-*a*]isoquinolone 3a. General procedure

Methyllithium (6 mmol) was added drop wise over a suspension of CuI (3 mmol) in dry THF (10 mL) at 0 °C. After 30 min, the mixture was cooled to −78 °C, and a solution of lactam **4a** (1 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 3 h, allowed to warm up to 0 °C, and stirred at this temperature for 12 h. After allowing the mixture to warm up to rt, methyl or allyl iodide (1.2 mmol) was added and the reaction mixture was stirred for

24 h. The reaction was quenched by sequential addition of NH_4OH (12% aq) (10 mL), the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silicagel, 70% hexane/AcOEt) afforded pyrroloisoquinolones **9**.

*4.10.1. (1SR,2RS,10bSR)-2-Benzyloxycarbonyl-8,9-dimethoxy-1,2,10b-trimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**9a**) and (1SR,2SR,10bSR)-2-benzyloxycarbonyl-8,9-dimethoxy-1,2,10b-trimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**9a**′)*

According to the general procedure, a solution of **4a** (144 mg, 0.4 mmol) in dry THF (10 mL) was treated with the organocuprate, prepared from CuI (209 mg, 1.1 mmol) and MeLi (1.4 mL of a 1.6 M solution in hexanes, 2.2 mmol) and quenched by addition of MeI (0.03 mL, 04 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **9a** and **9a**′ in an 86:14 diastereomeric ratio (88 mg, 57%). Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **9a**, oil (76 mg, 49%): IR (KBr) ν=1733, 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.25 (d, J=7.5 Hz, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 2.24 (q, J=7.5 Hz, 1H), 2.64 (dd, J=15.7, 3.0 Hz, 1H), 2.89 (ddd, J=15.7, 12.3, 6.3 Hz, 1H), 3.12 (td, J=12.3, 4.4 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 4.40 (dd, J=12.9, 5.0 Hz, 1H), 5.12 (d, J=12.3 Hz, 1H), 5.28 (d, J=12.3 Hz, 1H), 6.55 (s, 1H), 6.64 (s, 1H), 7.27–7.39 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=11.8, 21.7, 22.6, 28.7, 35.0, 50.7, 55.8, 56.0, 56.4, 61.8, 67.0, 107.4, 111.7, 124.4, 128.4, 128.5, 128.6, 135.3, 135.8, 147.7, 147.8, 170.7, 171.5. LRMS (EI, 70 eV): m/z (%)=424 (M^++1, 6), 423 (M^+, 22), 409 (27), 408 (M^+−15, 100), 274 (6), 273 (6), 258 (22), 91 (24), 83 (6), 55 (6). $C_{25}H_{29}NO_5$: calcd C 70.90, H 6.90, N 3.31; found C 70.68, H 7.03, N 3.24. Minor diastereomer **9a**′, oil (12 mg, 8%): IR (KBr) ν=1743, 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.99 (d, J=7.5 Hz, 3H), 1.53 (s, 3H), 1.58 (s, 3H), 2.33–2.48 (m, 1H), 2.56–2.70 (m, 1H), 2.82–2.94 (m, 1H), 3.08 (td, J=12.7, 3.2 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 4.27–4.35 (m, 1H), 4.68 (d, J=12.3 Hz, 1H), 4.83 (d, J=12.3 Hz, 1H), 6.36 (s, 1H), 6.47 (s, 1H), 6.96–7.28 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.5, 21.1, 28.9, 32.7, 35.7, 50.7, 56.0, 56.2, 63.6, 66.6, 107.9, 112.0, 127.4, 128.0, 128.2, 128.3, 130.4, 135.9, 147.1, 148.1, 171.4, 172.9. LRMS (EI, 70 eV): m/z (%)=424 (M^++1, 5), 423 (M^+, 20), 422 (15), 409 (28), 408 (M^+−15, 100), 273 (5), 258 (25), 91 (21), 85 (15), 83 (26), 71 (8), 57 (11), 55 (9). $C_{25}H_{29}NO_5$: calcd C 70.90, H 6.90, N 3.31; found C 70.58, H 7.05, N 3.26.

*4.10.2. (1SR,2RS,10bSR)-2-Allyl-2-benzyloxycarbonyl-8,9-dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**9b**) and (1SR,2SR,10bSR)-2-allyl-2-benzyloxycarbonyl-8,9-dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**9b**′)*

