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Stereoselectivity

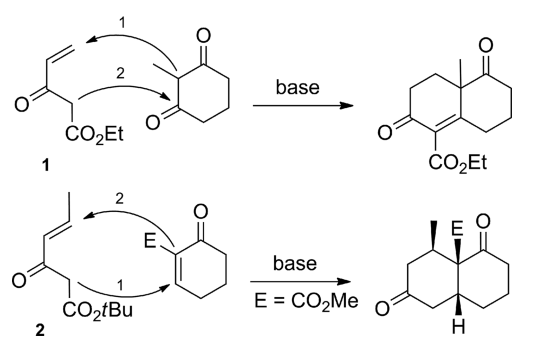
Origin of the Base-Dependent Facial Selectivity in Annulation Reactions of Nazarov-Type Reagents with Unsaturated Indolo[2,3-*a*]quinolizidine Lactams

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: Methyl-substituted Nazarov reagent **4** reacts stereoselectively with N_{ind}-Boc indoloquinolizidine lactams to give the expected 3-H/15-H *cis* pentacyclic yohimbine-type adducts when using 1,8-diazabicyclo[5.4.0]undec-7-ene (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 analogue 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 annulating agent that is 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]



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

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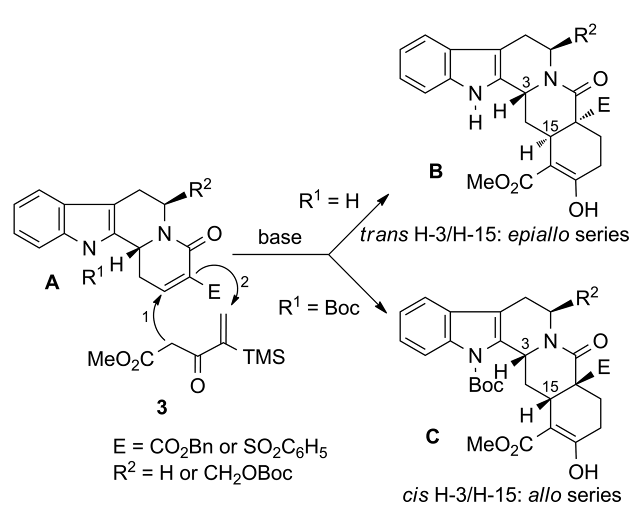
rapidly at room temperature has stimulated the development of more stable analogues of **1** bearing alkyl substituents on the vinyl moiety, such as **2**.[5] These Nazarov-type reagents are able to undergo alternative annulations involving base-catalyzed double Michael addition reactions with α,β-unsaturated 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 3-H/15-H *trans* adducts **B** were generated from N_{ind}-unsubstituted



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

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lactams, but the corresponding *cis* isomers **C** were formed when the indole nitrogen atom bears a Boc substituent (Scheme 2).[9] This dramatic reversal in the facial selectivity was rationalized based on theoretical calculations, which indicated that the initial nucleophilic attack under stereoelectronic control is hampered by the presence of the bulky Boc group.[8] The reactions were performed using either 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) [in tetrahydrofuran (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 analogues of heteroyohimbine alkaloids bearing their characteristic C-19 methyl substituent (Figure 1). By following this rationale, we report here the enantioselective synthesis of 17a-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 directing the stereoselective outcome.

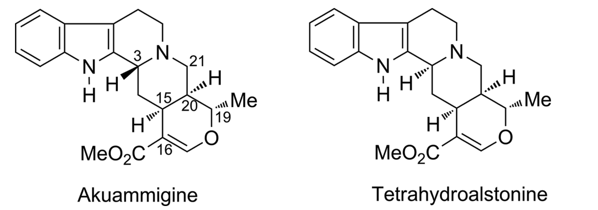


Figure 1. Heteroyohimbine alkaloids akuammigine and tetrahydroalstonine.

