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# Origin of the Base-Dependent Facial Selectivity in Annulation Reactions of Nazarov-Type Reagents with Unsaturated Indolo[2,3-*a*]quinolizidine Lactams.

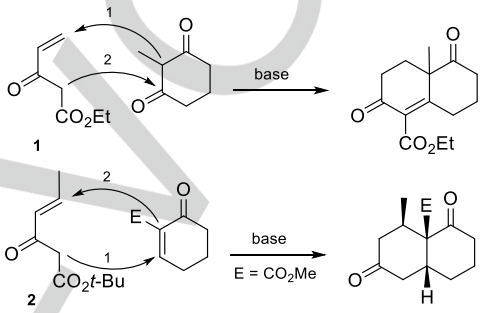
Carolina Estarellas,[a] Federica Arioli,[b] Maria Pérez,[a] Celeste Are,[b] David Hevia,[b] Elies Molins,[c] F. Javier Luque,*[a] Joan Bosch,[b] and Mercedes Amat*[b]

**Abstract:** The methyl-substituted Nazarov reagent **4** stereoselectively reacts with $N_{ind}$-Boc indoloquinolizidine lactams to give the expected H-3/H-15 *cis* pentacyclic yohimbine-type adducts when using DBU as the base. However, a dramatic change of the facial selectivity was observed when the reaction was performed in the presence of $Cs_2CO_3$, leading to the corresponding *trans* adducts. This annulation is the key step of a stereocontrolled synthesis of the 17a-carba-analog of the heteroyohimbine alkaloid akuammigine. Theoretical calculations were used to rationalize the facial selectivity of these double Michael addition reactions.

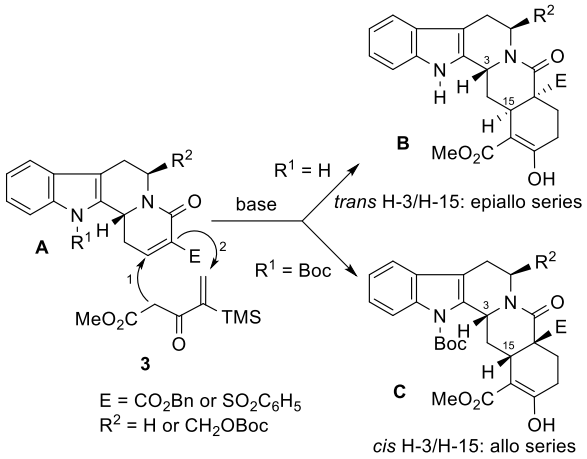
## Introduction

Ethyl (or methyl) 3-oxo-4-pentenoate (**1**), known as the Nazarov reagent,[1] is a versatile annelating agent widely used in a variety of Robinson-type annulations, in which it sequentially acts as an electrophilic reagent in a Michael addition and as a nucleophile to promote the cyclization[2,3] (Scheme 1). The fact that **1** is unstable under basic conditions and polymerizes[4] rapidly at rt has stimulated the development of more stable analogs of **1** bearing alkyl substituents on the vinyl moiety, such as **2**.[5] These Nazarov-type reagents are able to undergo alternative annulations involving base-catalyzed double Michael addition reactions with α,β-unsaturated carbonyl compounds, in which the reagent successively acts as a nucleophile and an electrophilic Michael acceptor.[6]

In previous work[7] we have reported the preparation of the silylated derivative **3**, which behaves as a stable synthetic equivalent of the original Nazarov reagent **1**. Derivative **3** can participate in base-promoted double Michael annulations (Scheme 2), avoiding the polymerization problem associated with **1**. Using unsaturated indolo[2,3-*a*]quinolizidine lactams **A**, this reagent opened up straightforward stereodivergent routes to yohimbine-type derivatives.[7,8] Interestingly, pentacyclic H-3/H-15 *trans* adducts **B** were generated from $N_{ind}$-unsubstituted lactams, but the corresponding *cis* isomers **C** were formed when the indole nitrogen bears a Boc substituent (Scheme 2).[9] This dramatic reversal in the facial selectivity was rationalized by means of theoretical calculations, which indicated that the initial nucleophilic attack under stereoelectronic control is hampered




**Scheme 1.** Typical reactivity of the Nazarov reagent (**1**) and its methyl substituted analog **2**.




**Scheme 2.** Stereocontrolled annulations with the silylated Nazarov reagent **3**.

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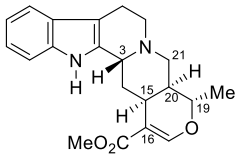
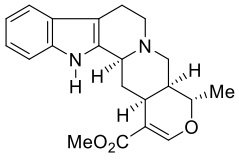
by the presence of the bulky Boc group.[8] The reactions were performed using either DBU (in THF)[10] or $Cs_2CO_3$ (in $CH_2Cl_2$) as the base, although with the latter, when E = $SO_2C_6H_5$, the stereoselectivity was lower and dependent on the concentration of $Cs_2CO_3$.

On the basis of these findings, we envisaged that the use of the methyl-substituted Nazarov reagent **4** (Scheme 3) in double Michael annulations with unsaturated indolo[2,3-*a*]quinolizidine lactams **A** would afford pentacyclic carba-analogs of heteroyohimbine alkaloids bearing their characteristic C-19 methyl substituent (Figure 1). Following this rationale, we report here the enantioselective synthesis of 17*a*-carbaakuammigine, taking advantage of an unexpected base-dependent stereoselective addition in double Michael annulations with Nazarov reagent **4**. Furthermore, theoretical calculations allow us to justify the facial selectivity of these reactions and to disclose the key role played by cesium cations in the stereoselective outcome.



Akuammigine



Tetrahydroalstonine

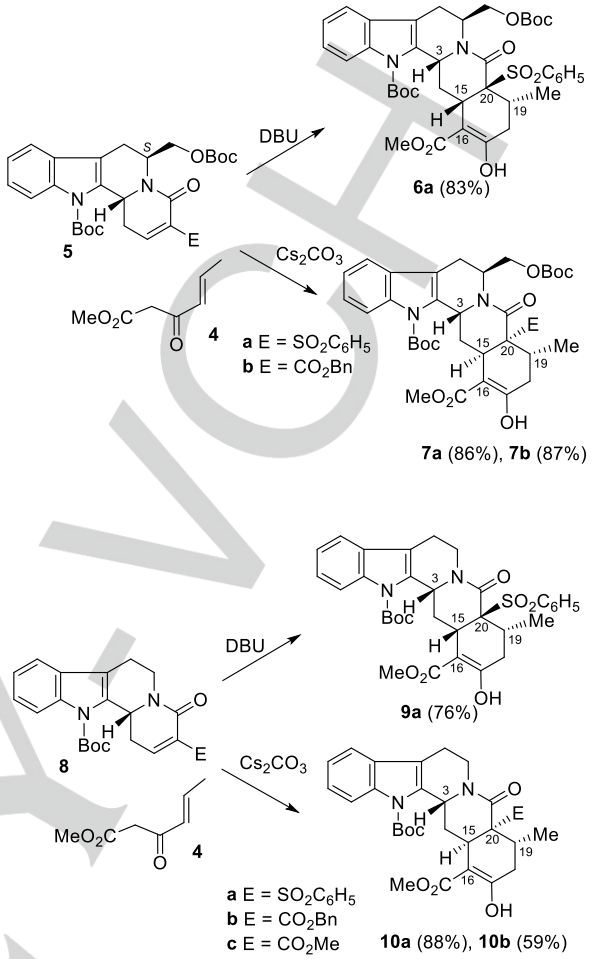
**Figure 1.** Heteroyohimbine alkaloids akuammigine and tetrahydroalstonine.

## Results and Discussion

### Base-dependent stereoselective double Michael addition reactions with Nazarov reagent 4

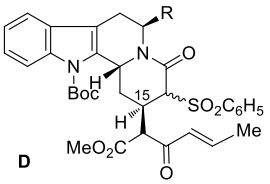
Reaction of enantiopure $N_{ind}$-Boc lactam **5a** with the Nazarov reagent **4** using DBU as the base afforded the pentacyclic adduct **6a**, with the expected H-3/H-15 *cis* configuration, in excellent yield.[11] However, to our surprise, when the reaction was performed in the presence of $Cs_2CO_3$, which is the most commonly used base for the generation of the enolate salt of Nazarov reagents, the H-3/H-15 *trans* adduct **7a** was obtained in 86% yield. A similar unexpected stereochemical result was observed in the $Cs_2CO_3$-promoted double Michael addition of **4** to unsaturated lactam **5b**: the pentacyclic H-3/H-15 *trans* adduct **7b** was obtained in 87% yield (Scheme 3).

To further investigate the influence of the base on the facial selectivity of the process, we also studied the annulations of the Nazarov reagent **4** with racemic $N_{ind}$-Boc indoloquinolizidin-2-ones **8a** and **8b**, which lack the protected hydroxymethyl substituent. From a stereochemical standpoint, the results matched those previously observed from **5**. When the reaction of **8a** was performed in the presence of DBU, the H-3/H-15 *cis* pentacycle **9a** was obtained in excellent yield.[11] In contrast, when $Cs_2CO_3$ was used as the base, the corresponding H-3/H-15 *trans* adducts **10a** and **10b**[12] were stereoselectively formed in 88% and 59% yields, respectively.