According to the general procedure, a solution of **4a** (151 mg, 0.4 mmol) in dry THF (10 mL) was treated with the organocuprate, prepared from CuI (220 mg, 1.1 mmol) and MeLi (1.43 mL of a 1.6 M solution in hexanes, 2.3 mmol) and quenched by addition of $CH_2{=}CHCH_2I$ (0.04 mL, 0.5 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **9b** and **9b**′ in an 80:20 diastereomeric ratio (83 mg, 50%). Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **9b**, oil (67 mg, 40%): IR (KBr) ν=1730, 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.20 (d, J=7.1 Hz, 3H), 1.39 (s, 3H), 2.44 (q, J=7.1 Hz, 1H), 2.52–2.88 (m, 4H), 3.02–3.14 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 4.40 (dd, J=13.1, 4.7 Hz, 1H), 4.94–5.04 (m, 2H), 5.12 (d, J=12.3 Hz, 1H), 5.30 (d, J=12.3 Hz, 1H), 5.51–5.67 (m, 1H), 6.53 (s, 1H), 6.61 (s, 1H), 7.26–7.39 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=11.8, 23.0, 29.0, 37.9, 35.2, 45.2, 55.7, 55.9, 59.8, 61.9, 67.0, 107.3, 111.6, 119.9, 124.4, 128.4, 128.5, 128.7, 132.7, 135.2, 135.6, 147.7, 147.7, 169.3, 171.0. LRMS (EI, 70 eV): m/z (%)=450 (M^++1, 7), 449 (M^+, 23), 436 (27), 434 (M^+−15, 100), 300(13), 298 (11), 284 (13), 258 (27), 91 (72), 83 (11), 71 (15), 57 (19), 55 (11). $C_{27}H_{31}NO_5$: calcd C 72.14, H 6.95, N 3.12; found C 72.21, H 7.29, N 2.97. Minor diastereomer **9b**′, oil (16 mg, 10%): IR (KBr) ν=1736, 1687 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.98 (d, J=7.1 Hz, 3H), 1.53 (s, 3H), 2.28–2.36 (m, 1H), 2.47–2.60 (m, 2H), 2.80–2.93 (m, 2H), 3.05 (td, J=12.7, 3.6 Hz, 1H), 3.79 (s, 3H), 3.83 (s, 3H), 4.26–4.33 (m, 1H), 4.68 (d, J=11.9 Hz, 1H), 4.78 (d, J=11.9 Hz, 1H), 5.14–5.21 (m, 2H), 5.70–5.86 (m, 1H), 6.32 (s, 1H), 6.47 (s, 1H), 6.87–7.25 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=12.9, 28.1, 32.5, 36.7, 36.8, 45.2, 55.7, 55.9, 59.3, 63.4, 66.7, 110.4, 111.9, 119.8, 127.5, 128.1, 128.2, 128.6, 130.3, 133.5, 134.9, 146.4, 147.2, 170.6, 172.0. LRMS (EI, 70 eV): m/z (%)=450 (M^++1, 11), 449 (M^+, 36), 435 (30), 434 (M^+−15, 100), 284 (13), 258 (25), 91 (37), 79 (4), 71 (6), 57 (7), 55 (4). $C_{27}H_{31}NO_5$: calcd C 72.14, H 6.95, N 3.12; found C 72.33, H 7.7.31, N 2.94.

4.11. Conjugate addition reactions of enolate anions to pyrrolo[2,1-*a*]isoquinolones 4a,b. General procedure

Methyl cyanoacetate or dimethyl malonate (2 mmol) was added drop wise over a solution of $NaNH_2$ (1 mmol) and DMPU (22 or 12 mmol) in dry THF (30 mL) at rt. After 5 min, a solution of lactams **4a**,**b** (1 mmol) in dry THF (10 mL) was added. The reaction mixture was heated under reflux for 3–8 h. Then the reaction was quenched by addition of H_2O (10 mL) at rt. The organic layer was separated, and the aqueous phase was extracted with AcOEt (3×15 mL). The combined organic extracts were washed H_2O (2×10 mL) and NaCl (sat) (2×10 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography afforded pyrroloisoquinolones **10** and/or **11**.

*4.11.1. (1RS,2SR,10bSR)-2-Benzyloxycarbonyl-1-(cyano-methoxycarbonylmethyl)-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**10a**)*

According to the general procedure, **4a** (195 mg, 0.5 mmol) was treated with a solution of $NaNH_2$ (20 mg, 0.5 mmol), DMPU (1.3 mL, 10.9 mmol) and methyl cyanoacetate (0.1 mL, 1.0 mmol) in dry THF (15 mL) for 3 h under reflux. Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded **10a** (157 mg, 64%) as a white solid: mp (AcOEt) 185–186 °C. IR (KBr) ν=1755, 1700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.65 (s, 3H), 2.63–2.70 (m, 1H), 2.89 (ddd, J=15.6, 11.1, 5.5 Hz, 1H), 3.02–3.14 (m, 1H), 3.41 (dd, J=11.1, 2.0 Hz, 1H), 3.56 (s, 3H,), 3.84 (s, 3H), 3.86 (s, 3H), 4.02 (d, J=11.1 Hz, 1H), 4.23–4.30 (m, 1H), 4.29 (d, J=2.0 Hz, 1H), 5.18 (s, 2H), 6.59 (s, 1H), 6.65 (s, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=23.5, 28.4, 35.4, 38.5, 47.5, 51.5, 53.9, 55.8, 56.3, 61.6, 67.6, 106.9, 112.2, 114.8, 125.3, 132.3, 135.1, 127.9, 128.1, 128.4, 148.1, 148.5, 164.7, 165.0, 168.2. LRMS (EI, 70 eV): m/z (%)=492 (M^+, 2), 477 (M^+−15, 2), 393 (13), 380 (23), 379 (25), 378 (100), 350 (8), 322 (27), 284 (10), 246 (20), 245 (21), 244 (53), 149 (8), 105 (14), 97 (12), 92 (9), 91 (95), 85 (21), 83 (18), 79 (12), 77 (12), 71(24), 69 (19), 68 (31), 67 (10), 65 (12), 59 (41), 57 (42), 55 (26). $C_{27}H_{28}N_2O_7$: calcd C 65.84, H 5.73, N 5.69; found: C 65.45, H 5.50, N 5.40.