Results and Discussion

Base-Dependent Stereoselective Double Michael Addition Reactions with Nazarov Reagent 4

Reaction of enantiopure N_{ind}-Boc lactam **5a** with Nazarov reagent **4** using DBU as base afforded pentacyclic adduct **6a**, with the expected 3-H/15-H *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 3-H/15-H *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 3-H/15-H *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 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 3-H/15-H *cis* pentacycle **9a** was obtained in excellent yield.[11] In contrast, when Cs_2CO_3 was used as the base, the corresponding 3-H/15-H *trans* adducts **10a** and **10b**[12] were formed stereoselectively in 88 % and 59 % yield, respectively.

In agreement with a stepwise double Michael process, when the Cs_2CO_3-promoted reaction from **5a** was stopped after 2 h, 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 spectroscopic analysis in all the annulations shown in Scheme 3, including the reactions in the presence of DBU.

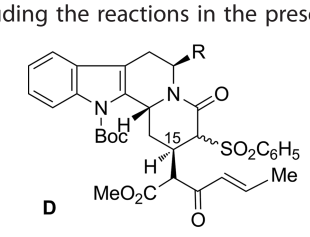
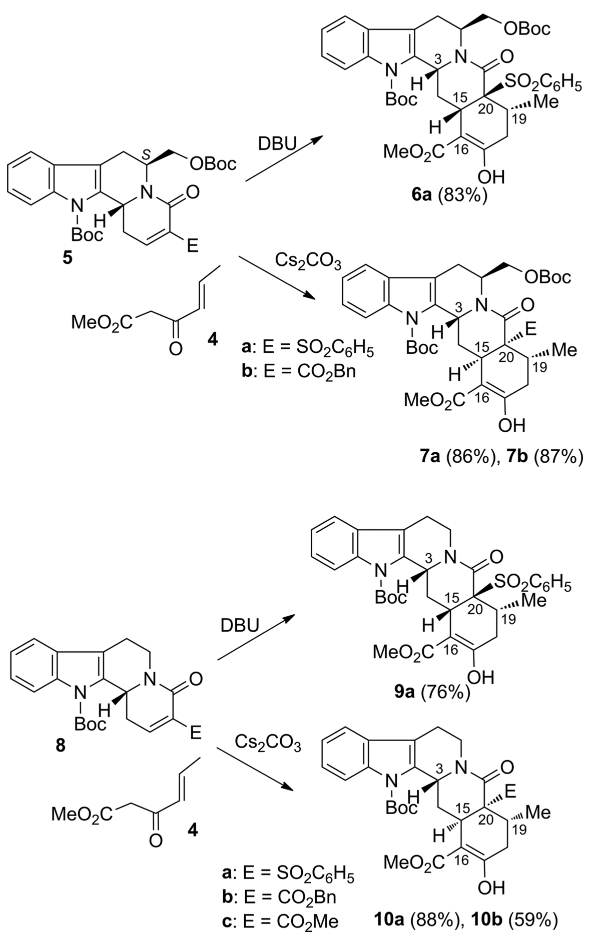


Figure 2. Tetracyclic intermediate **D**.

The observation of positive NOE effects between 3-H/15-H, C19-Me/Hα-14, and C19-Me/Hα-18 in **6a** and **9a**, and between 3-H/19-H, 3-H/Hβ-18, C19-Me/15-H, and C19-Me/Hα-18 in **10a** is 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).



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).

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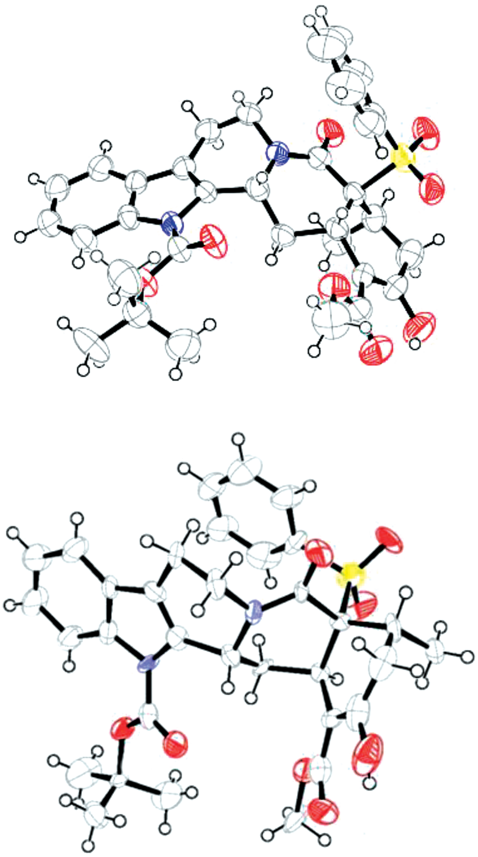


