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Bicyclic Lactams

Simple Access to Highly Functional Bicyclic γ- and δ-Lactams: Origins of Chirality Transfer to Contiguous Tertiary/Quaternary Stereocenters Assessed by DFT

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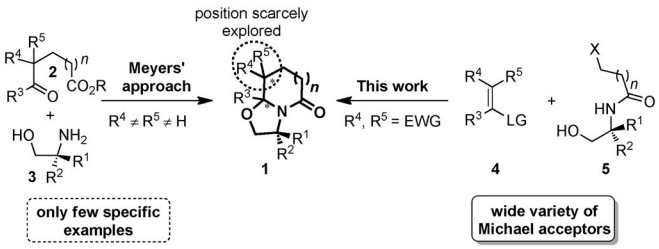
Dedicated to Dr. Cathy Kadouri on the occasion of her retirement

Abstract: This paper describes the synthesis of both polysubstituted oxazolo-pyrrolidinones and -piperidinones by a domino process. The methodology is based on the reaction between hydroxyl halogenoamides and Michael acceptors, which leads efficiently to bicyclic lactams. The process is compatible with unsymmetrical electron-withdrawing groups on the Michael acceptor, which allows the formation of two contiguous and fully controlled tertiary and quaternary stereocenters. In the case of tetrasubstituted Michael acceptors, two adjacent quaternary stereocenters are formed in good yield. Starting from (*R*)-phenylglycinol derived amides results in the formation of enantioenriched bicyclic lactams in low to good yields and with high levels of stereoselectivity, thus greatly increasing the scope and interest of this strategy. The origins of chirality transfer and diastereoselectivity were studied by DFT calculations and have been attributed to a kinetic control in one of the last two steps of the reaction sequence. This selectivity is dependent upon both the substituents on the Michael acceptor and the sodium cation chelation.

Introduction

Functionalized pyrrolidines, piperidines, and their corresponding lactams are important N-heterocyclic structures, and they are found in many biologically relevant compounds.[1] Nowadays, bicyclic lactams **1** are attractive scaffolds for the synthesis of compounds that are based on such five- and six-membered ring systems (Scheme 1).[2] These building blocks were first prepared by Meyers through a stereocontrolled cyclodehydration of a δ- or γ-keto acid/ester **2** and a chiral amino alcohol, such as (*R*)-phenylglycinol **3**, and they are still used as key intermediates in current total syntheses. As these bicyclic lactams are efficient templates for the synthesis of functionalized N-heterocycles, many alternative strategies for their preparation have been developed in recent years[3] in conjunction with the total synthesis of enantioenriched natural or synthetic products.[4]



Scheme 1. Meyers' approach and our synthetic route to bicyclic lactams **1**.

To this end, considerable effort has been focused on the stereoselective functionalization of the lactam ring, and important contributions in this field of research have been published by Amat and Bosch.[5] These authors managed to synthesize polysubstituted oxazolo-piperidinones that contained a tertiary or quaternary stereocenter ($R^4 \neq R^5$) at the 5-position of the piperidine ring[6] by a smart, dynamic kinetic resolution and desymmetrization process.[7] However, Meyers' methodology to access such substituted bicyclic lactams presents two major drawbacks that limit its scope: 1) it is restricted to prochiral, δ-oxo diesters, and 2) to the best of our knowledge, no example of oxazolo pyrrolidinones has been described.

Considering our interest in tandem/domino reactions,[8] which are powerful tools for the formation of multiple bonds

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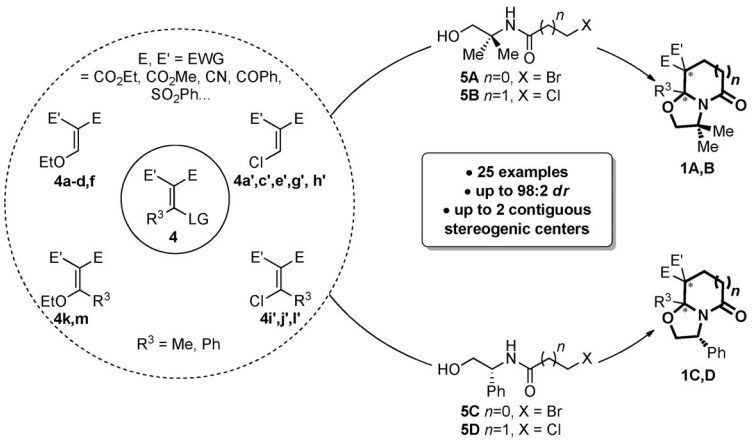
in one synthetic operation,[9] we have recently reported a new acid-free domino process for the synthesis of oxazolo-pyrrolidinones or -piperidinones, which was optimized by an ab initio study.[10] However, in this preliminary paper the scope of this process was limited to simple substrates and no stereoselective approaches were described. Nevertheless, with the help of a complementary DFT study the process was identified to proceed through a multistep sequence, which involved up to four transition states. Herein, we present our findings on the diastereoselective synthesis of bicyclic γ- and δ-lactams **1**, in a one-pot domino reaction from commercially available or easily synthesized Michael acceptors **4** or **4′** and amido alcohols **5 A–D** (Schemes 1 and 2). This domino process is compatible with a wide variety of Michael acceptors, both symmetrical (E=E′) and unsymmetrical (E≠E′). For the latter, this methodology allows the formation of two contiguous stereogenic centers in high dr and good yield. Notably, the construction of quaternary stereocenters that bear two electron-withdrawing groups, which are unavailable by classical approaches, can be formed through this process. Furthermore, this domino reaction is compatible with chiral amido alcohols **5 C** and **5 D**, derived from (*R*)-phenylglycinol, which enable the formation of enantioenriched γ- and δ-lactams, respectively, with high levels of diastereocontrol and, in some cases, double chirality transfer (bottom part of Scheme 2). This diastereoselective process was extended to a variety of structures and is rationalized by a DFT study of the key transition states (TS).



Scheme 2. Scope of the proposed methodology.

Results and Discussion

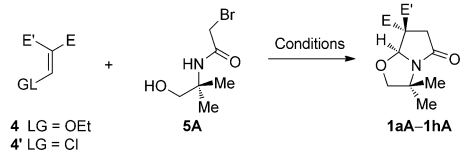
The reactivity was first probed by using the achiral amide **5 A** with various Michael acceptors **4** (LG=OEt) and **4′** (LG=Cl) that contain two electron-withdrawing groups (E=E′ or E≠E′, Table 1).[11] For this purpose, three different conditions were tested: NaH in THF at 0 °C (conditions **I**), K_2CO_3 in CH_3CN heated at reflux (conditions **II**), and Cs_2CO_3 in THF at room temperature in the presence of molecular sieves (conditions **III**). Moreover, in certain cases both of the leaving groups OEt and Cl were examined owing to the reactivity of the Michael acceptors, which has been justified in our previous paper.[10] Initially, Michael acceptors that possessed symmetrical electron-withdrawing groups (E=E′) were engaged. The results obtained from the reactions of diethyl chloromethylene malonate **4 a′** and commercially available ethoxymethylene malononitrile **4 b** have already been reported,[10] and these substrates reacted to give the desired bicyclic γ-lactams **1 aA**[12] and **1 bA** in 67 and 70% yield, respectively (Table 1, entries 1 and 2). When ethoxymethylene diphenylketone **4 c** was reacted with achiral amide **5 A** under conditions **I**, the domino process led to the bicyclic lactam **1 cA** in 64% yield (Table 1, entry 3). The 1,3-indanedione derived Michael acceptor **4 d** proved to be very unstable in conditions **I** and **II**, and only conditions **III** led to the formation of spiro-product **1 dA**, which was isolated in a good yield (Table 1, entry 4). Our investigations then turned to a more challenging domino process with substrates that contained unsymmetrical electron-withdrawing groups (E≠E′), which would furnish contiguous tertiary/quaternary stereocenters.

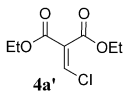
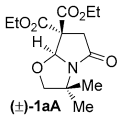
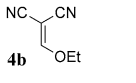
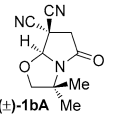
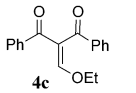
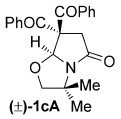
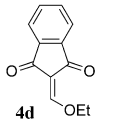
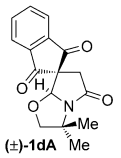
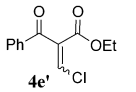
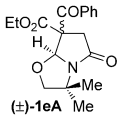
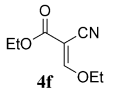
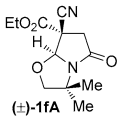
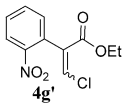
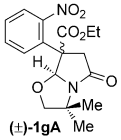
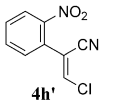
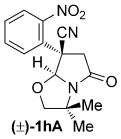
As observed with the other diester and diketone substrates, conditions **I** proved to be the best reaction conditions for the chlorinated Michael acceptor **4 e′**, but the product **1 eA** was obtained with a poor 60:40 diastereomeric ratio (d.r.) in 60% yield (Table 1, entry 5). Fortunately, the reaction of commercially available ethyl 2-cyano-3-ethoxyacrylate **4 f** under the same conditions led to the formation of **1 fA** in almost the same yield but this time with high levels of diastereoselectivity (>98:2 d.r., Table 1, entry 6). We then turned our attention to the less reactive Michael acceptor **4 g′**, which possessed both ester and 2-nitrophenyl functional groups and was synthesized in four steps from the commercially available 2-nitrophenylacetic acid.[13] However, regardless of which reaction conditions were used, we observed both poor yields and no diastereoselectivity for the bicyclic product **1 gA** (Table 1, entry 7).

The diastereoselective outcome of this domino process could be explained by either specific chelation of the cation or steric effects of the electron-withdrawing groups. The replacement of the ketone in **4 e′** by a 2-nitrophenyl functional group in **4 g′**, which exhibits a similar level of steric hindrance but very different chelating properties (Table 1, entries 5 vs. 7), led to reduced levels of diastereoselectivity in the corresponding product **1 gA**. This observation suggests that the steric effect has a stronger influence on the diastereoselectivity than chelation. Based on these results, we anticipated that the significant steric difference between the nitrile functional group and the 2-nitrophenyl group should allow us to achieve high levels of diastereoselectivity in the domino reaction of Michael acceptor **4 h′** (Table 1, entries 7 vs. 8). This hypothesis was confirmed under conditions **I**, which led to the formation of oxazolo-pyrrolidinone **1 hA** with an excellent >98:2 dr and in 78% yield due to the higher activation of the nitrile group compared to the ester moiety.