*4.11.2. (1RS,2SR,10bSR)-2-Benzyloxycarbonyl-10b-butyl-1-(cyanomethoxycarbonylmethyl)-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**10b**)*

According to the general procedure, **4b** (207 mg, 0.5 mmol) was treated with a solution of $NaNH_2$ (20 mg, 0.5 mmol), DMPU (1.3 mL, 10.9 mmol) and methyl cyanoacetate (0.1 mL, 1.0 mmol) in dry THF (15 mL) for 3 h under reflux. Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded **10b** (141 mg, 64%yield, 76% conversion) as an oil: IR (KBr) ν=1750, 1692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.82 (t, J=7.1 Hz, 3H), 1.01–1.40 (m, 4H), 1.97–2.03 (m, 2H), 2.64 (dd, J=13.9, 2.0 Hz, 1H), 2.76–2.89 (m,

1H), 2.97–3.09 (m, 1H), 3.22 (dd, *J*=11.9, 2.0 Hz, 1H), 3.53 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.06 (d, *J*=11.9 Hz, 1H), 4.23 (d, *J*=2.0 Hz, 1H), 4.40 (dd, *J*=12.9, 4.2 Hz, 1H), 5.18 (d, *J*=2.0 Hz, 2H), 6.59 (s, 1H), 6.65 (s, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 22.9, 27.1, 29.4, 37.2, 38.0, 37.5, 49.5, 51.7, 53.9, 55.8, 56.4, 64.6, 67.7, 106.9, 112.6, 114.6, 126.5, 129.7, 135.2, 127.9, 128.2, 128.5, 148.2, 148.5, 165.0, 166.4, 168.4. LRMS (EI, 70 eV): *m*/*z* (%)=535 (M^++1, 4), 534 (M^+, 10), 478 (30), 477 (M^+−57, 100), 379 (22), 378 (84), 342 (20), 316 (35), 284 (7), 245 (8), 244 (33), 91 (62), 59 (8). $C_{30}H_{34}N_2O_7$: calcd C 67.40, H 6.41, N 5.24; found: C 67.44, H 6.43, N 5.26.

*4.11.3. (1SR,2RS,10bSR)-2-Benzyloxycarbonyl-1-[bis(methoxycarbonyl)methyl]-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**11c**) and (1RS,2SR,10bSR)-2-benzyloxycarbonyl-1-[bis(methoxycarbonyl)methyl]-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**10c**)*

According to the general procedure, **4a** (100 mg, 0.25 mmol) was treated with a solution of $NaNH_2$ (10 mg, 0.25 mmol), DMPU (0.4 mL, 3.3 mmol) and dimethyl malonate (0.06 mL, 0.5 mmol) in dry THF (10 mL) for 4 h under reflux. Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **11c** and **10c** in an 80:20 diastereomeric ratio (81 mg, 61%). Both diastereomers were separated by chromatography and characterized separately. Major diastereomer **11c**, oil (65 mg, 49%): IR (KBr) ν=1750, 1692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.66 (s, 3H), 2.49 (dd, *J*=15.5, 2.2 Hz, 1H), 2.72 (ddd, *J*=15.5, 12.3, 5.1 Hz, 1H), 2.92 (ddd, *J*=12.6, 12.3, 3.6 Hz, 1H), 3.25 (s, 3H), 3.47–3.50 (m, 4H), 3.67 (d, *J*=3.9 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 3.92 (d, *J*=1.9 Hz, 1H), 4.33 (dd, *J*=12.7, 5.1 Hz, 1H), 5.18 (d, *J*=12.3 Hz, 1H), 5.27 (d, *J*=12.3 Hz, 1H), 6.50 (s, 1H), 6.51 (s, 1H), 7.28–7.41 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=28.4, 31.0, 35.4, 46.7, 51.8, 52.4, 52.7, 55.8, 56.2, 63.1, 67.3, 109.8, 111.4, 127.5, 128.1, 128.4, 128.5, 135.5, 147.8, 148.1, 166.3, 166.7, 168.4, 169.7. LRMS (EI, 70 eV): *m*/*z* (%)=526 (M^++1, 9), 525 (M^+, 5), 511 (31), 510 (99), 434 (12), 403 (12), 402 (52), 401 (13), 374 (28), 342 (31), 244 (43), 206 (10), 107 (10), 91 (100), 65 (13), 59 (10). $C_{28}H_{31}NO_9$: calcd C 63.99, H 5.94, N 2.66; found: C 63.97, H 5.97, N 2.68. Minor diastereomer **10c**, oil (16 mg, 12%): IR (KBr) ν=1739, 1692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.46 (s, 3H), 2.57–2.62 (m, 1H), 2.86–3.08 (m, 2H), 3.56 (dd, *J*=9.5, 5.1 Hz, 1H), 3.61 (s, 3H), 3.71 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.07 (d, *J*=5.1 Hz, 1H), 4.16 (d, *J*=15.5 Hz, 1H), 4.23–4.36 (m, 1H), 5.14 (s, 2H), 6.54 (s, 1H), 6.74 (s, 1H), 7.27–7.31 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=23.8, 28.5, 35.5, 46.6, 50.8, 51.1, 52.9, 53.0, 55.7, 56.1, 62.5, 67.2, 107.7, 111.9, 125.3, 127.9, 128.3, 132.8, 135.4, 147.8, 148.0, 166.8, 168.2, 169.0. LRMS (EI, 70 eV): *m*/*z* (%)=526 (M^++1, 19), 525 (M^+, 34), 511 (11), 510 (36), 434 (13), 403 (7), 402 (32), 401 (8), 379 (11), 374 (18), 344 (10), 342 (21), 244 (31), 206 (28), 107 (11), 91 (100), 65 (13), 59 (9). $C_{28}H_{31}NO_9$: calcd C 63.99, H 5.94, N 2.66; found: C 63.94, H 5.96, N 2.69.