9a

10a

Figure 3. X-ray crystal structures of the 3-H/15-H *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 3-H/15-H *trans* adducts **7** and **10**,[14] a *trans* C19-Me/C20-$SO_2C_6H_5$ relationship was found in the 3-H/15-H *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]

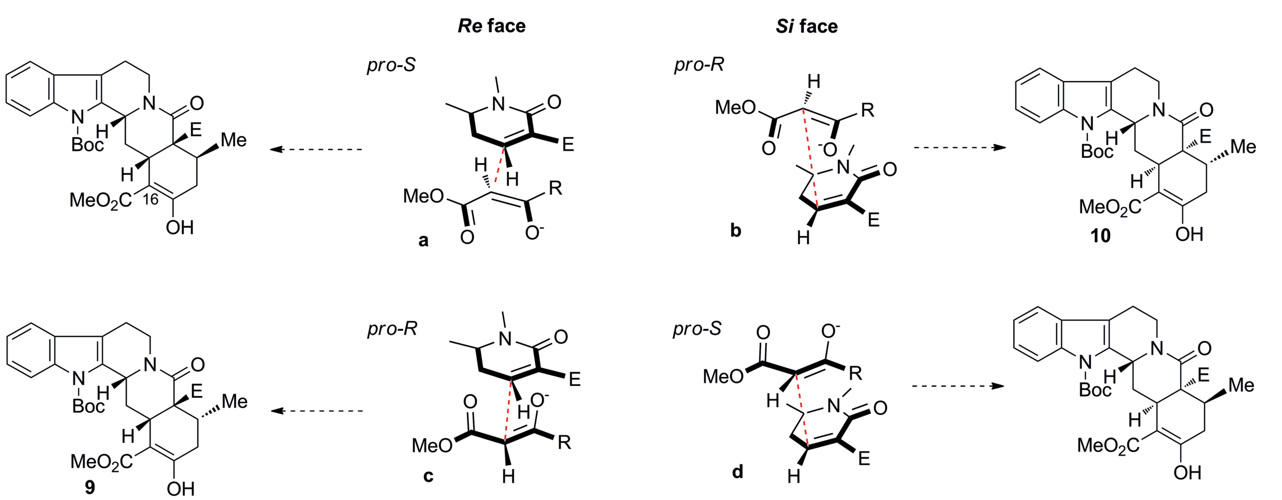
Conformational Preferences of Nazarov Reagents 3 and 4

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 the Experimental Section 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 the Supporting Information). The results point 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 conversion into the *s-cis* arrangement.

Double Michael Additions with Silylated Nazarov Reagent 3

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_2Me 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 stereocen-



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**.

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ter 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.

The stereoselective formation of the *cis* 3-H/15-H 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, because the barrier (8.2 kcal/mol) for the first Michael addition is higher 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 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.