The proposed mechanism for this domino reaction is a three to four step process that starts from **4** or **4′** and **5** (see

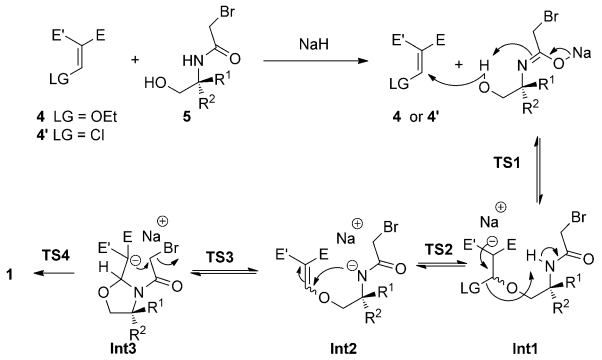
Table 1. Direct access to racemic bicyclic lactams **1**.



Entry	Michael acceptor **4** or **4′**	**1**	Yield [%][a] and conditions[b]	d.r.[c]
1	 **4a'**	 (±)-**1aA**	67[10] **I**	–
2	 **4b**	 (±)-**1bA**	70[10] **II**	–
3	 **4c**	 (±)-**1cA**	64 **I**	–
4	 **4d**	 (±)-**1dA**	78 **III**	–
5	 **4e'**	 (±)-**1eA**	60 **I**	60:40[d]
6	 **4f**	 (±)-**1fA**	59 **I**	>98:2
7	 **4g'**	 (±)-**1gA**	17 **I**	50:50
8	 **4h'**	 (±)-**1hA**	78 **I**	>98:2

[a] Yields of isolated products. [b] Conditions **I**: NaH, THF, 0 °C; **II**: K_2CO_3, CH_3CN, heated at reflux; **III**: Cs_2CO_3, THF, molecular sieves, RT. [c] d.r. determined by ^1H NMR analysis of the crude reaction mixture. [d] d.r. = diastereomeric ratio. The stereochemistry of the major diastereoisomer was not determined.

Scheme 3 for a simplified mechanism).[10] After deprotonation by the base, NaH in this case, an addition–elimination process takes place between **5** and **4** or **4′**, which leads to the intermediate **Int2**. An aza-Michael addition of the resulting amidate onto the double bond provides **Int3** and a subsequent intramolecular nucleophilic substitution furnishes the bicyclic adduct **1**.

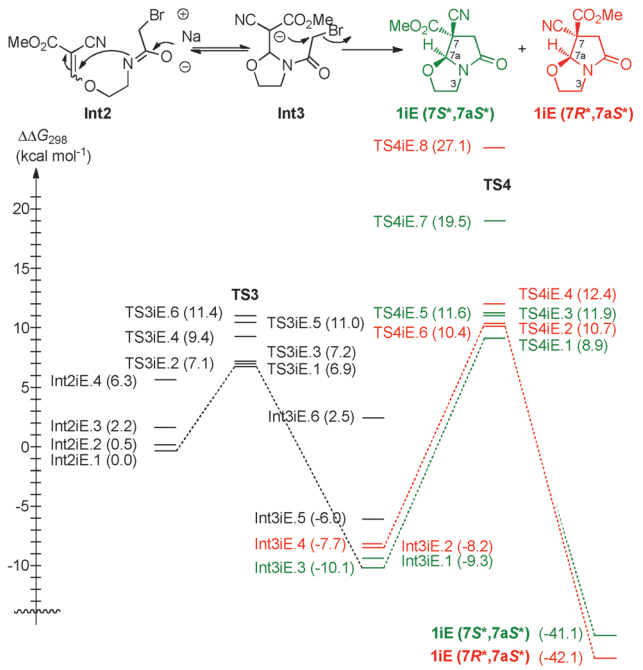


Scheme 3. Proposed mechanism for the domino process.

To confirm the hypothesis that it is predominately steric effects that govern the stereochemical outcome of the reaction, a DFT study was performed to identify the main factors that influence the selectivity of this multistep sequence. The DFT calculations were performed with Gaussian 09[14] at M06-2X/6-311+G(d,p) by using the polarizable continuum model (IEFPCM) for the description of THF as the solvent. The study was first performed on Michael acceptors that contained both nitrile and methyl ester functionalities. The methyl ester functional group was chosen instead of the ethyl ester to limit the number of possible conformations and subsequent CPU costs. The counterion (Na^+) was included in the model to make the system neutral and to study the influence of its position in the reaction sequence. For each intermediate, a full conformer search was first performed by using Spartan'10[15] and the most stable conformers were progressively optimized with increasing levels.

Initially, the four TS of the sequence were resolved on a model reaction that involved **5E** ($R^1 = R^2 = H$) and **4i** ($E = CO_2Me$, $E' = CN$) with a systematic search of the limited number of possible conformers for each TS, and evaluation of the potential positions of the cation close to the groups that bear the negative charge. The first two steps of the sequence involved an energy profile similar to the one previously calculated (see the Supporting Information, page 7).[10] However, compared to previous results, the use of Truhlar's density functional theory M06-2X[16] improved the energy calculation for **TS2** as expected for systems that involve hydrogen bonds and dispersion interactions.[17]

The favored **TS2** leads to the formation of the most stable intermediates **Int2iE.1** and **Int2iE.2**. In addition, the pathway to the previous intermediate **Int1** (Scheme 3) is fully reversible (see the Supporting Information, page 7), which ensures the preferential existence of these two stable intermediates by placing the amido alcohol chain *syn* to the nitrile group. The study was then focused on the last two steps of the sequence, which control the diastereoselectivity of the reaction. The corresponding TS were calculated to examine the energy profile of this part of the process (Scheme 4 and Figure 1). As expected, the pathways that involve **TS3iE.1** and **TS3iE.2**, which are derived from **Int2iE.1** and **Int2iE.2**, respectively, are the preferred ones. However, **TS3iE.3**, which was derived from the



Scheme 4. Energy profile of the second part of the reaction sequence on the model bicyclic lactam **1 iE (7*S**,7 a*S**)**. Gibbs free energies quoted in kcal mol^{-1} at 298 K.

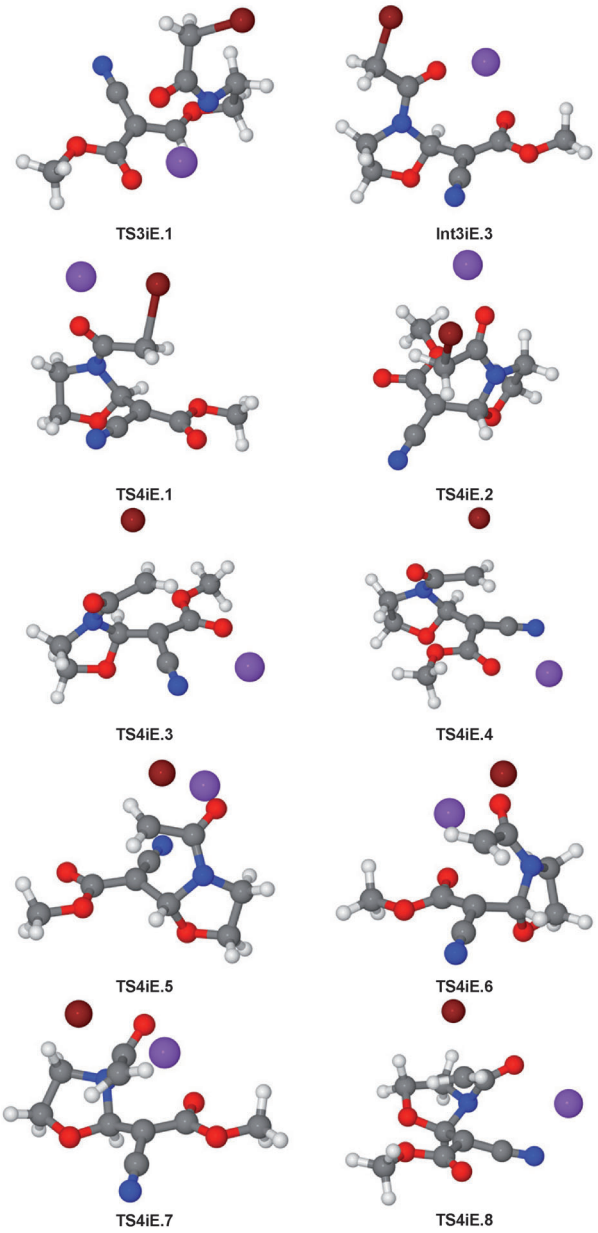
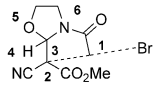


Figure 1. Geometry of the main intermediates and TS in the reaction between **4 i** and **5 E** to give **1 iE**.

less probable intermediate **Int2 iE.3**, was identified at approximately the same level of energy. These TS are all in the same energy range and they are lower in energy than **TS4**, which ensures a full reversibility of the first cyclization step. Therefore, the selectivity of the complete sequence is largely related to the last TS (**TS4**). The preferred conformation of all the transition states were studied by considering both the possible chelation of the sodium cation with the nitrile, the ester, or the carbonyl group of the amide, and the possible orientation of the oxazolidine ring, which drives the configuration of the diastereoisomer that is formed. Among the eight conformers of **TS4 iE** that were found, six appear in the same energy range, and two (**TS4 iE.7** and **TS4 iE.8**) are notably higher. The six lowest energy TS display an optimal orientation of the oxazolidine ring (ϕ between 84° and 88°, Table 2), which optimizes the overlap of the σ^*_{C-O} and σ^*_{C-N} orbitals; whereas, **TS4 iE.7** and **TS4 iE.8** cannot benefit from the same stabilization. The conformation that is adopted by the oxazolidine ring in these TS ($\phi = 161.3°$ and $\phi = 167.5°$, Table 2) prevents any possible contribution of the σ^*_{C-O} orbital. In order to assess this hypothesis, a Natural Bond Orbital (NBO) analysis was performed by using NBO 6.0.[18] The second order perturbation theory analysis on the NBO basis provided an estimation of the interaction between the occupied p orbital at C(2) and the closest σ* orbitals. As expected, for **TS4 iE.7** and **TS4 iE.8** the contribution of the σ^*_{C-O} orbital is considerably reduced and the contribution of the σ^*_{C-H} orbital is not sufficient to counterbalance this effect. The contribution of the three σ* orbitals are summed in the last column of Table 2 and this illustrates the contribution of the overlap with the σ* orbitals towards the stabilization of the negative charge of the carbanion. The difference between the sum of the three orbital contributions in **TS4 iE.7** and **TS4 iE.5** is 7.7 kcal mol^{-1}. Consequently, this can account for the main contribution to the energy difference that exists between these two TS (7.9 kcal mol^{-1}).