**Scheme 3.** Double Michael addition reactions of the methyl-substituted Nazarov reagent **4** with unsaturated lactams **5** and **8** (compounds **8**-**10** are racemic mixtures).

In agreement with a stepwise double Michael process, when the $Cs_2CO_3$-promoted reaction from **5a** was stopped after 2h, the tetracyclic intermediate **D** (R = $CH_2OBoc$) arising from the initial Michael addition was isolated in 23% yield (Figure 2). Minor amounts of similar open intermediates were detected by NMR in all the annulations shown in Scheme 3, including the reactions in presence of DBU.



**D**

**Figure 2.** Tetracyclic intermediate **D**.

The observation of positive NOE effects between H-3/H-15, $C_{19}$-Me/H$\alpha$-14, and $C_{19}$-Me/H$\alpha$-18 in **6a** and **9a**, and between H-3/H-

19, H-3/Hβ-18, $C_{19}$-Me/H-15, and $C_{19}$-Me/Hα-18 in **10a** was in agreement with the stereochemical assignments made for the above pentacyclic derivatives. Additionally, the relative configuration of **9a** and **10a** was unambiguously established by X-ray crystallographic analysis[13] (Figure 3).

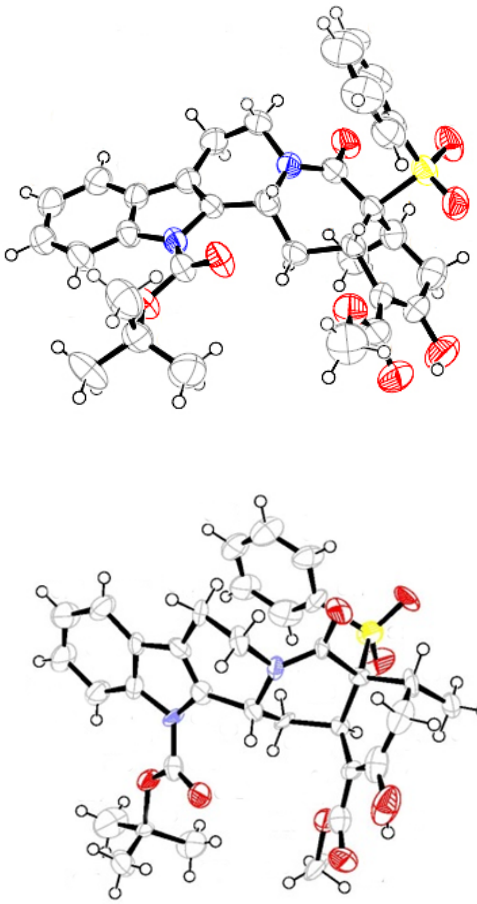



**Figure 3.** X-ray crystal structures of the H-3/H-15 *cis* and *trans* adducts **9a** and **10a**, respectively.

Another striking aspect from the stereochemical standpoint was the relative configuration of the C-19 stereocenter. Whereas the expected *cis* relative configuration for the substituents at positions 19 and 20 was observed in the H-3/H-15 *trans* adducts **7** and **10**,[14] a *trans* $C_{19}$-Me/$C_{20}$-$SO_2C_6H_5$ relationship was found in the H-3/H-15 *cis* pentacycles **6a** and **9a**.[15] In all cases, the resulting *cis* D/E ring junction arises from stereoelectronic control during the Michael cyclization step.[6b,15b]

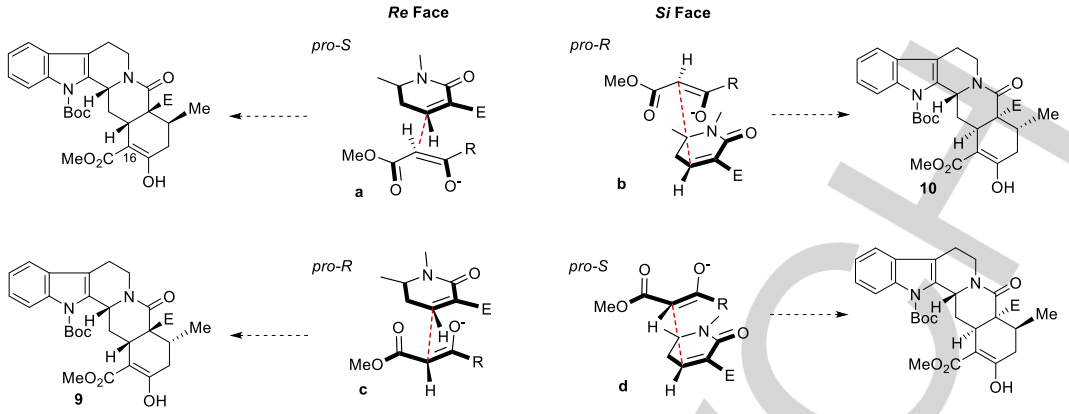
**Conformational preferences of Nazarov reagents 3 and 4**

Theoretical calculations were performed to understand the unexpected reversal of the facial selectivity of $Cs_2CO_3$-catalyzed annulation reactions of methyl-substituted Nazarov reagent **4** with unsaturated $N_{ind}$-Boc indoloquinolizidine lactams **5** and **8** as compared with similar reactions catalyzed by DBU. Calculations were performed using the M06-2X density functional[16] and the 6-31G(d) basis set,[17] and solvent effects were accounted for by using the SMD version[18] of the IEFPCM model (see Experimental for details).

In a preliminary step, the conformational preference of the anionic species generated from Nazarov reagents **3** and **4** was determined (Figure S1 in Supporting Information). The results pointed out that the s-*cis* species of **3** is favored by 1.7 kcal/mol in $CH_2Cl_2$ relative to the s-*trans* conformer. It is worth noting that the s-*cis* conformation has the appropriate arrangement required for the annulation reaction that gives rise to fused pentacyclic products (**B** and **C** in Scheme 2). In contrast, the s-*cis* species of **4** is destabilized by 2.4 kcal/mol relative to the s-*trans* conformation, which suggests that the population of the s-*cis* species is less than 2% at 298 K. Accordingly, the reaction of **4** should primarily proceed through attack of the s-*trans* species, which does not have the configuration required for ring closure. Therefore, it can be expected that the double Michael addition occurs through an intermediate step that involves the conversion to the s-*cis* arrangement.

**Double Michael additions with silylated Nazarov reagent 3**

In order to rationalize the stereochemical outcome of the double Michael addition reactions, we first determined the free energy profile for the reaction of the anionic form of **3** to lactam **A** (Scheme 2, with $R^1$=Boc, $R^2$=H, and E=$CO_2$Me in calculations; **8c** in Scheme 3) as a reference system. Calculations were performed for the Michael additions through the *Si* and *Re* faces of lactam **8c**. Furthermore, the addition reaction was considered to occur through the two faces of reagent **3** (denoted *pro-S* and *pro-R* depending on the stereochemistry of the $C_{16}$ stereocenter initially formed in the first Michael addition), thus leading to four plausible reaction channels that are schematically shown in Scheme 4. For the specific case of the reaction between reagent **3** and lactam **8c**, however, the steric hindrance arising from the TMS group allowed us to limit calculations to only two reactive pathways, as will be explained below.




**Scheme 4.** Representation of the four plausible pathways for the initial Michael addition reactions between the Nazarov reagent (**3** [R = C(TMS)=$CH_2$] or **4** [R = (*E*)-CH=CHMe]) and the lactam, and the resulting possible annulation products formed from the reaction with **4**.

The stereoselective formation of the *cis* H-3/H-15 isomer (**C** in Scheme 2) stems from the preferential attack of the silylated reagent **3** (*pro-S* face) through the *Re* face. This is reflected in the lower stability of the transition state (TS1) formed in the first Michael addition through the *Si* face, which is destabilized by 3.1 kcal/mol relative to the *Re* attack (Figures 4 and 5). This process is the rate-limiting step of the annulation reaction, as the barrier (8.2 kcal/mol) for the first Michael addition is larger than the barrier required for ring closure (6.1 kcal/mol; TS2), which ultimately leads to a large stabilization of the annulated product (by nearly 24 kcal/mol relative to the pre-reactant complex). It is worth noting that the free energy profile determined from M062X computations is supported by the similar free energy differences between pre-reactant, intermediate, and transition states obtained from single-point calculations at the SCS-MP2/6-31G(d) and B2PLYP-D3/def2-SVPP levels, as noted from the data reported in Table 1.