*4.11.4. (1SR,2RS,10bSR)-2-Benzyloxycarbonyl-1-[bis(methoxycarbonyl)methyl]-10b-butyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-one (**11d**)*

According to the general procedure, **3b** (105 mg, 0.24 mmol) was treated with a solution of $NaNH_2$ (9.44 mg, 0.24 mmol), DMPU (0.38 mL, 3.15 mmol) and dimethyl malonate (0.05 mL, 0.48 mmol) in dry THF (5 mL) for 6 h under reflux. Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded **11d** (62 mg, 51% yield, 90% conversion) as an oil: IR (KBr) ν=1735, 1690 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.74 (t, *J*=6.7 Hz, 3H), 0.77–1.40 (m, 4H), 1.90–2.16 (m, 2H), 2.33–2.67 (m, 1H), 2.70–2.97 (m, 1H), 3.01–3.26 (m, 1H), 3.27 (s, 3H), 3.41–3.50 (m, 1H), 3.51 (s, 3H), 3.61 (d, *J*=4.3 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 3.93–3.95 (m, 1H), 4.41 (dd, *J*=12.3, 5.5 Hz, 1H), 5.24 (s, 2H), 6.63 (s, 2H), 7.25–7.43 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.7, 22.9, 27.3, 28.4, 37.9, 45.8, 47.4, 51.8, 52.1, 52.5, 52.7, 55.8, 56.2, 66.2, 67.4, 109.5, 111.4, 126.5, 128.2, 128.8, 128.3, 128.5, 135.5, 147.9, 148.1, 166.8, 167.9, 168.6, 169.8. LRMS (EI, 70 eV): *m*/*z* (%)=567 (M^+, 1), 511 (33), 510 (100), 420 (24), 403 (14), 402 (58), 401 (12), 376 (28), 374 (24), 342 (36), 379 (24), 378 (93), 316 (22), 24 (43), 91 (70), 57 (10). $C_{31}H_{37}NO_9$: calcd C 65.59, H 6.57, N 2.47; found: C 65.62, H 6.59, N 2.46.

4.12. (1*RS*,2*RS*,10b*SR*)-2-Benzylcarbonyl-1-(1,1,1,3,3,3-hexamethyldisilazan-2-yl)-10b-methyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (12)

A solution of lactam **4a** (110 mg, 0.28 mmol) in dry THF (5 mL) was added via canola to a solution of LiHMDS (0.4 mL of a 0.7 M solution in hexanes, 0.28 mmol) at −78 °C. After 10 min, the reaction mixture was allowed to reach rt and stirred at this temperature for 24 h. Then the reaction was quenched by addition of 12% NH_4OH (10 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (1×10 mL) and CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (silicagel, MeOH/$CHCl_3$ 96%) afforded pyrroloisoquinolone **12** (114 mg, 71%) as a single diastereomer: oil; IR (KBr) ν=1740, 1694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=−0.12 (s, 6H), −0.08 (s, 3H), 0.35 (s, 6H), 0.40 (s, 3H), 1.61 (s, 3H), 2.56–2.62 (m, 1H), 2.84–2,91 (m, 2H), 3.86–3.93 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.10 (d, *J*=11.1, Hz, 1H), 4.35–4.41 (m, 1H), 5.19 (d, *J*=4.8, Hz, 2H), 6.58 (s, 1H), 6.78 (s, 1H), 7.33–7.34 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=3.1, 5.6, 24.0, 29.3, 35.0, 55.2, 55.7, 56.3, 63.8, 67.0, 67.4, 110.2, 111.8, 125.6, 128.1, 128.2, 128.4, 131.5, 135.3, 147.3, 147.9, 166.8, 169.6. LRMS (EI, 70 eV): *m*/*z* (%)=555 (M^++1, 5), 554 (M^+, 12), 539 (6), 455 (8), 378 (22), 364 (19), 306 (15), 262 (8), 258 (11), 244 (11), 214 (13), 206 (47), 205 (100), 204 (9), 190 (12), 146 (14), 130 (8), 100 (7), 99 (6), 91 (63), 79 (5), 77 (5), 73 (39), 65 (5). $C_{29}H_{42}N_2O_5Si_2$: calcd C 62.78, H 7.63, N 5.05; found: C 62.49, H 7.46, N 5.12.