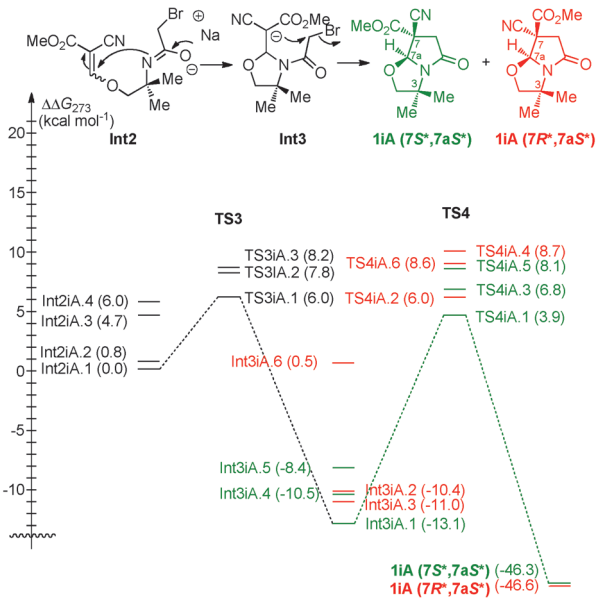
The two lowest energy **TS4 iE** conformers (**TS4 iE.1** and **TS4 iE.2**) place the sodium cation close to the bromine in order to assist the departure of the leaving group; the cation also chelates to the carbonyl of the amide (Figure 1). In addition to the stabilization from the electron-withdrawing groups, chelation with the oxygen of the amide group also contributes to stabilization of the negative charge of the carbanion by an improved overlap of the σ^*_{C-O} and σ^*_{C-N} orbitals (Table 2, entries 1 and 2). The lowest energy **TS4 iE** conformer (**TS4 iE.1**)

Table 2. Second order perturbation theory analysis of Fock matrix in NBO basis



	ϕ[a]	pC(2)→ σ*C(3)–O(5)[b]	pC(2)→ σ*C(3) –N(6)[b]	pC(2)→ σ*C(3) –H(4)[b]	Σ[c]
TS4 iE.1	83.1	19.2	11.9	–	31.1
TS4 iE.2	86.4	19.0	12.0	–	31.0
TS4 iE.3	87.7	13.6	12.2	–	25.8
TS4 iE.4	86.0	15.3	10.5	–	25.9
TS4 iE.5	84.1	15.9	11.5	–	27.5
TS4 iE.6	86.5	15.9	10.8	–	26.7
TS4 iE.7	161.3	0.5	10.1	9.14	19.8
TS4 iE.8	167.5	1.8	7.2	9.36	18.4

[a] H(4)-C(3)-C(2)-C(1) dihedral angle. [b] Second order perturbative estimate of full p orbital at C(2) and σ* interactions in kcal mol^{-1}. [c] Sum of the stabilization energies associated with these interactions in kcal mol^{-1}.



Scheme 5. Energy profile of the last steps of the reaction sequence with amido alcohol **5 A** to give **1 iA**. Gibbs free energies quoted in kcal mol^{-1} at 273 K.

lies sufficiently lower in energy than **TS4 iE.2** and **TS4 iE.6** such that it induces a good level of diastereoselectivity in favor of the adduct **1 iE** (7*S**,7a*S**) (Scheme 4). In this preferred TS, the oxazolidine ring is located preferentially on the side of the nitrile group in order to minimize unfavorable steric interactions.

After excluding the least favored TS and the corresponding intermediates, the second part of the reaction sequence was studied with the amido alcohol **5 A** that contained the more realistic methyl groups as substituents (Scheme 5). For this new energy profile that leads to **1 iA**, the Gibbs free energies were calculated at 273 K in order to best describe the reaction pathway that gives **1 fA** (compare Scheme 5 and Table 1, entry 6). The calculations showed a greater discrimination between the various TS and intermediates, which led to the emergence of a single favorable pathway (**Int2 iA.1**–**TS3 iA.1**–**Int3 iA.1**–**TS4 iA.1**). This favored reaction pathway, and therefore the resulting selectivity, is mainly kinetically controlled by the steric interactions that occur in **TS4** between the oxazolidine ring, which bears the *gem*-dimethyl group, and the CN or the bulkier ester group. The presence of real substituents, such as the *gem*-dimethyl group, obviously has a significant effect on the preferred conformation of **Int3** and **TS4** because of steric repulsion between the oxazolidine ring and the ester moiety. Therefore, the conformation that is preferentially adopted by **Int3 iA.1** will place the oxazolidine ring on the side of the nitrile group in order to reduce the steric interaction (Figure 2). It should be noted that if **TS4 iA.1** is close in energy to the previously described **TS4 iE.1**, and places the sodium cation in the same position, the energy of **TS4** compared to **TS3** must be significantly lower (compare Schemes 4 and 5). In addition to this significant modification of the energy gap at **TS4**, some perturbations are also observed for **TS3** with a redistribution of the TS. For example, the TS that best corresponds to the previously most stable **TS3** conformer (**TS3 iE.1**) is **TS3 iA.3**. Additionally, in the present case only three **TS3** conformers could be obtained. All attempts to locate the missing confomers by comparison with **TS3 iE** during the optimization

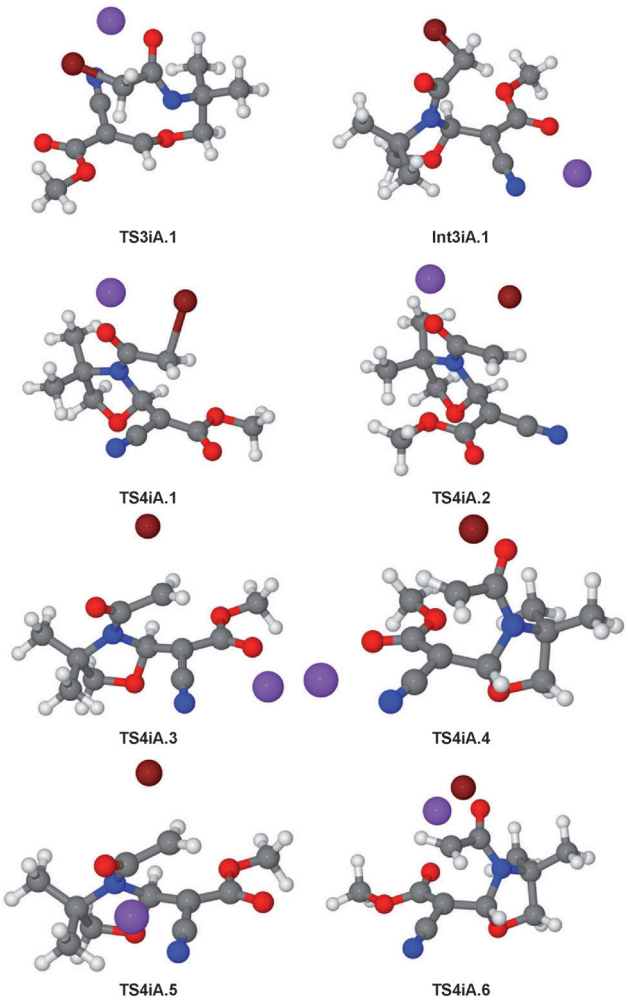


Figure 2. Geometry of the main intermediates and TS in the reaction between **4 i** and **5 A** to give **1 iA**.

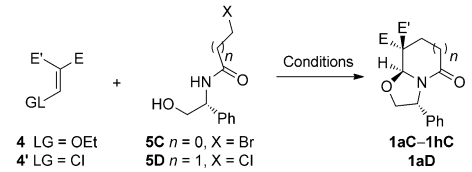
process were unsuccessful due to a very flat energy profile, which invariably led to the corresponding **Int2** or **Int3**.

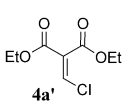
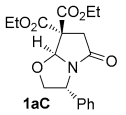
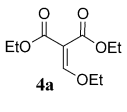
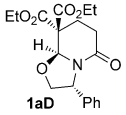
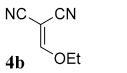
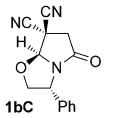
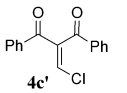
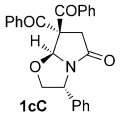
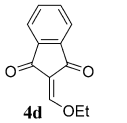
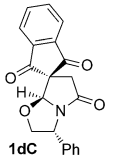
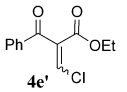
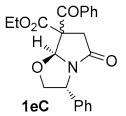
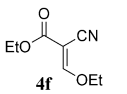
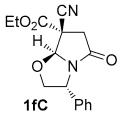
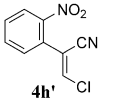
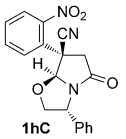
Next, the synthesis of the more interesting enantioenriched γ- and δ-lactams from the (*R*)-phenylglycinol derivatives **5C** and **5D** (Table 3) were investigated by employing the optimum conditions for the domino process that were reported in Table 1. Beginning with the diester Michael acceptor **4a′**, the oxazolo-pyrrolidinone **1aC** was isolated in a good yield and with excellent diastereomeric ratio (Table 3, entry 1). In addition, the chiral six-membered ring oxazolo-piperidinone **1aD** was also obtained using our strategy with >98:2 d.r. and an acceptable yield (Table 3, entry 2). In this case, the poor reactivity of the β-chlorophenylglycinol derivative **5D** led to preponderant side reactions as a consequence of the survival of the malonic carbanion that corresponds to **Int3**, as previously demonstrated.[10] This led us to use the Michael acceptor **4a** that contains an ethoxy substituent, which is more stable and therefore less prone to the formation of side products. The reaction of Michael acceptor **4b** also led to the formation of the target bicyclic compound **1bC** in 41% yield and an excellent diastereomeric ratio (>98:2 d.r., Table 3, entry 3). The Michael acceptor with two phenyl ketone groups **4c′** and the substrate that is derived from 1,3-indanedione **4d** both reacted to give the corresponding lactams in satisfactory yields and with complete diastereocontrol (Table 3, entries 4 and 5). As observed with the achiral amide **5A** (Table 1, entry 5), the reaction between the keto–ester Michael acceptor **4e′** and the (*R*)-phenylglycinol derivative **5C** gave the product **1eC** with a low diastereomeric ratio but a good yield (Table 3, entry 6). Alternatively, unsymmetrical Michael acceptors **4f** and **4h′** furnished the desired bicyclic lactams **1fC** and **1hC** with high levels of diastereoselectivity (both >98:2 dr), which allowed the construction of two contiguous stereocenters with total stereocontrol (Table 3, entries 7 and 8).