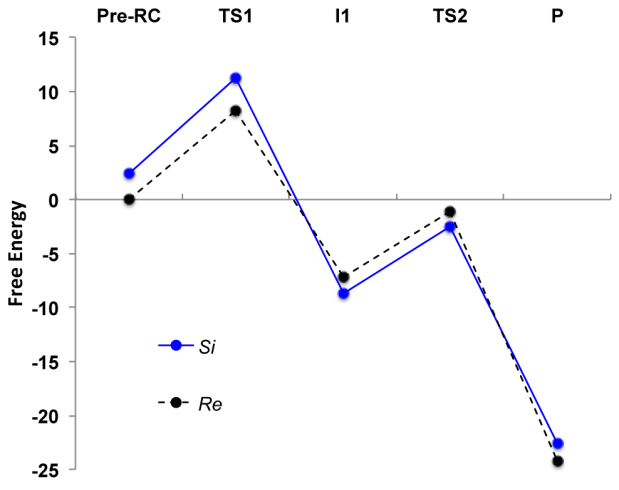



**Figure 4.** Free energy (kcal/mol) profile for the double Michael addition of the anionic species of Nazarov reagent **3** (*pro-S* and *pro-R* faces for *Re* and *Si* attacks, respectively) to lactam **8c** derived from M062X/6-31G(d) calculations in $CH_2Cl_2$.

**Table 1.** Comparison of the free energy differences (kcal/mol) determined at the M062X/6-31G(d), SCS-MP2/6-31G(d), and B2PLYP-D3/def2-SVPP levels in $CH_2Cl_2$ for the addition of the anionic form of Nazarov reagent **3** (*pro-S* and *pro-R* faces for *Re* and *Si* attacks, respectively) to lactam **8c**.

| | M062X | | SCS-MP2 | | B2PLYP-D3 | |
|---|---|---|---|---|---|---|
| | *Re* | *Si* | *Re* | *Si* | *Re* | *Si* |
| Pre-RC | 0.0 | 2.5 | 0.0 | 3.1 | 0.0 | 2.7 |
| TS1 | 8.2 | 11.3 | 11.5 | 14.9 | 7.3 | 10.1 |
| I1 | -7.2 | -8.7 | -9.7 | -11.0 | -8.0 | -9.5 |
| TS2 | -1.1 | -2.5 | -3.1 | -4.7 | -5.5 | -6.6 |
| P | -24.2 | -22.6 | -30.6 | -29.4 | -29.0 | -26.6 |

Assuming that these reactions are under the Curtin-Hammett control, the relative free energy of the transition states (TS1), which is estimated to be around 3 kcal/mol (see Table 1), would lead to a ratio of 160:1 for the H-3/H-15 *cis* and *trans* isomers **C** and **B**, respectively (Scheme 2), in agreement with the experimental data. Inspection of the rate-limiting transition state for the *Re* addition (Figure 5) suggests that the steric hindrance of the bulky *N*-Boc group counterbalances the stereochemical preference for attack through the convex face of the α,β-unsaturated lactam. Furthermore, Figure 6 shows the asynchronicity of the double Michael addition, as the length of the forming C···C bonds is 2.29 and 3.27 Å. Finally, Figure 6 also shows that the attack occurs with an antiperiplanar arrangement (**a**, Scheme 4) of the carbon atoms involved in the first Michael addition (H–C···C–H dihedral angle of -172.8 degrees), which locates the double bond in the appropriate arrangement for ring closure, and avoids steric clashes between the bulky TMS group and the lactam **8c**. In contrast, the attack through the pro-*R* face of reagent **3** (**c**, Scheme 4) is unfeasible

due to the steric hindrance originated by the TMS group (data not shown).

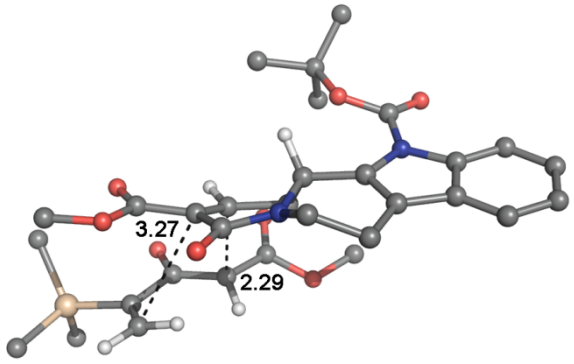



**Figure 5.** Representation of the transition state (TS1) formed in the *Re* attack of reagent **3** (*pro-S* face) to lactam **8c**. For the sake of clarity, only selected hydrogen atoms are shown. Complete geometrical data of pre-reactants, transition states, and intermediates is available in Supporting Information.

### Double Michael additions with methyl-substituted Nazarov reagent 4

Next, we examined the annulation reaction between lactam **8a** and Nazarov reagent **4**. It is worth noting that the stereochemical outcome obtained for H-3/H-15 and C-19/C-20 centers is different depending on the base, DBU or $Cs_2CO_3$, used to catalyze the reaction (see Scheme 3). As noted above (see Figure 4), the addition reaction was performed considering the attack of the s-*trans* species of **4**, which was found to be the predominant form in solution. The annulation reaction was studied through the *Re* and *Si* faces of lactam **8a**. In contrast to the Nazarov reagent **3**, the absence of the bulky TMS group permits the attack of **4** through both *pro-R* and *pro-S* faces (see Scheme 4).

Compared to the reaction of the silylated reagent **3**, the free energy profile for the DBU-promoted attack of reagent **4** to lactam **8a** shows distinctive trends (see Figure 6). First, in the most favored approach of the reactants the Nazarov reagent is oriented with the carbonyl oxygens opposite to the sulfonyl group in the lactam, leading to a *gauche* arrangement for the C-H groups that participate in the first Michael addition (H–C···C–H dihedral angle of 58.1 and 61.6 degrees in the TSs formed for the *Re* and *Si* attacks; note that this approach was sterically impeded by the bulky TMS unit in the reaction of **3** with lactam **8c**). This arrangement avoids the repulsion between the lone pairs of the oxygen atoms in the Nazarov reagent and the sulfonyl group, while it permits the formation of C-H···O interactions between the reactants. Indeed, this approach leads to pre-reactant complexes that are more favored (by 3-4 kcal/mol) than those obtained for an antiperiplanar approach.

The stability of the transition state for the first Michael addition (TS1; Figure 7) is similar for the *Re* and *Si* attacks, leading to intermediates (I1) with geometrical features unfeasible for the second addition, as the distance between the reactive C atoms involved in the second Michael addition is close to 3.7 Å due to the s-*trans* arrangement of the Nazarov reagent. In fact, the second Michael addition is preceded by the internal rotation of the **4** moiety, which involves a small barrier (through a rotational transition state; Ts-rot) for the conversion of the *s-trans* conformation in intermediate I1 to the *s-cis* arrangement in the novel intermediate I2. This would facilitate the formation of the second bond, as the distance between the C atoms is close to 3.1 Å. The barriers for the second Michael addition (TS2; Figure 7) through the *Re* and *Si* face are 11.1 and 12.3 kcal/mol, respectively. The relative free energy of the transition states (1.2 kcal/mol) would lead to a ratio of 7.6:1 for the *Re* and *Si* products, **9a** and **10a**, respectively. Finally, between the two cyclized products, the *Re* annulation is also found to be more stable (by 2.1 kcal/mol) than the *Si* addition, in agreement with the experimental outcome (see Scheme 3).

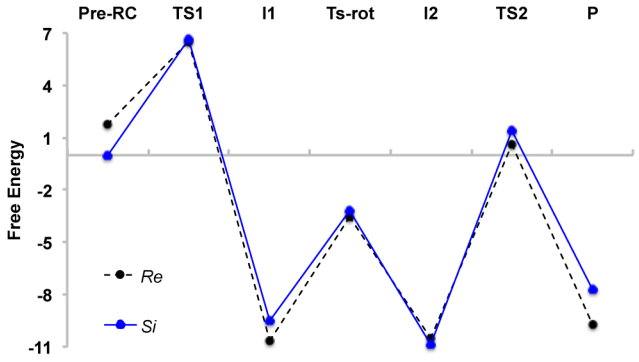



**Figure 6.** Free energy (kcal/mol) profile for the DBU-catalyzed double Michael addition of the anionic species of Nazarov reagent **4** to lactam **8a** derived from M062X/6-31G(d) calculations in $CH_2Cl_2$.

This reactive pathway leads to the experimental stereochemical outcome (see Scheme 3), as noted in the transition state for the second Michael addition (TS2) through the *Re* face of lactam **8a**, which shows the proper orientation of the reactants for the *cis* H-3/H-15 and *trans* $C_{19}$-Me/$C_{20}$-E($SO_2$Ph) arrangements of the final product **9a** (Figure 7). The barrier for the cyclization can be ascribed to the formation of a boat-like structure in the forming six-membered ring, which is assisted by a significant pyramidalization (20.6 and 30.5 degrees) of the carbon atoms involved in ring closure. On the other hand, the transition state is stabilized by the formation of several C–H···O hydrogen bonds between the sulfonyl oxygens of the lactam and hydrogen atoms of the Nazarov reagent.

As a final remark, the transition state corresponding to the *Re* attack of reagent **4** in the less stable *s-cis* conformation (Figure S1 in Supporting Information) to lactam **8a** was also identified. Compared to the transition state formed upon attack of the *s-trans* conformation (TS1 in Figure 7) through the *Re* face, it was found to be destabilized by 0.6 kcal/mol. This finding, in conjunction with the low population of the *s-cis* conformer (< 2%; see above), supports the mechanistic pathway shown in Figure 6.