4.13. (1*SR*,2*SR*,10b*SR*)-1-Benzylamino-2-*N*-benzylcarbamoyl-10b-methyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (13)

Benzylamine (0.04 mL, 0.4 mmol) and water (0.02 mL, 1.0 mmol) were added drop wise over lactam **4d** (80 mg, 0.2 mmol) at rt and the reaction mixture was stirred for 18 h. Crystallization from ethyl acetate afforded **13a** (71 mg, 72%) as a white solid: mp (AcOEt) 125–126 °C. IR (KBr) ν=3300, 1690, 1660 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.55 (s, 3H), 1.55–1.64 (br s, 1H), 2.67 (dd, *J*=15.7, 3.4 Hz, 1H), 2.82–2.96 (m, 1H), 3.08 (td, *J*=12.7, 4.0 Hz, 1H), 3.23 (d, *J*=10.3 Hz, 1H), 3.69 (s, 3H), 3.82 (d, *J*=10.3 Hz, 1H), 3.84 (s, 3H), 3.92 (d, *J*=13.5 Hz, 1H), 4.33 (d, *J*=13.5 Hz, 1H), 4.30–4.36 (m, 1H), 4.45 (dd, *J*=15.0, 5.5 Hz, 1H), 4.58 (dd, *J*=15.0, 6.1 Hz, 1H), 6.54 (s, 1H), 7.22–7.46 (m, 11H), 7.81 (t, *J*=5.5 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=22.6, 28.3, 34.7, 43.5, 53.4, 53.9, 55.8, 61.3, 65.9, 107.8, 111.0, 123.6, 126.9, 127.3, 127.5, 127.6, 128.3, 128.6, 133.4, 138.0, 140.8, 147.8, 147.9, 167.1, 167.8. LRMS (EI, 70 eV): *m*/*z* (%)=499 (M^+, 3), 485 (22), 484 (67), 377 (40), 272 (35), 245 (25), 244 (15), 115 (9), 107 (18), 99 (11), 97 (23), 91 (36), 77 (6). $C_{30}H_{33}N_3O_4$: calcd C 72.12, H 6.66, N 8.41; found: C 72.33, H 6.82, N 8.34.

4.14. (10b*R*)-(+)-2-[(1*S*,2*R*,4*R*,*SR*)-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methylsulfinyl]-8,9-dimethoxy-10b-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-one [(10b*R*)-15]

A solution of isoindoloisoquinoline (10b*R*)-**14**[9b] (84 mg, 0.16 mmol) in *o*-DCB (5 mL) was refluxed for 24 h. The evolution of the reaction was monitored by ^{1}H NMR. The crude product was

purified by column chromatography (silica gel, 98% ethyl acetate/NEt_3) to afford dihydropyrroloisoquinoline (10b*R*)-**15** (33 mg, 54%) as a white solid: mp (pentane) 109–110 °C; $[\alpha]_D^{23}$ +99.8 (*c* 0.5, $CHCl_3$). The enantiomeric excess determined on the corresponding desulfinylated product [(10b*R*)-(+)-8,9-dimethoxy-10b-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-one[9b]] by CSP HPLC was >99% by comparison with the racemic mixture. Chiralcel OD, 20% hexane/2-propanol, 0.4 mL/min; t_R [(10b*R*)]=23.2 min (>99%); t_R[(10b*S*)]=21.9 min (<1%): IR (KBr) ν=3482, 1676, 1010 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.86 (s, 3H), 1.03–1.07 (m, 2H), 1.07 (s, 3H), 1.20–1.31 (m, 1H), 1.49–1.56 (m, 1H), 1.59 (s, 3H), 1.65–1.81 (m, 3H), 2.67 (dd, *J*=16.1, 4.0 Hz, 1H), 2.81 (d, *J*=11.0 Hz, 1H), 2.88–3.00 (m, 1H), 3.06 (d, *J*=11.0 Hz, 1H), 3.22–3.27 (m, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 3.95–3.97 (m, 1H), 4.43 (dd, *J*=13.2, 6.4 Hz, 1H), 6.59 (s, 1H), 6.71 (s, 1H) 6.99 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=20.0, 20.7, 27.1, 27.2, 29.3, 30.4, 31.2, 35.1, 39.2, 45.2, 47.7, 51.8, 55.8, 56.2, 64.4, 76.1, 109.1, 111.9, 124.9, 129.3, 133.6, 144.3, 147.7, 148.2, 167.4. LRMS (EI, 70 eV): *m*/*z* (%)=459 (M^+, <1), 127 (6), 125 (6), 113 (7), 111 (9), 99 (10), 98 (6), 97 (15), 95 (7), 86 (9), 85 (62), 84 (8), 83 (100), 82 (7), 81 (9), 71 (35), 70 (18), 69 (33), 67 (12), 57 (77), 56 (14), 55 (51). $C_{25}H_{33}NO_5S$: calcd C 65.33, H 7.24, N 3.05; found: C 65.63, H 7.48, N 2.95.