The *cis* relationship between the phenyl group and the C(7a)-hydrogen atom of the oxazolidine ring was confirmed by X-ray structural analysis of the domino products **1aC** and **1hC** (Figure 3). This analysis also proved the *cis* relationship between the C(7a)-hydrogen atom and the 2-nitrophenyl functional group of the bicyclic lactam **1hC**, which confirms that the biggest substituent on the C(7) atom is preferentially located on the side of this hydrogen atom.

To rationalize the double diastereoselectivity that is observed with nitrile–ester Michael acceptor substrates, based on previous results, the most reliable TS and intermediates were calculated at M06-2X/6-311+G(d,p) level by using the polarizable continuum model for the description of THF, and the Gibbs free energies are given at 273 K (Scheme 6, Figure 4, and Table 3, entry 7). The diastereoselectivity that is induced by the phenyl group was studied together with the selectivity that is induced by the last step of the sequence. The energy profile shown in Scheme 6 suggests that the stereoselectivity of the reaction sequence is mainly controlled in the last step. The transfer of chirality from C(3) to C(7a) is controlled in the first cyclization step via **TS3**; however, the calculated energy gap between **TS3iC.1α** and **TS3iC.2β** (0.9 kcal mol^{-1}) fails to fully explain the complete diastereocontrol that is observed in the formation of **1fC**. In fact, this step was found to be fully reversible as **TS4iC.1β** (10.8 kcal mol^{-1}) lies significantly higher in energy than **TS3iC.2β** (8.3 kcal mol^{-1}). As a consequence, the intermediate **Int3iC.1α**, which is consumed faster, can be regenerated from **Int3iC.1β** through a reverse step to **Int2**. The stereochemistry of the product is thus mainly controlled by the kinetics of the last step of the sequence (**TS4**). The diaste-

Table 3. Direct access to enantioenriched bicyclic lactams.



Entry	Michael acceptor	1	Yield [%][a] and conditions[b]	d.r.[c]
1	 **4a′**	 **1aC**	76 **I**	>98:2
2	 **4a**	 **1aD**	59 **I**[e]	>98:2
3	 **4b**	 **1bC**	41 **II**	>98:2
4	 **4c′**	 **1cC**	61 **I**	>98:2
5	 **4d**	 **1dC**	64 **III**	>98:2
6	 **4e′**	 **1eC**	77 **I**	60:40[d]
7	 **4f**	 **1fC**	60 **I**	>98:2
8	 **4h′**	 **1hC**	53 **I**	>98:2

[a] Yields of isolated products. [b] Conditions **I**: NaH, THF, 0 °C; **II**: K_2CO_3, CH_3CN, heated at reflux; **III**: Cs_2CO_3, THF, molecular sieves, RT. [c] d.r. determined by ^1H NMR analysis of the crude mixture. [d] The stereochemistry of the major diastereoisomer was not determined. [e] 2.4 equiv of NaH were used.

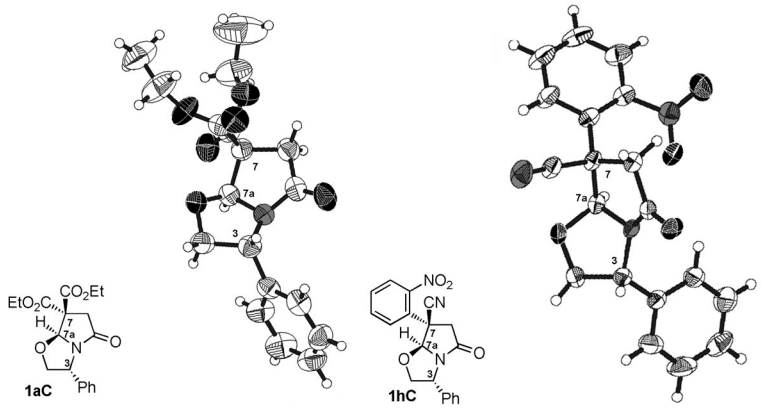
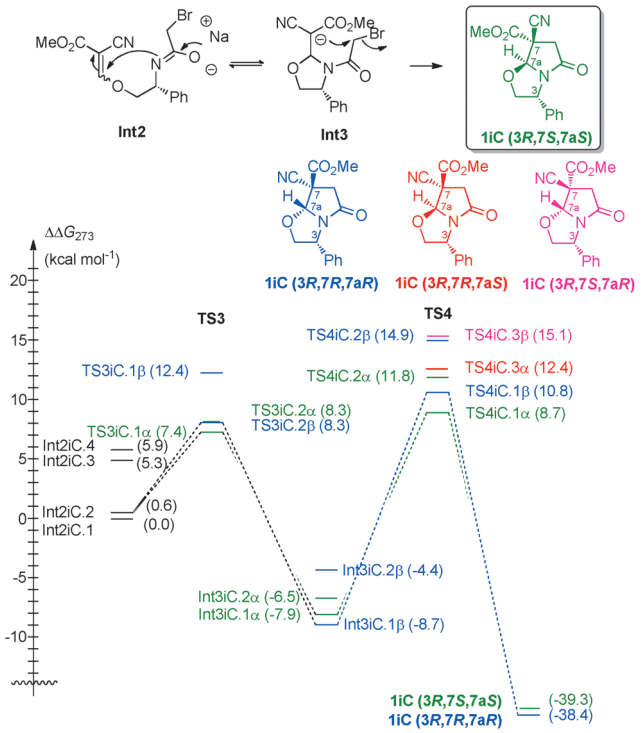


Figure 3. Stick model plots of the crystal structures of **1 aC** and **1 hC**. ORTEP representation of compound **1 aC**, only one molecule of the asymmetric unit (Z′ = 2) is displayed.

The stereoselectivity of the reaction is strongly correlated to the steric interactions that occur between the oxazolidine ring and the activating group of the Michael acceptor in **TS4**. A simple study of this final TS in the reaction sequence should give the desired data on the diastereocontrol of the reaction. For example, the lack of diastereoselectivity that is observed with the compounds that contain electron-withdrawing groups that possess a similar degree of



Scheme 6. Energy profile of the last two steps of the reaction sequence with amido alcohol **5 C** to give **1 iC**. Gibbs free energies quoted in kcal mol^{-1} at 273 K.

reoselectivity that is observed in the oxazolidine ring is mainly a consequence of the placement of the phenyl ring in the least sterically hindered position, which leads to a significant energy gap between **TS4 iC.1 α** and **TS4 iC.1 β**. The other four calculated **TS4** conformers are significantly higher in energy, corroborating the facts that the preferred lowest energy TS conformers place the sodium cation in a position where it is able to chelate to both the bromine atom and the carbonyl of the amide group (energy gap of 3.1 kcal mol^{-1} between **TS4 iC.1 α** and **TS4 iC.2 α**), and that the oxazolidine ring lies on the side of the nitrile group during the cyclization step (energy gap of 3.7 kcal mol^{-1} between **TS4 iC.1 α** and **TS4 iC.3 α**).

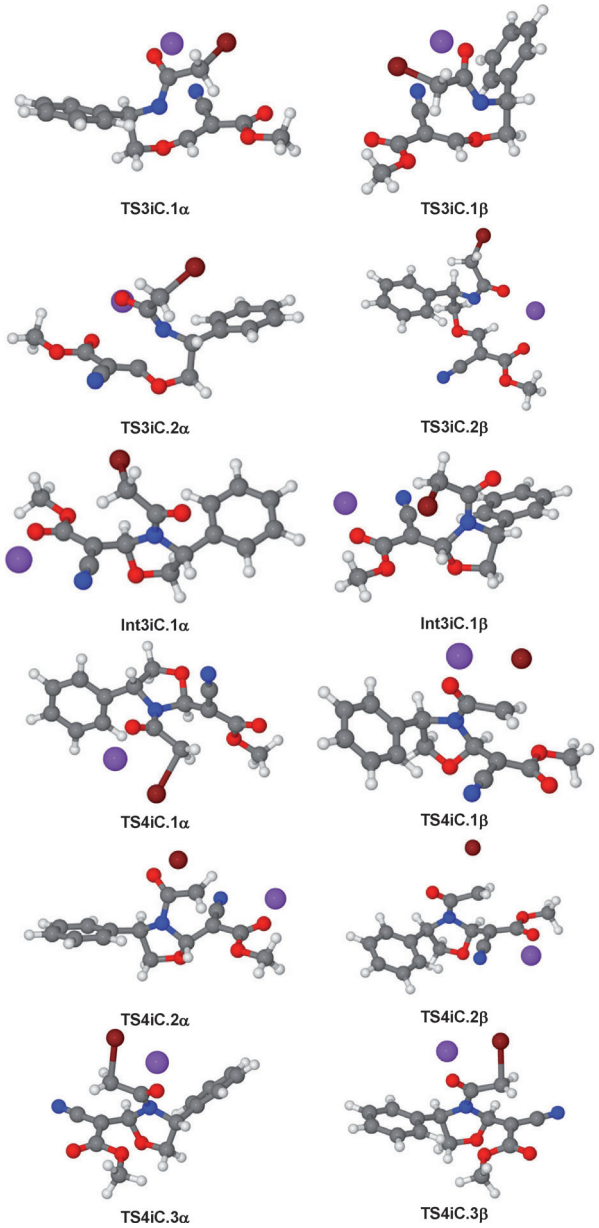
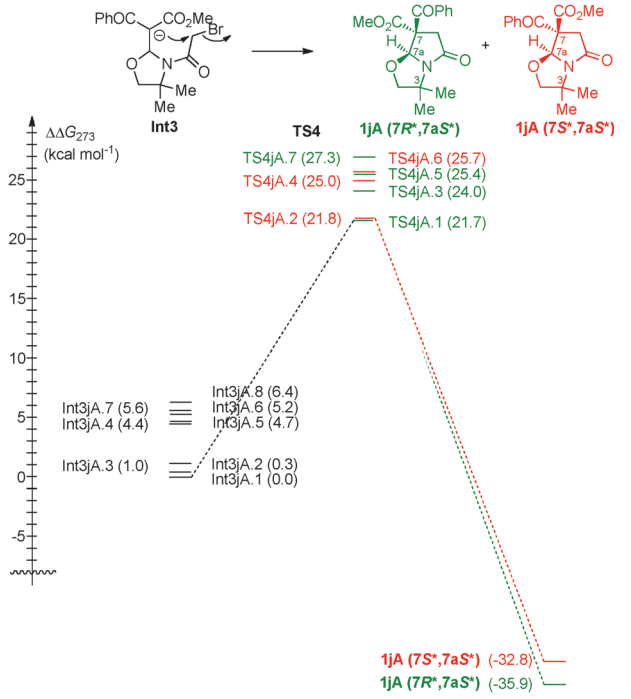