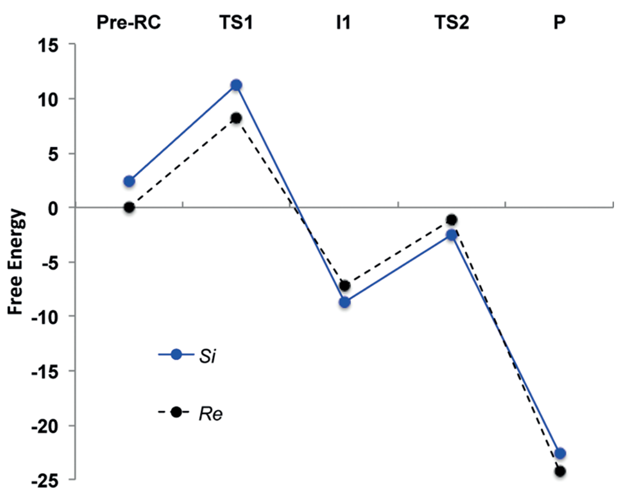

Figure 4. Free energy [kcal/mol] profile for the double Michael addition of the anionic species of Nazarov reagent **3** (*pro-S* and *pro-R* faces for *Re* and *Si* attacks, respectively) to lactam **8c** derived from M062X/6-31G(d) calculations in CH_2Cl_2.

Assuming that these reactions are under 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 3-H/15-H *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

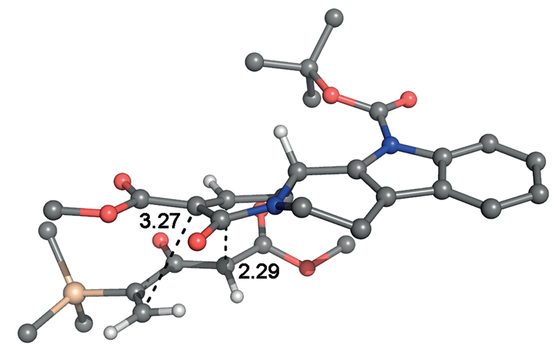

Figure 5. Representation of the transition state (TS1) formed in the *Re* attack of reagent **3** (*pro-S* face) to lactam **8c**. For clarity, only selected hydrogen atoms are shown. Complete geometrical data of pre-reactants, transition states, and intermediates are available in the Supporting Information.

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

addition (H–C•••C–H dihedral angle –172.8°), 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 imparted by the TMS group (data not shown).

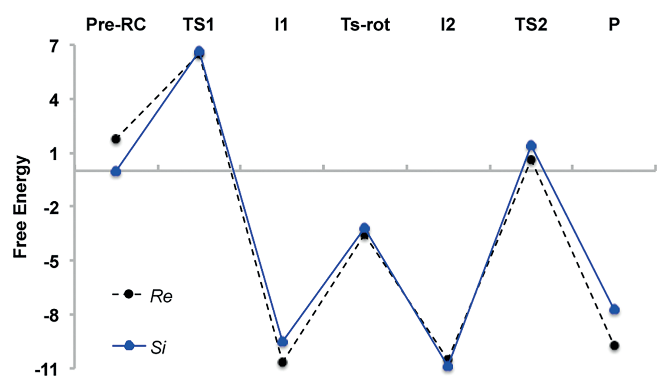

Figure 6. Free energy [kcal/mol] profile for the DBU-catalyzed double Michael addition of the anionic species of Nazarov reagent **4** to lactam **8a** derived from M062X/6-31G(d) calculations in CH_2Cl_2.

Double Michael Additions with Methyl-Substituted Nazarov Reagent 4

We then examined the annulation reaction between lactam **8a** and Nazarov reagent **4**. It is worth noting that the stereochemical outcome obtained for 3-H/15-H and C-19/C-20 centers is different depending on the base, DBU or Cs_2CO_3, used to cata-

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lyze 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 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 oxygen atoms 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 58.1 and 61.6° in the TSs formed for the *Re* and *Si* attacks, respectively; 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, whereas 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, because the distance between the reactive C atoms involved in the second Michael addition is close to 3.7 Å because of the *s-trans* arrangement of the Nazarov reagent. In fact, the second Michael addition is preceded by 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).

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* 3-H/15-H and *trans* C19-Me/C20-E(SO_2Ph) 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°) 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 oxygen atoms of the lactam and hydrogen atoms of the Nazarov reagent.