4.15. (1*R*,2*R*,10b*R*)-(+)-2-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-ylmethylsulfinyl)-8,9-dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one [(1*R*,2*R*,10b*R*)-16]

Methylmagnesium chloride (1.01 mL of a 3.0 M solution in THF, 3.04 mmol) was added drop wise over a suspension of CuI (289 mg, 1.52 mmol) in dry THF (7 mL) at −20 °C. After 15 min, the mixture was cooled to −78 °C, and a solution of lactam **15** (70 mg, 0.15 mmol) and TMSCl (0.04 mL, 0.30 mmol) in dry THF (3 mL) was added. The reaction mixture was allowed to warm up to 0 °C, and stirred at this temperature for 16 h. The reaction was quenched by sequential addition of NH_4OH (12% aq) (20 mL) and NH_4Cl (satd) (10 mL) at 0 °C. After allowing the mixture to warm up to rt, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silicagel, 70% hexane/AcOEt, 2% NEt_3) afforded tetrahydropyrroloisoquinolone (1*R*,2*R*,10b*R*)-**16** (41 mg, 56%) as an oil: $[\alpha]_D^{23}$ +131.3 (*c* 0.5, $CHCl_3$). The enantiomeric excess was determined on the corresponding desulfinylated product (see below). IR (KBr) ν=3422, 1675 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.73 (s, 3H), 0.97 (s, 3H), 1.01–1.09 (m, 1H), 1.13–1.25 (m, 1H), 1.39–1.47 (m, 1H), 1.43 (s, 3H), 1.50 (d, *J*=6.7 Hz, 3H), 1.57–1.79 (m, 4H), 2.15–2.20 (m, 2H), 2.49 (d, *J*=10.7 Hz, 1H), 2.67 (dd, *J*=16.0, 2.1 Hz, 1H), 2.78–2.84 (m, 1H), 2.98–3.04 (m, 1H), 3.21 (d, *J*=11.7 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.03–4.06 (m, 1H), 4.31 (br s, 1H), 4.42 (dd, *J*=12.8, 5.4 Hz, 1H), 6.60 (s, 1H), 6.75 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=13.1, 19.8, 20.6, 22.0, 27.1, 29.5, 29.9, 35.3, 38.7, 45.0, 46.1, 47.4, 51.8, 53.4, 55.8, 56.1, 61.6, 75.8, 108.0, 111.9, 125.0, 133.4, 147.8, 147.9, 169.7. LRMS (EI, 70 eV): *m*/*z* (%)=459 (M^+, <1), 127 (6), 125 (6), 113 (7), 111 (9), 99 (10), 98 (6), 97 (15), 95 (7), 86 (9), 85 (62), 84 (8), 83 (100), 82 (7), 81 (9), 71 (35), 70 (18), 69 (33), 67 (12), 57 (77), 56 (14), 55 (51). $C_{26}H_{37}NO_5S$: calcd C 65.65, H 7.84, N 2.94; found: C 65.89, H 7.96, N 2.83.

4.16. (1*R*,10b*R*)-(+)-8,9-Dimethoxy-1,10b-dimethyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one [(1*R*, 10b*R*)-7]

To a solution of (1*R*,10b*R*)-**16** (57 mg, 0.12 mmol) in dry THF (3 mL), *t*-BuOH (0.11 mL, 1.12 mmol), SmI_2 (12 mL of a 0.1 M solution in THF, 1.12 mmol), and HMPA (1.41 mL, 8.32 mmol) were added sequentially at rt. The resulting mixture was stirred at this temperature for 2 h and quenched by the addition of cold HCl (5 mL of a 1 M solution). Ethyl ether (5 mL) was added, the organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (3×10 mL) and brine (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (silicagel, AcOEt) afforded tetrahydropyrroloisoquinoline (1*R*,10b*R*)-**7** (18.5 mg, 56%) as an oil: $[\alpha]_D^{23}$+109.0 (*c* 0.1, $CHCl_3$). The enantiomeric excess determined by CSP HPLC was >99% by comparison with the racemic mixture. Chiralcel OD, 10% hexane/2-propanol, 0.4 mL/min; t_R [(1*R*,10b*R*)-**7**]=41.4 min (> 99%); t_R[(1*S*,10b*S*)-**7**]=46.7 min (<1%). The spectroscopic data were identical to those reported for the racemate.

Acknowledgements

Financial support from MICINN (CTQ2006-01903), Gobierno Vasco (GIC07/92-IT-227-07), and Universidad del País Vasco is gratefully acknowledged.