Figure 4. Geometry of the main intermediates and TS in the reaction between **4 i** and **5 C** to give **1 iC**.

steric bulk, such as **1 eA** and **1 gA** (Table 1, entries 5 and 7), can certainly be explained by the poor discrimination between the two most plausible conformers in the last key step of the reaction sequence. To this end, the **TS4** conformers that lead to both **1 jA**, which is analogous to **1 eA** (Table 1, entry 5) and **1 kA**, which is analogous to **1 gA** (Table 1, entry 7), were calculated at the same level as previously described (M06-2X/6-311+G(d,p)) with IEFPCM model for the description of THF. As before, the ethyl ester groups in **1 eA** and **1 gA** were replaced by methyl ester groups in **1 jA** and **1 kA** to limit the number of possible conformations of the ester moiety. The Gibbs free energies are given in kcal mol^{-1} at 273 K.

Among the seven **TS4 jA** conformers that were obtained, the two most stable ones, **TS4 jA.1** and **TS4 jA.2**, were separated by only 0.1 kcal mol^{-1} and led to divergent diastereoisomers (Scheme 7, Figure 5). The third conformer **TS4 jA.3** lies significantly higher in energy. Interestingly, contrary to previous results, the sodium cation preferentially chelates the carbonyl groups of the ester and the ketone. This can be explained by the favorable chelation angle and the increased chelation ability of the carbonyl group compared to the nitrile group. The very small energy difference that was calculated between **TS4 jA.1** and **TS4 jA.2** explains the lack of diastereoselectivity that is observed in the formation of **1 jA** and, consequently, **1 eA** (Table 1, entry 5). The poor selectivity, in this case, is related to the absence of discrimination in the steric interactions between the oxazolidine ring and either the ester or the phenyl ketone groups. It is also important to notice that the energy barrier is significantly higher in this case, which shows the crucial role that is played by TS4.



Scheme 7. Energy profile of the last two steps of the reaction sequence starting from amido alcohol **5 A** to give **1 jA**. Gibbs free energies quoted in kcal mol^{-1} at 273 K.

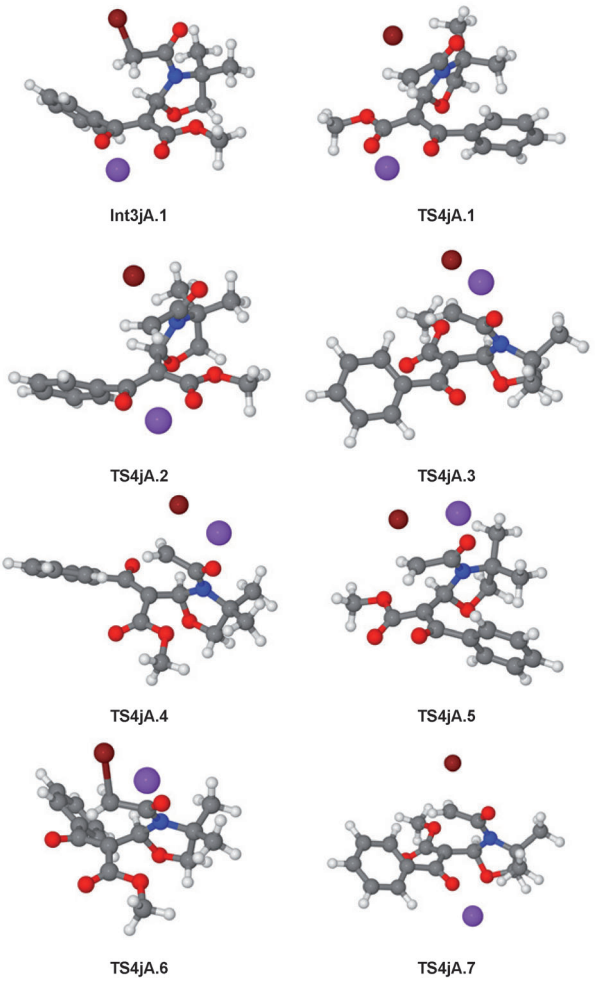
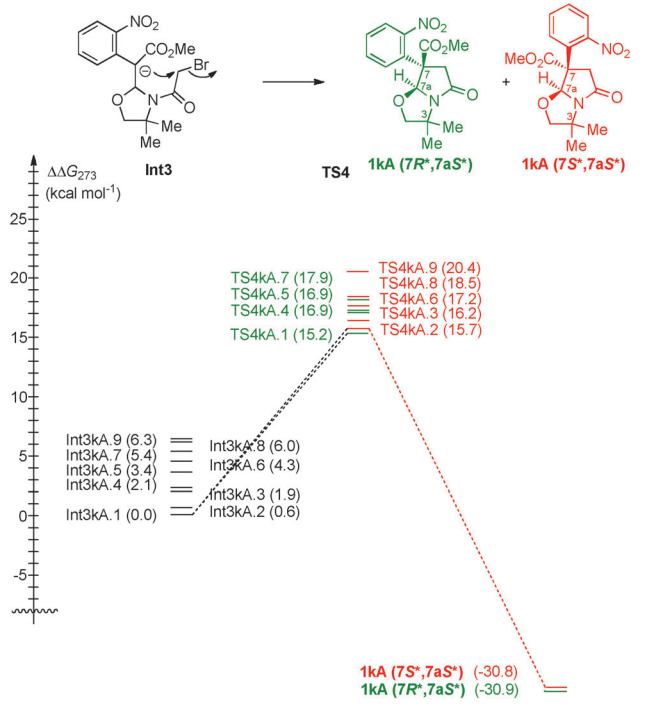


Figure 5. Geometry of the main intermediates and TS in the reaction to give **1 jA** from **Int3 jA**.

The favored **TS4** conformations for the final step in the reaction sequence was also studied for **1 kA** (**TS4 kA**, Scheme 8, Figure 6), the methyl ester analogue of **1 gA**. After DFT calculations, nine **TS4 kA** conformations were obtained, among which eight were very close in energy. As before, the two most stable conformations, **TS4 kA.1** and **TS4 kA.2**, were very close in energy and led to divergent diastereoisomers, which can explain the total lack of diastereoselectivity that is observed for **1 gA** (Table 1, entry 7). These results demonstrate the possibility of predicting the stereocontrol of the reaction from the calculation of the last TS conformers. In the most stable **TS4** conformers that were calculated (**TS4 kA.1** and **TS4 kA.2**), the sodium cation was placed in a position close to the bromine atom, as in **TS4 iE.1**, **TS4 iA.1**, and **TS4 iC.1** (Scheme 4–Scheme 6). However, the energy difference with the other calculated TS conformers is greatly reduced unlike in the previous cases.

The study was then extended to the selective formation of **1 hA** (Table 1, entry 8). Six possible conformers of **TS4** were identified, with **TS4 hA.1** lying significantly lower in energy than the others (Scheme 9, Figure 7), which explains the high levels of diastereoselectivity that were observed in the reaction



Scheme 8. Energy profile of the last two steps of the reaction sequence starting from amido alcohol **5 A** to give **1 kA**. Gibbs free energies quoted in kcal mol^{-1} at 273 K.