### The effect of the cesium cation

Why does the replacement of DBU by $Cs_2CO_3$ revert the stereochemical outcome of the reaction with Nazarov reagent **4**? We hypothesize that the cesium cation plays a dual role in this reaction. First, through coordination to the carbonyl oxygen atoms of **4**, the $Cs^+$ cation affords the electrostatic stabilization for generation of the anionic form of the Nazarov reagent (Scheme S1 in Supporting Information). Second, such electrostatic stabilization suggests that the ionic pair $Cs^+$-**4**$^-$ can be the reactive species for the addition to lactams **8**. This assumption is supported by the relatively low permittivity of dichloromethane (ε = 8.9 at rt), and by the excess of $Cs_2CO_3$ relative to the Nazarov reagent **4**, which were in a 2:1 ratio under the reaction conditions (see Experimental). On the other hand, although the presence of ionic pairs when DBU is used cannot be ruled out, delocalization of the positive charge in the amidinium unit and the much larger size of DBU compared to the localized unit charge and smaller size of the $Cs^+$ cation (and hence the stronger electrostatic potential) suggests that the presence of ionic pairs should be more relevant for the $Cs^+$ cation. Further support comes from both experimental and theoretical evidence about the formation of cesium-coordinated aggregates of diketones and carboxylic acids. [19-21]

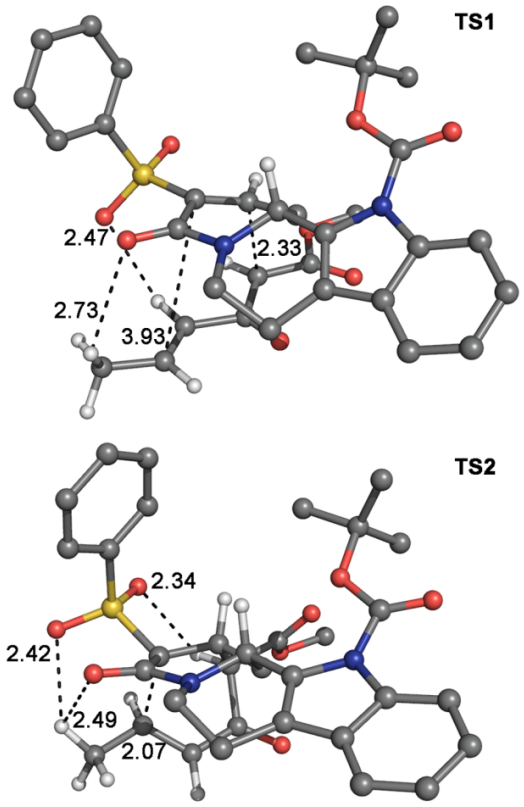



**Figure 7.** Representation of the transition states (TS1 and TS2) formed in the DBU-catalyzed double Michael additions of the anionic form of Nazarov reagent **4** to lactam **8a**. The approach occurs through the *pro-R* face of **4** and the *Re* face of the lactam. For the sake of clarity, only selected hydrogen atoms are shown. Complete geometrical data of pre-reactants, transition states, and intermediates is available in Supporting Information.

Under these circumstances, coordination of the $Cs^+$ cation to the oxygen atoms of the ester or sulfonyl groups of lactams **8** may affect the relative stability of the annulation reaction through the two diastereotopic faces of the lactam. To this end, the attack of the Nazarov reagent **4** should proceed via an antiperiplanar approach between the carbon atoms that will form the first C--C bond, as this approach would place the oxygen atoms of both **4** and the activating E group close for coordination to the $Cs^+$ cation. To check the feasibility of this mechanistic hypothesis, we determined the free energy profile for the addition of the $Cs^+$···**4** complex to lactam **8c** (see Scheme 3; note that the benzyl group of **8b** was replaced by methyl in present calculations).

The transition states (TS1) for the first Michael addition between reagent **4** and lactam **8c** (Figure 8) have similar stabilities, the *Re* approach being slightly more favorable (by 0.6 kcal/mol). As noted in Figure 9, the $Cs^+$ cation is coordinated to the carbonyl oxygens of **4** and to the carbonyl oxygen of the ester group in lactam **8b**, with distances close to 2.9 Å, thus assisting the proper arrangement of the reactants in the annulation reaction. As noted above, this requires the Nazarov reagent **4** to be oriented with the carbonyl oxygens pointing toward the molecular edge that contains the ester group in the lactam, so that the attack occurs with a slightly distorted antiperiplanar arrangement of the carbon atoms involved in the first Michael addition (H–C···C–H dihedral angle of -160.7 and 133.5 degrees for the *Re* and *Si* additions, respectively). Figure 9 also shows the asynchronicity of the double Michael addition, as the length of the forming C--C bonds is 2.11 (2.16) and 3.43 (3.49) Å for the *Si* (*Re*) addition, thus making necessary the internal rotation to the **4** s-*cis* conformation required for cyclization, as noted before for the DBU-catalyzed process.

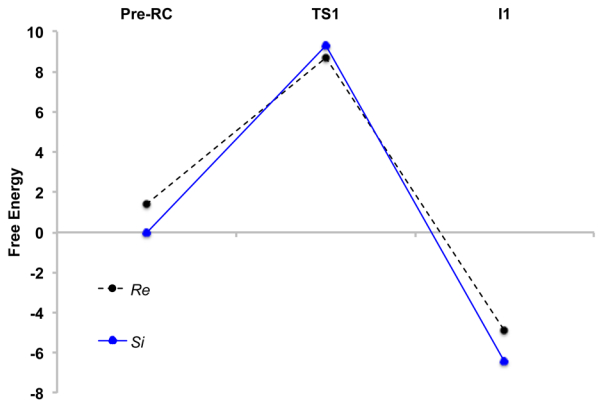



**Figure 8.** Free energy (kcal/mol) profile for the first Michael addition of the $Cs^+$···**4** complex to lactam **8c** derived from M062X/6-31G(d) calculations in $CH_2Cl_2$.

Whether the $Cs^+$ cation remains coordinated along the rest of the cyclization reaction is more questionable, because the formation of the first C–C bond in intermediate I1 is concomitant to a charge transfer from the Nazarov reagent to carbon atom $C_{20}$ in the lactam. Thus, the Mulliken charge of this latter atom changes from -0.05 *e* in the pre-reactant (Pre-RC) complex to -0.18 *e* in I1, whereas the net charge of the oxygen atoms in the Nazarov reagent varies from -0.63 *e* in Pre-RC to -0.52 *e* in I1. The charge transfer from **4** to **8c** should weaken the electrostatic stabilization between the Nazarov reagent and the $Cs^+$ cation, which presumably might be released to the solvent environment. The theoretical computation of the absolute free energy of $Cs^+$ coordination is challenging, especially due to the difficulty in estimating the solvation contribution in the complex environment of the reaction. However, this term cancels out when the relative free energy of $Cs^+$ release from the pre-reactant complex (Pre-RC) and the intermediate (I1) is determined, as noted in Scheme 5. Calculations performed for the corresponding species originated via the *Re* and *Si* addition of $Cs^+\cdots$**4** to lactam **8c** indicate that the cation release from the intermediate is favored by 4.6 kcal/mol in the two cases, as expected from the charge transfer from **4** to **8c**.

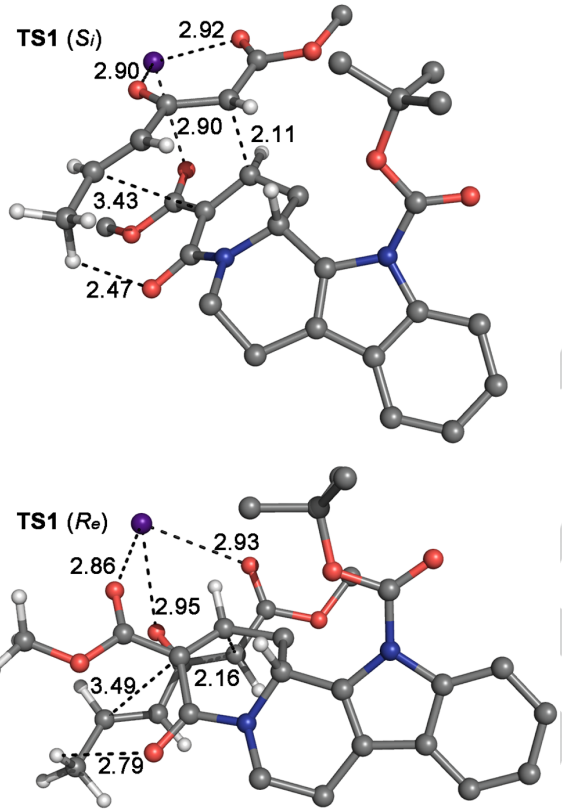
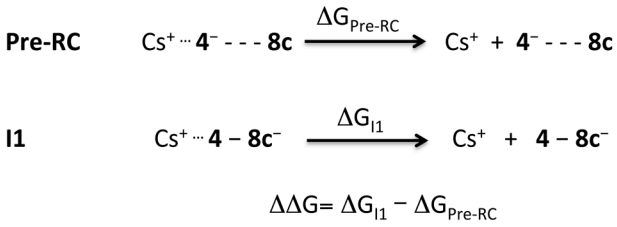



**Figure 9.** Representation of the transition state (TS1) formed in the first Michael addition of the $Cs^+\cdots$**4** complex to lactam **8c**. The approach occurs through the *Si* (top; *pro-R* face of **4**), and *Re* (bottom; *pro-S* face of **4**) faces of the lactam. For the sake of clarity, only selected hydrogen atoms are shown. The $Cs^+$ cation is shown as a violet sphere. Complete geometrical data of pre-reactants, transition states, and intermediates is available in Supporting Information.