References and notes

1. For a general review on properties, synthesis, and reactivity of pyrrolo[2,1-a]-isoquinolines, see: Mikhailovskii, A. G.; Shklyaev, V. S. *Chem. Heterocycl. Comp. (Translation of Khimiya Geterotsiklicheskikh Soedinenii)* **1997**, *33*, 243–265.
2. (a) Apodaca, R.; Barbier, A. J.; Carruthers, N. I.; Gomez, L. A.; Keith, J. M.; Lovenberg, T. W.; Wolin, R. L PCT Int. Appl. WO 2006/38604 A1, 2006; See also (b) Keith, J. M.; Gomez, L. A.; Wolin, R. L.; Barbier, A. J.; Wilson, S. J.; Boggs, J. D.; Mazur, C.; Fraser, I. C.; Lord, B.; Aluisio, L.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2603–2607 and references therein.
3. Loesel, W.; Roos, O.; Schnorrenberger, G. U. S. Patent 4694085, 1987; *Chem. Abstr.* **1988**, *108*, 204513.
4. Kuo, R.-Y.; Wu, C.-C.; Chang, F.-R.; Yeh, J.-L.; Chen, I.-J.; Wu, Y.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 821–823.
5. (a) Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem.* **1998**, *31*, 2097–2102; (b) Niewoehner, U.; Zhang, C.; Fan, D.; Wang, Y.; Li, T.; Boyer, S. J.; Burke, J.; Raudenbush, B. C.; Wong, W. C.; Ying, S.; Wang, M.; Zhao, Q.; Carter, C. A.; Burkhardt, N.; Pernerstorfer, J.; Niewoehner, M. PCT Int. Appl., WO 03 051877 A1, 2003; available from: http://www.espacenet.com.
6. For a review, see, for instance: (a) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444–463; For some selected examples of pyrroloisoquinolones as intermediates in synthesis, see: Aporphines; (b) Castedo, L.; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1982**, *47*, 513–517; Protoberberines; (c) Cobas, A.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 6765–6769; Cephalotaxus alkaloids; (d) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885–888; Erythrina alkaloids: (e) Osante, I.; Sotomayor, N.; Lete, E. *Lett. Org. Chem.* **2004**, *1*, 323–325; (f) Zhang, F.; Simpkins, N. S.; Wilson, C. *Tetrahedron Lett.* **2007**, *48*, 5942–5947; Lamellarin alkaloids: (g) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363–1366; (h) You, Y.-C.; Wang, A.-L.; Li, D.-P.; Yang, G. *Biomed.Mat.* **2006**, *1*, L7–L9.
7. For reviews on Parham cyclization, see: (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305; (b) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Exeter, UK, 1995; Vol. 11, pp 66–92; (c) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems*; Atanassi, O., Spinelli, D., Eds.; Italian Society of Chemistry: Roma, 2001; Vol. 5, pp 393–418; (d) Mealy, M. M.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *649*, 59–67; (e) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275–300; (f) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255–9303; (g) Rappoport, Z.; Marek, I. The Chemistry of Organolithium Compounds. In *Patai Series: The Chemistry of Functional Groups*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2004; (h) Arrasate, S.; Sotomayor, N.; Lete, E. In *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; Vicario, J. L., Badía, D., Carrillo, L., Eds.; Research Signpost: Trivandrum, India, 2005; pp 223–248.
8. For reviews on *N*-acyliminium ion cyclisations, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416; (b) Hiemstra, H.; Speckamp, W. N. *The Alkaloids*; Academic: New York, NY, 1988; Vol. 32, pp 271–339; (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047–1082; (d) de Koning, H.; Speckamp, W. N. In *Stereoselective Synthesis [Houben-Weyl]*, Workbench ed. E21; Helmchen, G., Hoffmann, R. W., Muzler, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1952–2010; (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (f) Marson, C. M. *Arkivoc* **2001**, 1–16; (g) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628; (h) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352; (i) Dobbs, A. P.; Rossiter, S. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 3, pp 419–450; (j) Huang, P.-Q. *Synlett* **2006**, 1133–1149; (k) Remuson, R. *Beilstein J. Org. Chem.* **2007**, *3*, 1–8; http://bjoc.beilstein-journals.org/content/pdf/1860-5397-3-32.pdf.