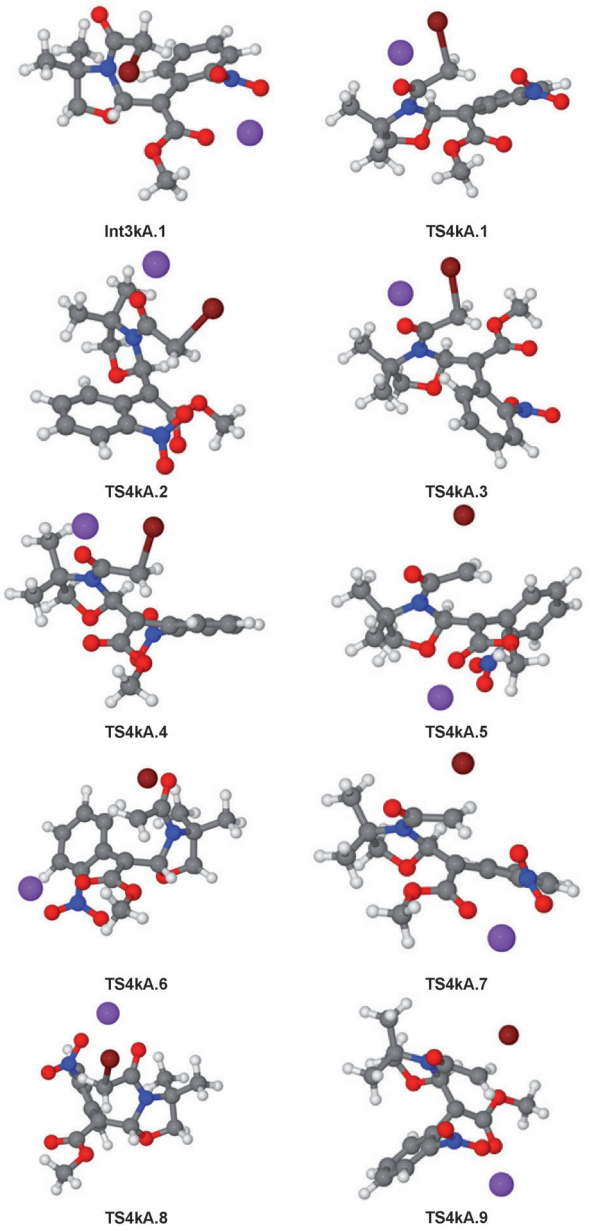


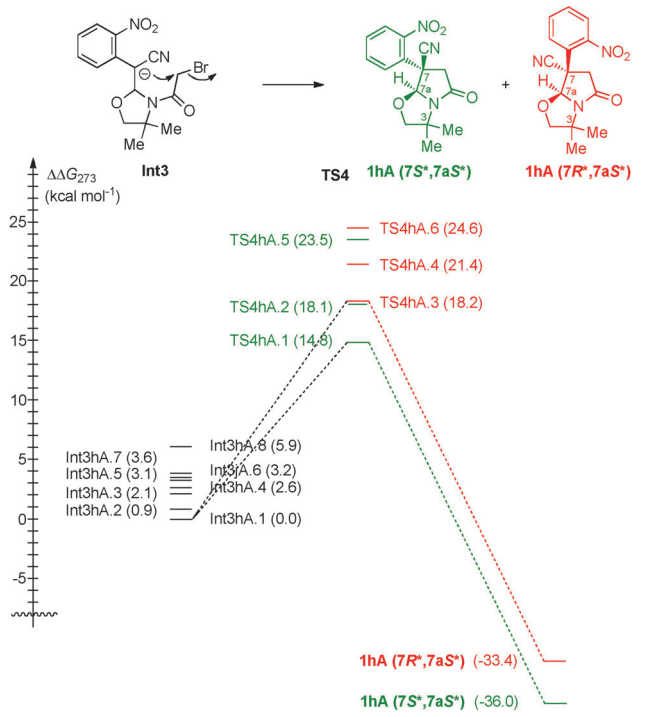
Figure 6. Geometry of the main intermediates and TS in the reaction to give **1 kA** from **Int3 kA**.

of **1 hA**, in favor of the (7*S**,7a*S**) diastereoisomer. **TS4 hA.1** is the **TS4** conformer that displays the best conjugation of the aromatic ring with the carbanion. In addition, the oxazolidine ring lies on the side of the nitrile group, which is the site of the least steric hindrance, and this further confirms that the stereochemical outcome of the reaction is mainly controlled by steric effects. Like with the other Michael acceptors that possess at least one nitrile group, the most stable TS conformer (**TS4 hA.1**) places the sodium cation close to the bromine atom, and the alternative TS are significantly higher in energy.

At this juncture, we turned our attention toward the more sterically hindered, and thus most challenging, Michael acceptors that contain four substituents on the double bond (Table 4). Once again, three sets of reaction conditions that employ three different bases: Cs_2CO_3, K_2CO_3, or NaH, were tested for this reaction; however, only the reactions that used NaH led to the desired bicyclic lactams, with low to good yields being observed. The first attempt, between **4 l**′ and **5 A**, was a failure and the desired product was never observed (Table 4, entry 1). By replacing one of the ester groups with a more reactive nitrile moiety, the lactam **1 mA** was obtained in only 4% yield but in a good >98:2 diastereomeric ratio (Table 4, entry 2). Thankfully, the more reactive dinitrile acceptor **4 n** reacted smoothly and in a good 64% yield to give **1 nA**, which has two contiguous quaternary centers (Table 4, entry 3). The low yield (10%) attained in the case of **4 o** is probably due to the acidity of the methyl protons on the CH_3 moiety of this acceptor, which are not compatible with the basic conditions used in this domino process (Table 4, entry 4). Nevertheless, the chiral amido alcohol **5 C** reacted with **4 n** to furnish the enantioenriched lactam **1 nC** in an excellent >98:2 d.r. and 65% yield (Table 4, entry 5). Finally, this process was also efficient for the formation of the spiro-compound **1 pA**, which was obtained in 61% yield (Table 4, entry 6).

In the case of **1 nC**, the *cis* relationship between both phenyl groups was determined by NOESY experiments with an NOE being observed between the *ortho*-phenyl protons (Figure 8).

To explain the good selectivity that was observed in the case of **1 nC** in favor of the (3*R*,7a*S*) diastereoisomer (Table 4, entry 5), the TS conformers that correspond to the last two steps of the reaction sequence were calculated at the same level as previously described (M06-2X/6-311+G(d,p)) by using the IEFPCM model for the description of THF (Scheme 10, Figure 9). The Gibbs free energies of the energy profile are



Scheme 9. Energy profile of the two last steps of the reaction sequence starting from amido alcohol **5 A** to give **1 hA**. Gibbs free energies quoted in kcal mol^{-1} at 273 K.

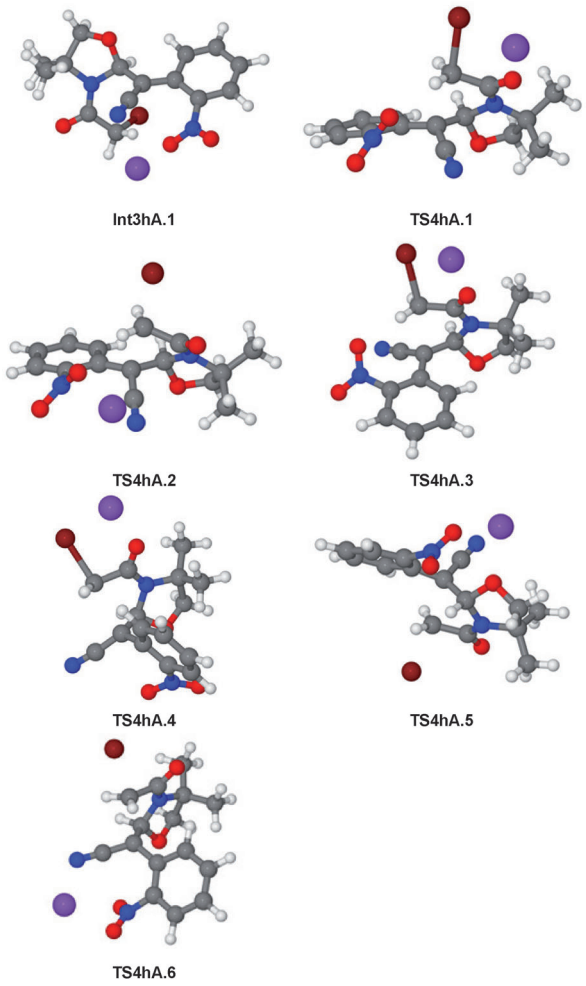


Figure 7. Geometry of the main intermediates and TS in the reaction to give **1 hA** from **Int3 hA**.

given in kcal mol^{-1} at 273 K. In this case, the stereoselectivity of the sequence was controlled by **TS3**, which governs the relative stereochemistry of the 3*R* and 7*aS* stereocenters of the oxazolidine. Two **TS3** and four **TS4** conformers were obtained. Interestingly, in this case, the **TS4** conformers lie slightly lower in energy than the corresponding **TS3** conformers, which indicates that the observed stereoselectivity is a consequence of the kinetic control that is imparted by the first cyclization. The presence of two nitrile groups allows complete discrimination between the two usual positions that are occupied by the sodium cation in favor of chelation with the carbonyl of the amide and the bromine atom. Therefore, this selectivity is not the sole consequence of steric effects, but it is also due to the position of the phenyl ring of the phenylglycinol in **TS3 nC.2** (Figure 9), which reduces the ability of the sodium cation to be complexed by the solvent. This contribution was partially taken into account by the PCM solvent model.

As demonstrated above, the domino process proved to be sensitive to steric effects. In this context, substrates that contained one or two bulky phenyl sulfones were then investigated in order to determine whether the final cyclization step would be possible under the same reaction conditions (Table 5). Only conditions **I** furnished the γ-lactams **1 qA** and **1 rA**, which were both isolated in a low 33% yield but with high levels of diastereoselectivity (>98:2 d.r., Table 5, entries 1 and 3). It was found that the lower yields attained in these cases were partly due to the formation of unsaturated side products **6** and **7**. The formation of these side products was due to the presence of an acidic proton in α-position of the carbonyl, which enabled the β-elimination of a phenyl sulfone moiety after the domino process. This hypothesis was confirmed by the sole formation of δ-lactam **1 rB** from the reaction of **4 r** and **5 B**, where no β-elimination was observed (Table 5, entry 5). In order to overcome this unwanted side reaction, modified reaction conditions **I′** were applied. Therefore, the reactions were carried out at −20 °C with a substoichiometric amount of the base to give the γ-lactams **1 qA** and **1 rA** both with high selectivities (Table 5, entries 2 and 4).[19] In addition, the diphenyl sulfone derivative **4 q′** furnished the corresponding lactam **1 qA** in a better yield (78%, Table 5, entry 2). However, the more reactive nitrile–phenyl sulfone Michael acceptor reacted to give **1 rA** with only 22% yield (Table 5, entry 4). In this case, the desired reaction is in competition with the degradation of the starting material **4 r′**; whereas, in most cases the domino process is predominant and only a few side products can be observed.

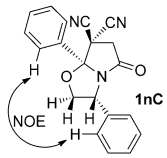
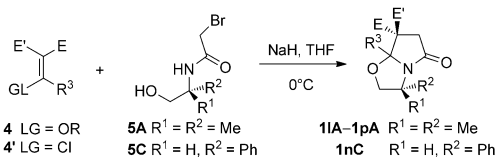


Figure 8. NOESY experiments for **1 nC**.