Based on the preceding discussion, the free energy profile leading from the intermediate I1 to the ring closure was determined with and without the presence of the coordinated $Cs^+$ cation (Figure 10). The results indicate that the transition state (TS2) for the second Michael addition via the *Si* face is favored in the two cases: the *Re* TS2 is destabilized by 1.1 kcal/mol in the presence of $Cs^+$, increasing up to 2.6 kcal/mol in the absence of $Cs^+$ coordination, which would lead to a stereochemical ratio of 81:1 for the *Si* and *Re* cyclized products. Compared to the reaction with the coordinated $Cs^+$ cation, this represents a 13-fold increase in the stereoselectivity of the annulation reaction.




**Scheme 5.** Calculation of the relative free energy of $Cs^+$ release between the pre-reactant complex and the intermediate formed after the first Michael addition between the anionic species of **4** and lactam **8c**.

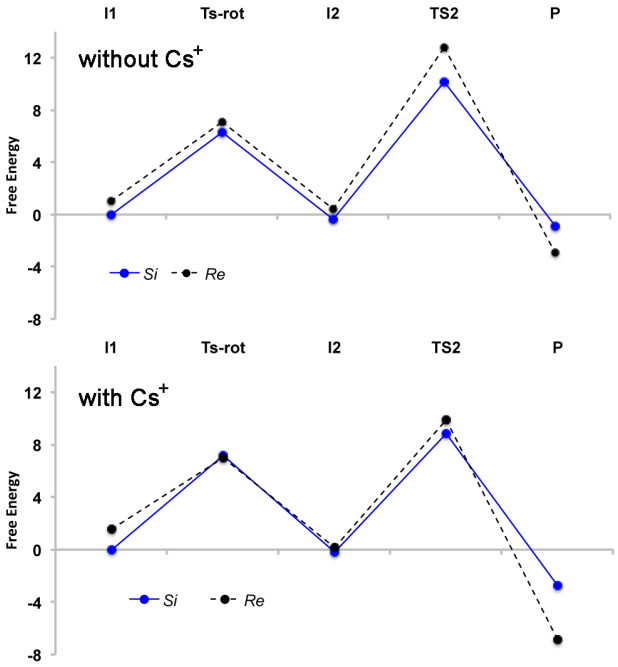


**Figure 10.** Free energy (kcal/mol) profile for the second Michael addition of the anionic species of Nazarov reagent **4** to lactam **8c** in the absence (top) and presence (bottom) of coordinated $Cs^+$ cation derived from M062X/6-31G(d) calculations in $CH_2Cl_2$.

Inspection of the transition state for the second Michael addition (Figure 11) reveals that the formation of the second C–C bond is more advanced in the absence of coordinated $Cs^+$, as noted in the shorter length of the forming bond (2.08 Å versus 2.18 Å in the absence and presence of $Cs^+$ cation, respectively; see Figure 11), as well as in the larger pyramidalization of the respective carbon atoms (close to 19 degrees in the absence of $Cs^+$ cation versus 15 degrees with coordinated $Cs^+$ cation). Let us note that the addition through the *Si* face yields the experimental stereochemistry characterized by *trans* H-3/H-15 and *cis* $C_{19}$-Me/$C_{20}$-$CO_2$Me relationships (Figure 11).

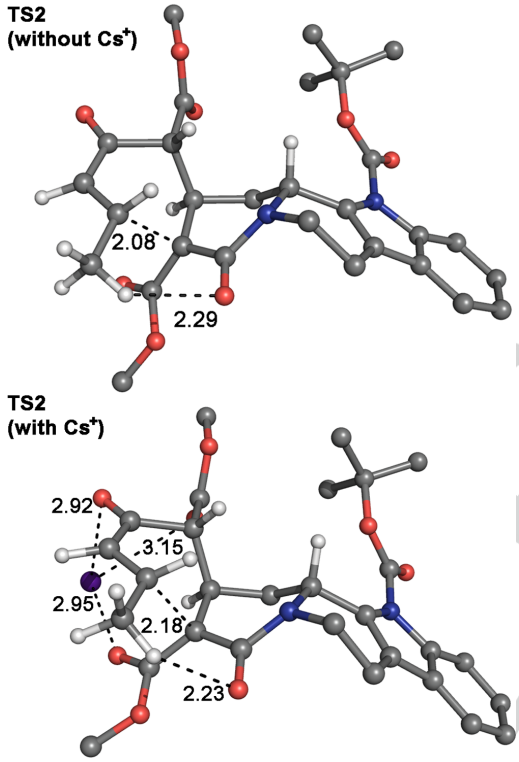


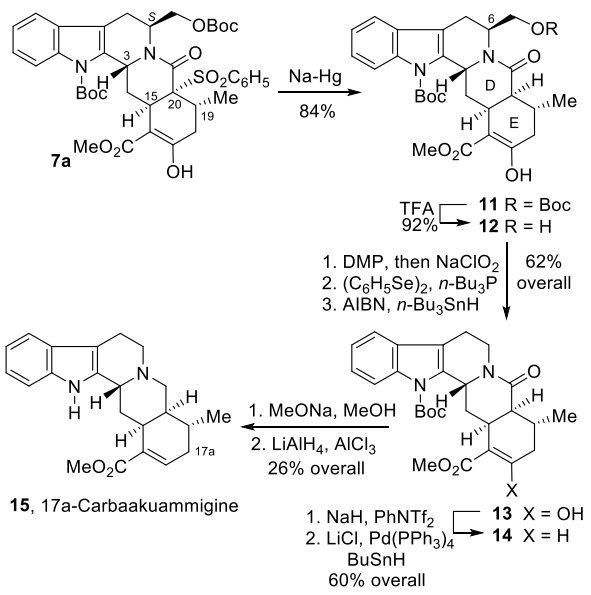

**Figure 11.** Representation of the transition state (TS2) formed in the second Michael addition of the anionic species of Nazarov reagent **4** to lactam **8c** in the absence (top) and presence (bottom) of coordinated $Cs^+$ cation. The approach occurs through the *pro-R* face of **4** and the *Si* face of the lactam. For the sake of clarity, only selected hydrogen atoms are shown. The $Cs^+$ cation is shown as a violet sphere. Complete geometrical data of pre-reactants, transition states, and intermediates is available in Supporting Information.

Overall, the present results suggest that coordination of the $Cs^+$ cation to the carbonyl oxygens of both the Nazarov reagent and the activating E group of the lactam is a key factor in promoting the proper arrangement of **4** relative to the lactam. The coordination forces the carbon atoms that participate in the first Michael addition to adopt an antiperiplanar orientation, which in turn determines the final stereochemical outcome of the cyclized product.

To further explore the crucial role of cesium in the mechanism of the double Michael addition, the reaction between lactam **8a** and Nazarov reagent **4** was performed using $Li_2CO_3$ instead of $Cs_2CO_3$. In this case, the tetracyclic intermediate **D** (Figure 2; R = H), resulting from the initial Michael addition, was isolated as a $C_{15}$ mixture of stereoisomers. An additional treatment ($CH_2Cl_2$, 20h) with $Li_2CO_3$ did not lead to any pentacyclic cyclized product. The different outcome obtained in the presence of $Li_2CO_3$ can be explained by the structural constraints imposed by the lower ionic radius of $Li^+$, which would perturb the structural and energetic features of the $Cs^+$-coordinated reactive complex. Thus, theoretical calculations revealed that the intrinsic stability of the TS (TS1) for the first Michael addition is penalized by around 4 and 7 kcal/mol upon replacement of the $Cs^+$ cation by $K^+$ and $Li^+$, respectively. A significant destabilization was also found for the intermediate I1 (data not shown). Overall, these findings point out the relevance of the cation in dictating the final outcome of the annulation process.