9. (a) González-Temprano, I.; Lete, E.; Sotomayor, N. *Synlett* **2002**, 593–597; (b) González-Temprano, I.; Osante, I.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2004**, *69*, 3875–3885.
10. (a) Perlmutter, P. Conjugate Addition Reactions in Organic Synthesis. In *Tetrahedron Organic Chemistry Series*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon: Oxford, 1992; Vol. 9; (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806; (c) Leonard, J.; Díez-Barra, E.; Merino, S. E. *J. Org. Chem.* **1998**, 2051–2061; (d) Yamamguchi, M. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp 1121–1139; (e) Jha, S. C.; Joshi, N. N. *Arkivoc* **2002**, 167–196; (f) Iguchi, M.; Yamada, K.; Tomioka, K. Organolithiums in Enantioselective Synthesis. In *Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Berlin, 2003; Vol. 5, pp 21–36; (g) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596–2616; (h) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188; (i) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716; (j) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823; (k) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.
11. Brewster, A. G.; Broady, S.; Hughes, M.; Moloney, M. G.; Woods, G. *Org. Biomol. Chem.* **2004**, *2*, 1800–1810 and references therein.
12. See, for example: (a) Mpango, G. B.; Mahalanabis, K. K.; Damghani, Z. M.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823–4826; (b) Mpango, G. B.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4827–4830; (c) Hashimoto, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron* **1996**, *52*, 1931–1943; (d) Forns, P.; Díez, A.; Rubiralta, M. *Tetrahedron* **1996**, *52*, 3563–3574; (e) Forns, P.; Díez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882–7888; (f) Amat, M.; Pérez, P.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787–2790.
13. García, E.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2006**, *71*, 6776–6784.
14. Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719–730 and references therein.
15. (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084; (b) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681–8693; (c) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848; (d) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923.
16. Osante, I.; Abdullah, M. N.; Arrasate, S.; Sotomayor, N.; Lete, E. *Arkivoc* **2007**, 206–219.
17. For preliminary communication, see: Camarero, C.; González-Temprano, I.; Lete, E.; Sotomayor, N. *Synlett* **2007**, 1101–1105.
18. Etxarri, B.; González-Temprano, I.; Manteca, I.; Sotomayor, N.; Lete, E. *Synlett* **1999**, 1486–1488.
19. For representative examples of our synthetic work in this area, see: (a) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080–2092; (b) Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2001**, 1267–1277; (c) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, *5*, 1115–1117; (d) Osante, I.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2004**, *45*, 1253–1256; (e) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311–3324; (f) García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2005**, *70*, 10368–10374; (g) Ruiz, J.; Sotomayor, N.; Lete, E. *Tetrahedron* **2006**, *62*, 6182–6189; (h) Abdullah, M. N.; Arrassate, S.; Lete, E.; Sotomayor, N. *Tetrahedron* **2008**, *64*, 1329–1332; (i) Lage, S.; Villaluenga, I.; Sotomayor, N.; Lete, E. *Synlett* **2008**, 3188–3192; (j) Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Org. Lett.* **2009**, *11*, 1237–1240.
20. Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814–3819.
21. For the synthesis and properties of related systems, see: (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463–7471; (b) Cluzeau, J.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 1504–1512; (c) Landoni, N.; Lesma, G.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2007**, *72*, 9765–9768.
22. For a review, see: Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.
23. (a) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Treré, A. *J. Org. Chem.* **1993**, *58*, 5615–5619; (b) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700–702; (c) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616; (d) Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257–1260; (e) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (f) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052–9056; (g) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045–9048; (h) Sibi, M. P. *Org. Lett.* **2002**, *4*, 2933–2936; (i) Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 720–722; (j) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114.
24. BenAyed, T.; Amiri, H.; ElGaied, M. M.; Villieras, J. *Tetrahedron* **1995**, *51*, 9633–9642.
25. (a) Langlois, N.; Calvez, O. *Tetrahedron Lett.* **1998**, *39*, 857–860; (b) Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 9531–9533; (c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T.; Shankar, K. S. *Monatsh. Chem.* **2008**, *139*, 1317–1320.
26. You, L.; Feng, S.; An, R.; Wang, X.; Bai, D. *Tetrahedron Lett.* **2008**, *49*, 5147–5149.
27. For representative examples, see: (a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36–42; (b) Andres, C. J.; Lee, P. H.; Nguyen, T. H.; Meyers. *J. Org. Chem.* **1995**, *60*, 3189–3193; (c) Dyer, J.; Keeling, S.; Moloney, M. G. *Tetrahedron Lett.* **1996**, *37*, 4573–4576; (d) Dyer, J.; King, A.; Keeling, S.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2793–2804; (e) Mamal, A.; Hughes, N. E.; Wurthmann, A.; Madalengoitia, J. S. *J. Org. Chem.* **2000**, *66*, 6483–6486; (f) Chan, P. W. H.; Cottrel, J. F.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2997–3006. See also reference 21.
28. For selected reviews, see: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760; (b) Forristal, I.; Rayner, C. M. In *Advances in Sulfur Chemistry: Recent Advances in the Chemistry of α,β-Unsaturated Sulfoxides and Sulfones*; Rayner, C. M., Ed.; JAI: Stanford, 2000; pp 155–213; (c) Forristal, I. *J. Sulfur Chem.* **2005**, *26*, 163–195; (d) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559–5601.
29. For some representative examples, see: (a) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886–2888; (b) Marino, J. P.; Anna, L. J.; de la Pradilla, R. F.; Martinez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462–6473; (c) Matsuyama, H.; Itoh, N.; Matsumoto, A.; Ohira, N.; Hara, K.; Yoshida, M.; Iyoda, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2924–2930; (d) Garcia Ruano, J. L.; Cifuentes Garcia, M.; Laso, N. M.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2507–2509; (e) Garcia Ruano, J. L.; Cifuentes Garcia, M.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Org. Lett.* **2002**, *4*, 55–57; (f) Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281–288; (g) Sugiyama, S.; Satoh, T. *Tetrahedron: Asymmetry* **2005**, *16*, 665–673; (h) Piccardi, R.; Renaud, P. *Eur. J. Org. Chem.* **2007**, 4752–4757.