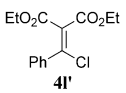
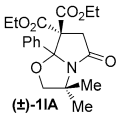
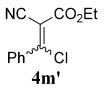
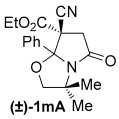
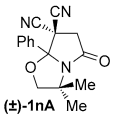
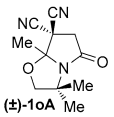
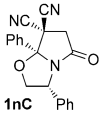
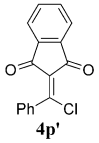
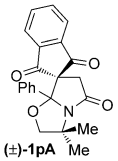
Table 4. Synthesis of bicyclic lactams **1** that bear two contiguous quaternary stereocenters.



4 LG = OR
4' LG = Cl

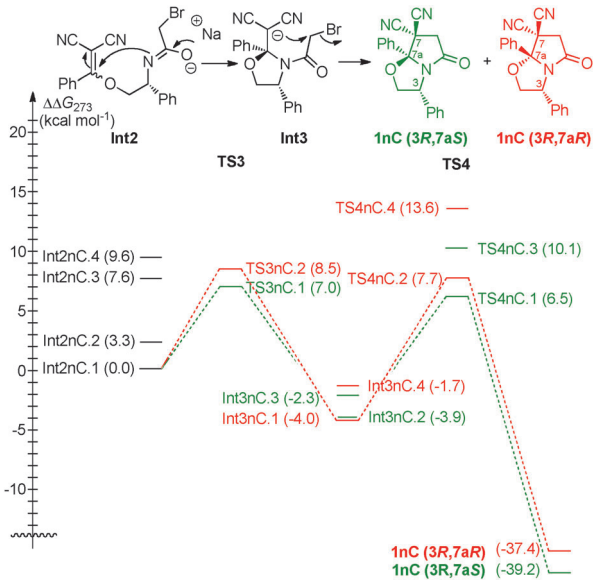
5A $R^1 = R^2 = Me$
5C $R^1 = H$, $R^2 = Ph$

1IA–1pA $R^1 = R^2 = Me$
1nC $R^1 = H$, $R^2 = Ph$

Entry	Michael Acceptor	1	Yield [%][a]	d.r.[b]
1	 **4l'**	 **(±)-1lA**	n.d.	–
2	 **4m'**	 **(±)-1mA**	4	>98:2[c]
3	 **4n**	 **(±)-1nA**	64	–
4	 **4o**	 **(±)-1oA**	10	–
5	 **4n**	 **1nC**	65	>98:2
6	 **4p'**	 **(±)-1pA**	61	–

[a] Yields of isolated products. [b] d.r. determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The stereochemistry of the major diastereoisomer was not determined.

Under the modified conditions **I'** (−20 °C), the lower temperature led to preponderant side reactions, which were further amplified by the high reactivity of the Michael acceptor (Table 5, entry 2 vs. 3). Similarly, as shown above (Table 1, entries 1 and 2) in the case of the reaction with the less reactive amido alcohol **1B**, the ethoxy substituted acceptor **4r** was used instead (Table 5, entry 5). The same behavior was observed for amido alcohol **5C**, which was derived from (*R*)-phenylglycinol, for the formation of γ-lactam **1qC** (Table 5, entries 6 and 7). It is worth highlighting that unsaturated compounds, such as **6**–**8**, are of interest from a synthetic point of view[20] and efforts will be devoted to their direct access in the near future.



Scheme 10. Energy profile of the two last steps of the reaction sequence starting from amido alcohol **5C** to give **1nC**. Gibbs free energies quoted in kcal mol^{-1} at 273 K.

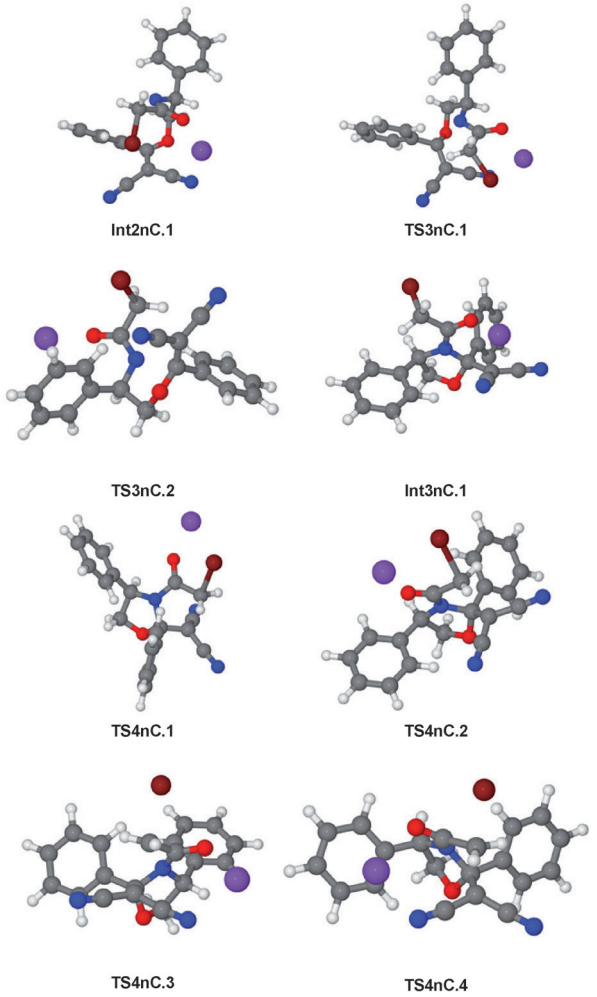
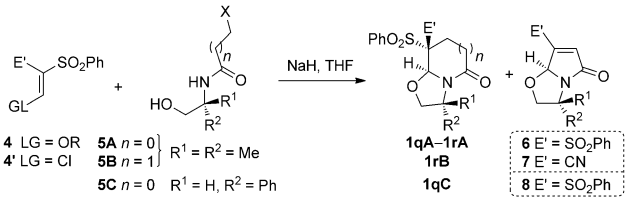
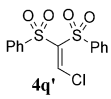
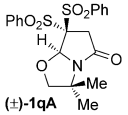
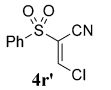
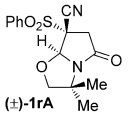
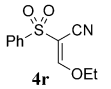
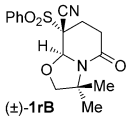
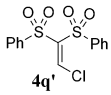
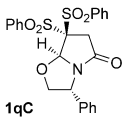


Figure 9. Geometry of the main intermediates and TS in the reaction to give **1nC** from **Int3nC**.

Table 5. Competitive formation of the unsaturated products **6**–**8**.



Entry	Michael acceptor	Temp. [°C][a]	1	Yield [%][b]	1:6–8[d]
1	 **4q'**	0	 **(±)-1qA**	33	94:6
2		−20		78	94:6
3	 **4r'**	0	 **(±)-1rA**	33[c]	79:21
4		−20		22[c]	92:8
5	 **4r**	0	 **(±)-1rB**	52[c]	–
6	 **4q'**	0	 **1qC**	18[c]	80:20
7		−20		51[c]	88:12

[a] Conditions **I**: NaH, THF, 0 °C or −20 °C. [b] Yields of isolated products. [c] > 98:2 d.r. determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture.

Conclusion

We have reported an efficient and highly diastereoselective synthesis of Meyers' bicyclic lactams by an acid-free domino process in which functionalized bicyclic systems are obtained from cheap, commercially available reagents. One breakthrough of this approach, compared to the existing protocols, is the formation of a tunable quaternary stereocenter at the 4-position of pyrrolidinone. Using our strategy, six-membered bicyclic δ-lactams were obtained in usually good yields and with high levels of diastereoselectivity. With the help of DFT calculations, the stereocontrol in the construction of the two contiguous diastereomeric centers was explained by a combination of steric and stereoelectronic effects that control the conformation in the final key steps. The role and the position of the cation proved to be highly dependent on the nature of the electron-withdrawing groups on the Michael acceptor. Interestingly, the transfer of chirality from the amido alcohol to the N,O-ketal or acetal carbon atom of the oxazolidine proved to be controlled by either the first cyclisation step or surprisingly, during the second cyclization. In other words, the stereochemistry of a stereogenic center that is formed through a domino process is not necessarily controlled during its formation but can also be controlled in a subsequent step of the reaction sequence. The total synthesis of heterocyclic alkaloids using this methodology is currently under study.

Experimental Section

Synthesis of δ- and γ-lactams

Conditions I: Michael acceptor (**4** or **4'**, 1.2 mmol, 1.2 equiv) and *N*-hydroxyalkyl α-bromoacetamide or β-chloropropanamide (**5 A-D**, 1.0 mmol, 1 equiv) were dissolved in freshly distilled THF (10 mL) at RT Sodium hydride (48 mg, 60% suspension in mineral oil, 1.2 mmol, 1.2 equiv for **4**; 96 mg, 60% suspension in mineral oil, 2.4 mmol, 2.4 equiv for **4'**) was then added at 0 °C. The mixture was stirred for 3 to 5 h and was then quenched carefully at 0 °C by addition of a saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (3×10 mL), the organic phases were combined, washed with brine, dried over $MgSO_4$ and solvent was removed under vacuum. The residue was then chromatographed on silica gel to afford the desired compound.

Conditions II: Michael acceptor (**4** or **4'**, 1.2 mmol, 1.2 equiv), *N*-hydroxyalkyl α-bromoacetamide or β-chloropropanamide (**5 A–D**, 1.0 mmol, 1 equiv), and potassium carbonate (152 mg, 1.1 mmol, 1.1 equiv) were dissolved in freshly distilled CH_3CN (10 mL) and the mixture was heated at reflux for 3 to 5 h. The resulting slurry was filtered through a small pad of Celite 545 using CH_2Cl_2. The organic phase was evaporated under vacuum and the residue was chromatographed on silica gel to afford the desired compound.

Conditions III: Michael acceptor (**4** or **4'**, 1.5 mmol, 1.5 equiv), *N*-hydroxyalkyl α-bromoacetamide or β-chloropropanamide (**5 A-D**, 1.0 mmol, 1 equiv), and cesium carbonate (152 mg, 1.2 mmol, 1.2 equiv) were dissolved in freshly distilled THF (10 mL) in the presence of molecular sieves. The resulting mixture was stirred for 7 days and was then quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (3×10 mL), the organic phases were combined, washed with brine, dried over $MgSO_4$, and solvent was removed under vacuum. The residue was then chromatographed on silica gel to afford the desired compound.