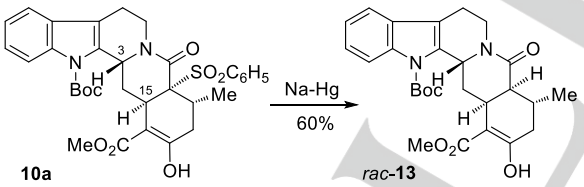
**Enantioselective synthesis of 17a-carbaakuammigine**

To illustrate the synthetic potential of the methodology and the versatility of pentacyclic Nazarov-derived adducts in the synthesis of yohimbine-type targets, we examined the conversion of the enantiopure epiallo derivative **7a** into 17a-carbaakuammigine (**15**). Reductive removal of the activating phenylsulfonyl group of **7a** using Na/Hg at −78 °C was completely stereoselective, with retention of configuration,[22] leading to the D/E *cis*-fused pentacycle **11** in excellent yield (Scheme 6). After chemoselective deprotection of the hydroxy group, the removal of the C-6 hydroxymethyl substituent of **12** was accomplished in 62% overall yield by oxidation to a carboxylic acid, followed by tin-mediated radical decarbonylation of the corresponding acyl selenide.[23] Then, the resulting enolizable β-ketoester **13** was converted to α,β-unsaturated ester **14** by palladium-catalyzed reductive coupling[24] of the corresponding vinyl triflate. Finally, after deprotection of the indole nitrogen, chemoselective alane reduction of the lactam carbonyl completed the enantioselective synthesis of 17a-carbaakuammigine (**15**).




**Scheme 6.** Enantioselective synthesis of 17a-carbaakuammigine.

The *cis* ring junction of the above pentacyclic derivatives **11**-**15** was initially deduced by $^1$H NMR, from the observation of positive NOE effects between H-15/H-20, H-15/$C_{19}$-Me, and H-20/$C_{19}$-Me in **11** and the triflate derived from **13**. Additionally, the H-3/H-15 *trans* stereochemistry in this series was unambiguously confirmed when the spectroscopic NMR data of enantiopure compound **13** proved to be identical to those of racemic **13** prepared by dephenylsulfonylation of **10a**, of known relative configuration (Scheme 7).




**Scheme 7.** Confirmation of the relative strereochemistry of **13**.

## Conclusions

The potential of the annulation reactions performed with different Nazarov-like reagents to accomplish the controlled stereoselective synthesis of complex heterocyclic compounds is well known, as illustrated here in the synthesis of yohimbine-type adducts. However, the present results highlight the dramatic change of the facial selectivity triggered by the apparently minor change originated upon replacement of DBU by $Cs_2CO_3$ as the base. We propose that this unexpected effect can be related to the coordination of the $Cs^+$ cation to the carbonyl oxygens of both the Nazarov reagent and the electron-withdrawing group in the lactam, as this determines the preferred orientation of the reactants, and eventually the final stereochemical outcome of the cyclized products. Support to the specific role of $Cs^+$ cation in determining the products of the double Michael addition comes from the very different outcome obtained upon replacement of $Cs_2CO_3$ by $Li_2CO_3$, since no pentacyclic cyclized product was isolated in this latter case. Overall, this study points out that the base can be an effective player for the control of the stereoselective addition, and hence choice of the base may be a crucial factor in dictating the most efficient way to attain the derised cyclized product. These findings open new avenues for the fine regulation of the targeted product obtained in these chemical reactions.

## Experimental Section

**Reaction of unsaturated lactams 5a and 8a with Nazarov reagent 4 using DBU.** A solution of unsaturated lactam **5a**[7] o **8a**[8] (1 equiv.) in anhydrous THF was added at 0 °C under an inert atmosphere to a solution of the Nazarov reagent **4** (2 equiv.) and DBU (1 equiv.) in anhydrous THF (0.02 M), and the mixture was allowed to warm slowly to room temperature. After 20h of stirring at room temperature, the mixture was quenched with $H_2O$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the resulting residue (9:1 hexane-EtOAc) afforded compounds **6a** (83%) or **9a** (76%), respectively, as pale yellow foams. **Compound 6a**: $[\alpha]_D^{22}$ +75.4 (*c*=0.86 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25°C, TMS): *δ*=0.97 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.43 [s, 9H, $(CH_3)_3C$], 1.44 (masked, 1H, H-14), 1.73 [s, 9H, $(CH_3)_3C$], 2.17 (dd, *J* = 18.4, 0.8 Hz, 1H, H-18), 2.77 (ddd, *J* = 16.8, 6.0, 2.4 Hz, 1H, H-6), 2.87 (dt, *J* = 16.8, 1.6 Hz, 1H, H-6), 3.05 (m, 1H, H-19), 3.14-3.21 (m, 2H, H-18, H-14), 3.67 (dd, *J* = 10.8, 5.2 Hz, 1H, $CH_2O$), 3.85 (dd, *J* = 10.8, 8.8 Hz, 1H, $CH_2O$), 3.92 (s, 3H, $CH_3O$), 3.96 (m, 1H, H-15), 5.14 (dd, *J* = 10.4, 2.0 Hz, 1H, H-3), 5.49 (m, 1H, H-5), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H, $H_{AR}$), 7.29 (td, *J* = 6.8, 1.2 Hz, 1H, $H_{AR}$), 7.40 (dd, *J* = 6.8, 1.2 Hz, 1H, $H_{AR}$), 7.57 (tt, *J* = 7.6, 0.8 Hz, 2H, H-*m* $C_6H_5$), 7.67 (tt, *J* = 7.6, 1.2 Hz, 1H, H-*p* $C_6H_5$), 7.94 (d, *J* = 7.6 Hz, 1H, $H_{AR}$), 8.01 (dd, *J* = 7.6, 0.8 Hz, 2H, H-*o* $C_6H_5$), 12.40 (s, 1H, OH); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=20.8 ($CH_3$), 22.2 (C-6), 27.7 [($CH_3$)$_3$C], 28.3 [($CH_3$)$_3$C], 30.5 (C-19), 31.5 (C-15), 33.1 (C-18), 35.0 (C-14), 45.7 (C-5), 52.1 ($CH_3O$), 52.7 (C-3), 64.8 ($CH_2O$), 76.0 (C-20), 82.4 [($CH_3$)$_3$*C*], 84.4 [($CH_3$)$_3$*C*], 97.3 (C-16), 114.4 ($C_{AR}$), 116.1 ($CH_{AR}$), 118.3 ($CH_{AR}$), 123.1 ($CH_{AR}$), 124.8 ($CH_{AR}$), 128.4 (2C-*m* $C_6H_5$), 128.8 ($C_{AR}$), 131.1 (2C-*o* $C_6H_5$), 133.4 ($C_{AR}$), 134.1 (C-*p* $C_6H_5$), 136.6 ($C_{AR}$), 136.7 ($C_{AR}$), 150.1 (CO), 153.0 (CO), 165.7 (CO), 170.9, 172.1 (C-17, CO); IR (ATR Pike) ν: 1645, 1739 cm$^{-1}$ (C=O); HRMS (ESI) calcd for $[C_{39}H_{46}N_2O_{11}S + Na]^+$: 773.2715, found 773.2717. **Compound 9a**: $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25°C, TMS): *δ*=0.97 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.42 (masked, 1H, H-14), 1.72 [s, 9H, $(CH_3)_3C$], 2.17 (dd, *J* = 17.6 Hz, 1H H-18eq), 2.55-2.68 (m, 3H, 2H-6, H-5), 3.02-3.17 (m, 3H, H-18, H-14, H-19), 3.88 (m, 1H, H-15), 3.92 (s, 3H, $CH_3O$), 4,84 (m, 1H, H-5), 5.12 (dd, *J* = 10.0, 2.4 Hz, 1H, H-3), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H, $H_{AR}$), 7.28 (td, *J* = 6.8, 1.2 Hz, 1H, $H_{AR}$), 7.39 (dd, *J* = 6.8, 1.2 Hz, 1H, $H_{AR}$), 7.56 (tt, *J* = 7.6, 0.8 Hz, 2H, H-*m* $C_6H_5$), 7.65 (tt, *J* = 7.6, 1.2 Hz, 1H, H-*p* $C_6H_5$), 7.91 (d, *J* = 7.6 Hz, 1H, $H_{AR}$), 7.99 (dd, *J* = 7.6, 0.8 Hz, 2H, H-*o* $C_6H_5$), 12.45 (s, 1H, OH); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=20.9 ($CH_3$), 21.6 (C-6), 28.3 [($CH_3$)$_3$C], 30.1 (C-19), 31.5 (C-15), 33.1 (C-18), 34.6 (C-14), 40.3 (C-5), 52.1 ($CH_3O$), 55.3 (C-3), 75.8 (C-20), 84.3 [($CH_3$)$_3$*C*], 97.3 (C-16), 115.9 ($CH_{AR}$), 118.3 ($CH_{AR}$), 118.4 ($C_{AR}$), 123.1 ($CH_{AR}$), 124.7 ($CH_{AR}$), 128.4 (2C-*m* $C_6H_5$), 128.6 ($C_{AR}$), 130.9 (2C-*o* $C_6H_5$), 134.0

(C-*p* $C_6H_5$), 134.9 ($C_{AR}$), 136.3 ($C_{AR}$), 136.7 ($C_{AR}$), 150.2 (CO), 165.2 (CO), 170.9, 172.0 (C-17, CO); IR (ATR Pike) ν: 1648, 1731 $cm^{-1}$ (C=O); HRMS (ESI) calcd for $[C_{33}H_{36}N_2O_8S + H]^+$: 621.2265, found 621.2272.