(±)-(7*R*,7a*S*)-Ethyl 7-cyano-hexahydro-3,3-dimethyl-5-oxopyrrolo[2,1-*b*]oxazole-7-carboxylate (1 fA): Obtained by reaction between **4 f** and **5 A** under conditions **I** and, after purification by flash chromatography (EtOAc/cyclohexane, 50:50), **1 fA** was isolated as a colorless oil. Yield: 59%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.13 (d, J = 8.4 Hz, 1H), 3.96 (d, J = 8.4 Hz, 1H), 3.29 (d, J = 16.5 Hz, 1H), 3.03 (d, J = 16.5 Hz, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 1.37 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 165.3, 114.8, 94.0, 83.0, 64.2, 59.2, 51.3, 44.6, 24.8, 22.1, 13.9 ppm; IR (neat): $\tilde{\nu}$ = 1744, 1710, 1392, 1246, 1041 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{12}H_{17}N_2O_4^+$: 253.1188 $[M+H]^+$; found 253.1196.

(3*R*,8a*S*)-Diethyl 5-oxo-3-phenyltetrahydro-2*H*-oxazolo[3,2-*a*]pyridine-8,8(3*H*)-dicarboxylate (1 aC): Obtained by reaction between **4 a'** and **5 C** under conditions **I** and, after purification by flash chromatography (EtOAc/cyclohexane, 50:50), **1 aC** was isolated as a colorless oil: Yield: 59%; $[\alpha]_D^{20}$ = −104.8 (c = 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 5H), 5.45–5.40 (m, 1H), 5.43 (s, 1H), 4.43 (t, J = 8.0 Hz, 1H), 4.33–4.21 (m, 4H), 3.92 (dd, J = 8.4, 5.6 Hz, 1H), 2.60–2.49 (m, 1H), 2.55–2.35 (m, 2H), 2.24–2.18 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.27 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 167.9, 166.9, 139.5, 128.9, 127.8, 126.2, 88.2, 72.1, 62.4, 62.1, 58.0, 56.0, 28.8, 24.5, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 1727, 1664, 1252, 1178, 1016, 700 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{19}H_{23}NO_6$+Na^+: 384.1423 $[M$+Na$]^+$; found: 384.1418.

(3*R*,7*S*,7a*S*)-Ethyl 7-cyano-hexahydro-5-oxo-3-phenylpyrrolo[2,1-*b*]oxazole-7-carboxylate (1 fC): Obtained by reaction between **4 f** and **5 C** under conditions **I** and, after purification by flash chroma-

tography (EtOAc/cyclohexane, 20:80), **1 fC** was isolated as a colorless oil: Yield: 60%; $[\alpha]_D^{20} = -147.4$ ($c = 0.38$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42–7.32$ (m, 3H), 7.29–7.27 (m, 2H), 5.67 (s, 1H), 5.33 (dd, $J = 7.0$, 4.3 Hz, 1H), 4.66 (dd, $J = 8.6$, 7.0 Hz, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 4.21 (dd, $J = 8.6$, 4.3 Hz, 1H), 3.49 (d, $J = 17.0$ Hz, 1H), 3.14 (d, $J = 17.0$ Hz, 1H), 1.40 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.4$, 165.5, 137.9, 129.1, 128.3, 125.9, 114.6, 93.2, 75.2, 64.4, 57.9, 50.4, 42.9, 13.9 ppm; IR (neat): $\tilde{\nu} = 1722$, 1391, 1250, 1033, 698 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{16}H_{17}N_2O_4^+$: 301.1188 $[M+H]^+$; found: 301.1195.

(3*R*,7*S*,7a*S*)-7-(2-Nitrophenyl)-5-oxo-3-phenylhexahydropyrrolo[2,1-b]oxazole-7-carbonitrile (1 hC): Obtained by reaction between **4 h'** and **5 C** under conditions **I** and, after purification by flash chromatography (EtOAc/cyclohexane, 30:70), **1 hC** was isolated as a white solid: Yield: 53%; m.p. 154 °C; $[\alpha]_D^{20} = -249.5$ ($c = 0.88$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89–7.85$ (m, 2H), 7.69 (t, $J = 7.6$ Hz, 1H), 7.58 (t, $J = 7.6$ Hz, 1H), 7.42–7.14 (m, 5H), 5.74 (s, 1H), 5.46–5.29 (m, 1H), 4.78 (t, $J = 7.7$ Hz, 1H), 4.26 (dd, $J = 8.4$, 4.0 Hz, 1H), 3.39 (d, $J = 16.7$ Hz, 1H), 3.23 ppm (d, $J = 16.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6$, 149.3, 138.1, 133.8, 130.9, 130.5, 129.2, 128.4, 128.3, 126.2, 125.9, 117.1, 96.1, 76.0, 57.8, 49.5, 44.3 ppm; IR (neat): $\tilde{\nu} = 2249$, 1716, 1525, 1347, 721, 701 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{19}H_{16}N_3O_4^+$: 350.1141 $[M+H]^+$; found: 350.1133.

(3*R*)-5-oxo-3,7a-Diphenyltetrahydropyrrolo[2,1-b]oxazole-7,7(7aH)-dicarbonitrile (1 nC): Obtained by reaction between **4 n** and **5 C** under conditions **I** and, after purification by flash chromatography (EtOAc/cyclohexane, 20:80), **1 nC** was isolated as a white solid: Yield: 65%; m.p. 115 °C; $[\alpha]_D^{20} = -52.1$ ($c = 0.70$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.58–7.54$ (m, 2H), 7.51–7.48 (m, 3H), 7.25–7.15 (m, 3H), 7.08–7.05 (m, 2H), 5.30 (t, $J = 7.4$ Hz, 1H), 4.94 (dd, $J = 9.0$, 7.6 Hz, 1H), 4.20 (dd, $J = 9.0$, 7.4 Hz, 1H), 3.59 (d, $J = 16.4$ Hz, 1H), 3.37 ppm (d, $J = 16.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.2$, 136.2, 134.6, 131.2, 129.4, 128.9, 128.5, 127.0, 126.3, 111.9, 111.3, 101.9, 76.2, 59.4, 44.8, 44.7 ppm; IR (neat): $\tilde{\nu} = 1728$, 1337, 749, 697, 667 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{20}H_{16}N_3O_2^+$: 330.1243 $[M+H]^+$; found: 330.1241.

Modified conditions I: Chlorinated Michael acceptor (**4'**, 1.5 mmol, 1.5 equiv) and *N*-hydroxyalkyl α-bromoacetamide (**5**, 1.0 mmol, 1 equiv) were dissolved in freshly distilled THF (10 mL) and cooled to −20 °C. Sodium hydride (80 mg, 60% suspension in mineral oil, 2.0 mmol, 2.0 equiv) was added and the mixture was stirred at −20 °C for 4 h. The reaction was quenched carefully at −20 °C by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (3×10 mL), the organic phases were combined, washed with brine, dried over $MgSO_4$ and solvent was removed under vacuum. The residue was then chromatographed on silica gel to afford the desired compound.

(3*R*,7a*S*)-3-Phenyl-7,7-bis(phenylsulfonyl)tetrahydropyrrolo[2,1-b]oxazol-5(6H)-one (1 qC): Obtained by reaction between **4 q'** and **5 C** under modified conditions **I** and, after purification by flash chromatography (EtOAc/cyclohexane, 30:70), **1 qC** was isolated as a white solid: Yield: 51%; m.p. 196 °C; $[\alpha]_D^{20} = -87.8$ ($c = 0.74$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.15$ (d, $J = 7.1$ Hz, 2H), 8.12 (d, $J = 6.4$ Hz, 2H), 7.83–7.62 (m, 6H), 7.48–7.31 (m, 3H), 7.22 (d, $J = 7.1$ Hz, 2H), 6.29 (s, 1H), 5.01 (t, $J = 6$ Hz, 1H), 4.73 (t, $J = 7.7$ Hz, 1H), 4.11 (dd, $J = 8.1$, 5.4 Hz, 1H), 3.93 (d, $J = 18.0$ Hz, 1H), 3.30 ppm (d, $J = 18.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.8$, 138.1, 136.9, 135.9, 135.5, 135.2, 132.0, 130.8, 129.3, 129.0, 128.7, 128.2, 125.8, 93.0, 89.0, 76.4, 57.3, 39.8 ppm; IR (neat): $\tilde{\nu} = 1713$, 1333, 1315, 1149, 714, 683 cm^{-1}; HRMS (FI): *m/z* calcd (%) for $C_{24}H_{21}NO_6S_2^+$: 483.0810 $[M]^+$ 483.0810,; found: 483.0838.

(3*R*,7a*S*)-3-Phenyl-7-(phenylsulfonyl)-2,3-dihydropyrrolo[2,1-b]oxazol-5(7aH)-one (8): Obtained as a side product from the domino reaction between **4 q'** and **5 C** and, after purification by flash chromatography (EtOAc/cyclohexane, 30:70), **1 fA** was isolated as a white solid: Yield: 7%; m.p. 135 °C; $[\alpha]_D^{20} = -20.1$ ($c = 0.23$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 7.6$ Hz, 2H), 7.74 (t, $J = 7.4$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 2H), 7.44–7.20 (m, 5H), 6.76 (s, 1H), 5.90 (s, 1H), 4.94 (t, $J = 7.3$ Hz, 1H), 4.72–4.57 (m, 1H), 4.05 ppm (dd, $J = 8.9$, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.5$, 157.9, 138.2, 138.0, 135.4, 135.1, 129.7, 129.1, 128.9, 128.3, 126.1, 91.4, 78.6, 58.1 ppm; IR (neat): $\tilde{\nu} = 3093$, 1702, 1325, 1150, 732, 719, 696, 682 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{18}H_{16}NO_4S^+$: 342.0801 $[M+H]^+$; found: 348.0793.

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Keywords: bicyclic lactams · DFT · diastereoselectivity · domino reactions · quaternary stereocenter

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[12] For all bicyclic lactams **1xY**, the **x** refers to the Michael acceptor substrate **4x** or **4x′** and the **Y** refers to the amido alcohol **5Y** substrate.

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