**Reaction of unsaturated lactams 5 and 8 with Nazarov reagent 4 using $Cs_2CO_3$.** A solution of unsaturated lactam **5a**[7], **5b**[7], **8a**[8] or **8b**[7] (1 equiv.) in anhydrous $CH_2Cl_2$ (0.02-0.005 M) was added at 0 °C under an inert atmosphere to a solution of the Nazarov reagent **4** (3 equiv.) and $Cs_2CO_3$ (6 equiv.) in anhydrous $CH_2Cl_2$, and the mixture was allowed to warm slowly to room temperature. After 20 h of stirring at room temperature, the mixture was concentrated under reduced pressure. Flash chromatography (9:1 hexane-EtOAc) of the resulting oil afforded compounds **7a** (86%), **7b** (87%), **10a** (88%) or **10b** (59%), respectively, as pale yellow foams. **Compound 7a** (enol-keto ratio, 9:1): m.p. 98-100 °C; $[\alpha]_D^{22}$ +20.5 (*c*=0.7 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25°C, TMS): *δ*=1.20 (d, *J* = 6.4 Hz, 3H, $CH_3$), 1.41 [s, 9H, $(CH_3)_3C$], 1.69 [s, 9H, $(CH_3)_3C$], 1.95 (dd, *J* = 18.0, 1.6 Hz, 1H, H-18), 2.25 (ddd, *J* = 14.0, 12.0, 3.2 Hz, 1H, H-14), 2.56 (d, *J* = 16.4 Hz, 1H, H-6), 2.69 (ddd, *J* = 16.4, 4.4, 2.4 Hz, 1H, H-6), 2.81 (m, 2H, H-18, H-19), 3.16 (dt, *J* = 14.0, 3.2, 3.2 Hz, 1H, H-14), 3.80 (m, 1H, $CH_2O$), 3.81 (s, 3H, $CH_3O$), 4.08 (m, 2H, H-15, $CH_2O$), 4.94 (d, *J* = 11.2 Hz, 1H, H-3), 5.63-5.71 (m, 1H, H-5), 7.20-7.60 (m, 6H, $H_{AR}$), 7.87 (dd, *J* = 8.0, 1.2 Hz, 1H, $H_{AR}$), 8.00 (dd, *J* = 8.0, 1.2 Hz, 2H, $H_{AR}$), 12.2 (s, 1H, OH); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=14.1 ($CH_3$), 21.8 (C-6), 27.6 [$(CH_3)_3C$], 28.3 [$(CH_3)_3C$], 28.7 (C-15), 29.3 (C-14), 31.6 (C-19), 35.2 (C-18), 45.6 (C-5), 49.3 (C-3), 52.0 ($CH_3O$), 64.3 ($CH_2O$), 70.0 (C-20), 82.3 [$(CH_3)_3C$], 84.3 [$(CH_3)_3C$], 96.7 (C-16), 114.9 ($C_{AR}$), 116.0 ($CH_{AR}$), 118.1 ($CH_{AR}$), 123.0 ($CH_{AR}$), 124.6 ($CH_{AR}$), 128.2, 131.2 (C-*o, m* $C_6H_5$), 128.8 ($C_{AR}$), 133.6, 133.7 ($C_{AR}$, C-*p* $C_6H_5$), 136.5 ($C_{AR}$), 138.7 (C-*i* $C_6H_5$), 150.1 (CO), 153.1 (CO), 166.4 (CO), 171.6 (C-17, CO); IR (film) ν: 1728, 1640 $cm^{-1}$ (C=O); HRMS (ESI) calcd for $[C_{39}H_{46}N_2O_{11}S + H]^+$: 751.2895, found: 751.2892; Anal. Cald for $C_{39}H_{46}N_2O_{11}S$: C, 62.38; H, 6.17; N, 3.73. Found: C, 62.15; H, 6.34; N, 3.36. **Compound 7b** (enol-keto ratio, >9:1): $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25°C, TMS): *δ*=1.26 (d, *J* = 11.2 Hz, 3H, $CH_3$), 1.45 [s, 9H, $(CH_3)_3C$], 1.68 [s, 9H, $(CH_3)_3C$], 2.01 (m, 1H, H-14), 2.10 (masked, 1H, H-14), 2.40 (m, 1H, H-19), 2.65 (d, *J* = 16.4 Hz, 1H, H-6), 2.68-2.79 (m, 2H, H-18), 2.76-2.90 (ddd, *J* = 16.4, 6.4, 2.4 Hz, 1H, H-6), 3.49 (m, 1H, H-15), 3.83 (s, 3H, $CH_3O$), 3.96 (t, *J* = 10.4 Hz, 1H, $CH_2O$), 4.11 (dd, *J* = 10.4, 7.2 Hz, 1H, $CH_2O$), 4.94 (dm, *J* = 8.4 Hz, 1H, H-3), 5.11 (d, *J* = 12.4 Hz, 1H, C$H_2C_6H_5$), 5.17 (d, *J* = 12.4 Hz, 1H, C$H_2C_6H_5$), 5.74 (m, 1H, H-5), 7.19-7.36 (m, 7H, $H_{AR}$), 7.39 (d, *J* = 7,6, 1,2 Hz, 1H, $H_{AR}$), 7.94 (d, *J* = 7,6, 1,2 Hz, 1H, $H_{AR}$), 12.2 (s, 1H, OH); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=14.1 ($CH_3$), 22.0 (C-6), 27.6 [$(CH_3)_3C$], 28.2 [$(CH_3)_3C$], 30.4 (C-19), 31.8 (C-15), 34.0 (C-14, C-18), 45.6 (C-5), 49.0 (C-3), 51.8 ($CH_3O$), 57.8 (C-20), 64.4 ($CH_2O$), 67.0 ($CH_2C_6H_5$), 82.2 [$(CH_3)_3C$], 84.0 [$(CH_3)_3C$], 97.0 (C-16), 114.9 ($C_{AR}$), 115.8 ($CH_{AR}$), 118.1 ($CH_{AR}$), 122.9 ($CH_{AR}$), 124.5 ($CH_{AR}$), 127.7-128.8 ($C_{AR}$, C-*o*, *m*, *p* $C_6H_5$), 134.4 ($C_{AR}$), 135.6 (C-*i* $C_6H_5$), 136.6 ($C_{AR}$), 149.9 (CO), 153.1 (CO), 168.3-172.1 (C-17, 3CO); IR (film) ν: 1728, 1646 $cm^{-1}$ (C=O); HRMS (ESI) calcd for $[C_{41}H_{48}N_2O_{11} + H]^+$: 745.3331, found 745.3322. **Compound 10a**: $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25°C, TMS): *δ*=1.18 (d, *J* = 6.8 Hz, 3H, $CH_3$), 1.69 [s, 9H, $(CH_3)_3C$], 2.00 (dd, *J* = 18.4, 2.0 Hz, 1H, H-18), 2.27 (ddd, *J* = 14.4, 11.6, 2.6 Hz, 1H, H-14), 2.48-2.61 (m, 3H, 2H-6, H-18), 2.74 (m, 2H, H-19, H-5), 3.25 (dt, *J* = 14.4, 4.0 Hz, 1H, H-14), 3.93 (s, 3H, $CH_3O$), 3.99 (br. s, 1H, H-15), 4.99 (m, 2H, H-3, H-5), 7.21-7.29 (m, 2H, $H_{AR}$), 7.37-7.42 (m, 3H, $H_{AR}$), 7.53 (tt, *J* = 8.0, 1.2 Hz, 1H, $H_{AR}$), 7.89 (dd, *J* = 8.0, 1.2 Hz, 1H, $H_{AR}$), 8.00 (dd, *J* = 8.0, 1.2 Hz, 2H, $H_{AR}$), 12.40 (s, 1H, OH); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=14.1 ($CH_3$), 21.4 (C-6), 28.3 [$(CH_3)_3C$], 28.5, 28.6 (C-15, C-14), 31.1 (C-19), 35.3 (C-18), 40.6 (C-5), 52.1 ($CH_3O$), 53.1 (C-3), 76.2 (C-20), 84.4 [$(CH_3)_3C$], 97.0 (C-16), 115.8 ($C_{AR}$), 118.2 ($CH_{AR}$), 118.9 ($CH_{AR}$), 122.9 ($CH_{AR}$), 124.4 ($CH_{AR}$), 128.2, 131.1 (C-*o, m* $C_6H_5$), 128.9 ($C_{AR}$), 133.7 (C-*p* $C_6H_5$), 135.1 ($C_{AR}$), 136.3 ($C_{AR}$), 138.6 (C-*i* $C_6H_5$), 150.3 (CO), 165.1 (CO), 170.9 (C-17), 171.9 (CO). **Compound 10b**: $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25°C, TMS): *δ*=1.18 (br s, 3H, $CH_3$), 1.67 [s, 10H, $(CH_3)_3C$, H-14], 2.00-2.40 (m, 2H, H-14, H-19), 2.45-2.90 (m, 5H, 2H-6, H-5, 2H-18), 3.38 (br s, 1H, H-15), 3.82 (s, 3H, $CH_3O$), 4.97-6.05 (m, 2H, H-5, H-3), 5.07 (d, *J* = 12.8 Hz, 1H, C$H_2C_6H_5$), 5.13 (d, *J* = 12.8 Hz, 1H, C$H_2C_6H_5$), 7.12-7.31 (3m, 7H, $H_{AR}$), 7.40 (d, *J* = 7.6 Hz, 1H, $H_{AR}$), 7.95 (d, *J* = 7.6 Hz, 1H, $H_{AR}$); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=15.1 ($CH_3$), 21.6 (C-6), 28.2 [$(CH_3)_3C$], 30.3 (C-19), 31.5 (C-15), 34.2, 34.9 (C-14, C-18), 42.5 (C-5), 51.9 ($CH_3O$), 53.6 (C-3), 57.4 (C-20), 66.8 ($CH_2C_6H_5$), 84.0 [$(CH_3)_3C$], 97.2 (C-16), 115.6 ($CH_{AR}$), 116.0 ($C_{AR}$), 118.2 ($CH_{AR}$), 122.9 ($CH_{AR}$), 124.4 ($CH_{AR}$), 127.6-128.3 ($C_{AR}$, C-*o*, *m*, *p* $C_6H_5$), 135.6 ($C_{AR}$, C-*i* $C_6H_5$), 136.6 ($C_{AR}$), 150.2 (CO), 168.1-172.1 (C-17, 3CO); IR (ATR Pike) ν: 1652, 1728 $cm^{-1}$ (C=O); HRMS (ESI) calcd for $[C_{35}H_{38}N_2O_8 + H]^+$: 615.2701, found: 615.2701.

When reaction from **5a** was carried out for 2 h at 0 °C, the intermediate **D** was isolated (23%) by flash chromatography (9:1 hexane-EtOAc). Major isomer: $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25°C, TMS): *δ*=1.42 [s, 9H, $(CH_3)_3$], 1.73 [s, 9H, $(CH_3)_3$], 1.74 (m, 1H, H-1), 1.94 (ddd, *J* = 11.6, 7.2, 1.6 Hz, 3H, $CH_3$), 2.54 (m, 1H, H-1), 2.91 (m, 2H, H-7), 3.61 (m 1H, H-2), 3.72 (s, 3H, $CH_3O$), 3.94 (tt, *J* = 10.8, 3.6 Hz, 1H, $CH_2O$), 4.17 (ddd, *J* = 10.8, 6.4, 5.6 Hz, 1H, $CH_2O$), 4.27 (d, *J* = 4.0 Hz, 1H, H-3), 4.32 (d, *J* = 6.0 Hz, 1H, CHCOO), 5.34-5.44 (m, 2H, H-6, H-12b), 6.20-6.28 (m 1H, CH=), 7.07-7.14 (dq, *J* = 15.8, 6.8 Hz, 1H, CH=), 7.23-7.33 (2m, 2H, $H_{AR}$), 7.41 (dm, *J* = 8.0 Hz, 1H, $H_{AR}$), 7.57 (m, 2H, $H_{AR}$), 7.68 (m, 1H, $H_{AR}$), 7.99 (m, 2H, $H_{AR}$), 8.11 (d, *J* = 8.0 Hz, 1H, $H_{AR}$); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=18.6 ($CH_3$), 21.7 (C-7), 27.7 [$(CH_3)_3C$], 28.2 [$(CH_3)_3C$], 31.6 (C-2), 34.2 (C-1), 45.6, 51.0 (C-6, C-12b), 52.6 ($CH_3O$), 58.4 (C-3), 65.6 ($CH_2O$), 70.1 (*C*HCOO), 82.3 [$(CH_3)_3C$], 84.9 [$(CH_3)_3C$], 113.6 ($C_{AR}$), 115.9 ($C_{AR}$), 118.1 ($CH_{AR}$), 122.9 ($CH_{AR}$), 124.8 ($CH_{AR}$), 128.4-131.7 ($CH_{AR}$), 134.1 (CH=), 136.8 ($C_{AR}$), 137.8 ($C_{AR}$), 146.1 (CH=), 153.2 (CO), 162.1 (CO), 168.9 (CO), 192.5 (CO). Minor isomer: $^1$H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25°C, TMS): *δ*=1.44 [s, 9H, $(CH_3)_3$], 1.52 (m, 1H, H-1), 1.77 [s, 9H, $(CH_3)_3$], 1.97 (ddd, *J* = 11.6, 7.2, 1.6 Hz, 3H, $CH_3$), 2.72 (m, 1H, H-1), 2.91 (m, 2H, H-7), 3.70 (m, 1H, H-2), 3.72 (s 3H, $CH_3O$), 4.00 (m, 1H, $CH_2O$), 4.02 (d, *J* = 6.0 Hz, 1H, H-3), 4.17 (m, 1H, $CH_2O$), 4.45 (d, *J* = 6.0 Hz, 1H, CHCOO), 5.34-5.44 (m, 2H, H-6, H-12b), 6.20-6.28 (m, 1H, CH=), 6.92-7.05 (dq, *J* = 15.8, 6.8 Hz, 1H, CH=), 7.23-7.33 (2m, 2H, $H_{AR}$), 7.41 (dm, *J* = 8.0 Hz, 1H, $H_{AR}$), 7.57 (m, 2H, $H_{AR}$), 7.68 (m, 1H, $H_{AR}$), 7.99 (m, 2H, $H_{AR}$), 8.15 (d, *J* = 8.0 Hz, 1H, $H_{AR}$); $^{13}$C NMR (100.6 MHz, $CDCl_3$, 25°C, TMS): *δ*=18.5 ($CH_3$), 21.5 (C-7), 27.7 [$(CH_3)_3C$], 28.3 [$(CH_3)_3C$], 31.2 (C-2), 36.0 (C-1), 45.6, 50.9 (C-6, C-12b), 52.7 ($CH_3O$), 58.4 (C-3), 65.5 ($CH_2O$), 68.9 (*C*HCOO), 82.3 [$(CH_3)_3C$], 85.1 [$(CH_3)_3C$], 113.6 ($C_{AR}$), 116.0 ($C_{AR}$), 118.0 ($CH_{AR}$), 123.0 ($CH_{AR}$), 124.8 ($CH_{AR}$), 128.4-131.7 ($CH_{AR}$), 133.9 (CH=), 136.9 ($C_{AR}$), 138.1 ($C_{AR}$), 145.4 (CH=), 149.8 (CO), 162.3 (CO), 168.5 (CO), 192.6 (CO).

**Computational methods.** Full geometry optimizations were performed with the M06-2X[16] density functional method by using the 6-31G(d)[17] basis set. The nature of the stationary points was verified by inspection of the vibrational frequencies within the harmonic oscillator-rigid rotor approximation. In specific cases the free energy profile of the annulation reactions was determined from single-point calculations performed at the spin-component scaled MP2 (SCS-MP2)[25] level with the 6-31G(d) basis, and from B2PLYPD3[26] calculations with the def2-SVPP[27] basis. These methods have proved valuable for the study of reactive processes.[28] The relative free energies were estimated by combining the energy differences with the thermal/entropy corrections derived from frequency analysis. To this end, the free energy corrections were calculated using Truhlar's quasiharmonic approximation,[29,30] where real harmonic vibrational frequencies lower than 100 $cm^{-1}$ were raised to 100 $cm^{-1}$, as has been utilized in other chemical reactivity studies.[31-33] Finally, the effect of solvation in dichloromethane was taken into account using the

SMD version[18] of the IEF-PCM[31] continuum solvation method. SMD calculations were performed at the B3LYP/6-31G(d)[35] level, which was one of the six electronic structure methods used in the optimization of the SMD method. All DFT computations were carried out using the keyword Integral(Grid=Ultrafine) as implemented in Gaussian09,[36] which was used to carry out these calculations.

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[13] The absolute configurations of compounds **9a** and **10a** were unambiguously determined by X-ray crystallographic analysis. CCDC-1528357 (**9a**) and CCDC-1528358 (**10a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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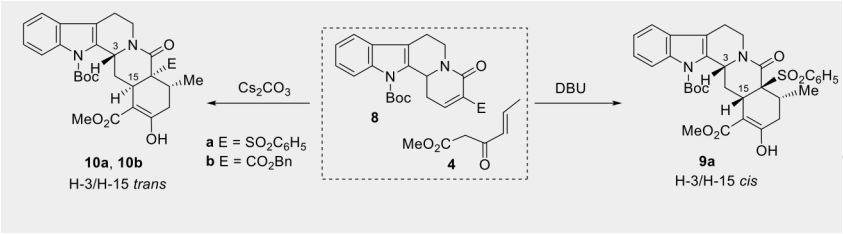


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**Origin of the Base-Dependent Facial Selectivity in Annulation Reactions of Nazarov-Type Reagents with Unsaturated Indolo[2,3-*a*]quinolizidine Lactams**

The reversal of the facial selectivity observed when $Cs_2CO_3$ is used as the base instead of DBU in double Michael addition reactions of the Nazarov reagent **4** with unsaturated $N_{ind}$-Boc indoloquinolizidine lactams is rationalized by theoretical calculations. The synthetic potential of these annulation reactions is illustrated with the enantioselective synthesis of 17*a*-carbaakuammigine.

Key topic: Stereoselectivity