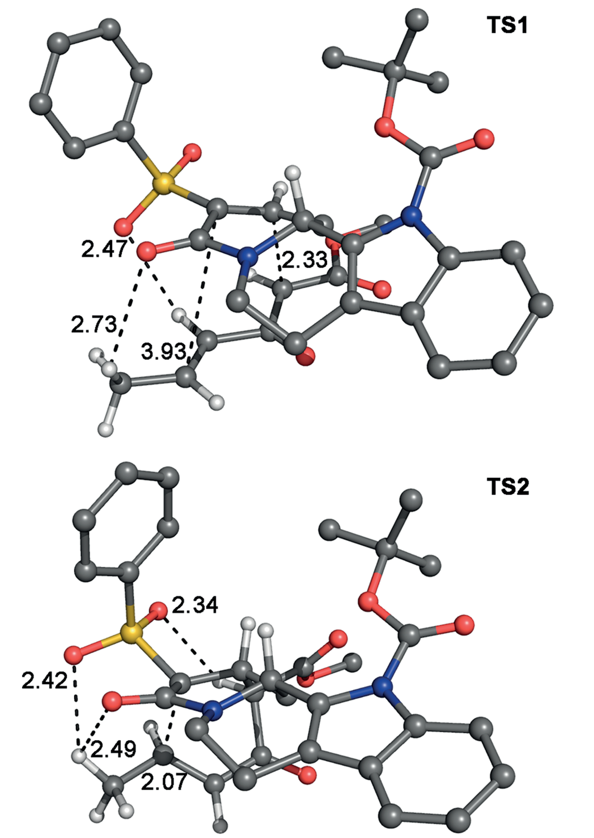

Figure 7. Representation of the transition states (TS1 and TS2) formed in the DBU-catalyzed double Michael additions of the anionic form of Nazarov reagent **4** to lactam **8a**. The approach occurs through the *pro-R* face of **4** and the *Re* face of the lactam. For clarity, only selected hydrogen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

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 the Supporting Information) to lactam **8a** was also identified. Compared with 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 the generation of the anionic form of the Nazarov reagent (Scheme S1 in the Supporting Information). Second, such electrostatic stabilization suggests that the ionic pair Cs^+-$\mathbf{4}^-$ 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 room temp.) and by the excess of Cs_2CO_3 relative to the Nazarov reagent **4**, which were used in a 2:1 ratio

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under the reaction conditions (see the Experimental Section). 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 with 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]

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 through an antiperiplanar approach between the carbon atoms that will form the first C–C bond, because 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 a methyl group in the present calculations).

The transition states (TS1) for the first Michael addition between reagent **4** and lactam **8c** (Figure 8) have similar stabilities, with 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 oxygen atoms of **4** and to the carbonyl oxygen atom 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 oxygen atoms 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 –160.7 and 133.5° for the *Re* and *Si* additions, respectively). Figure 9 also shows the asynchronicity of the double Michael addition, because 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.

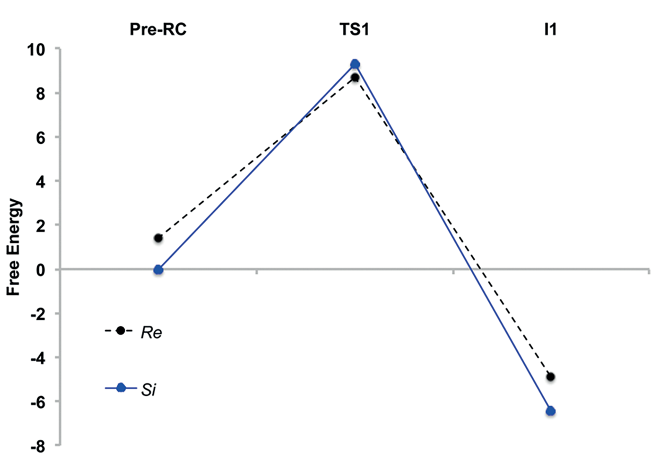

Figure 8. Free energy [kcal/mol] profile for the first Michael addition of the Cs^+···**4** complex to lactam **8c** derived from M062X/6-31G(d) calculations in CH_2Cl_2.

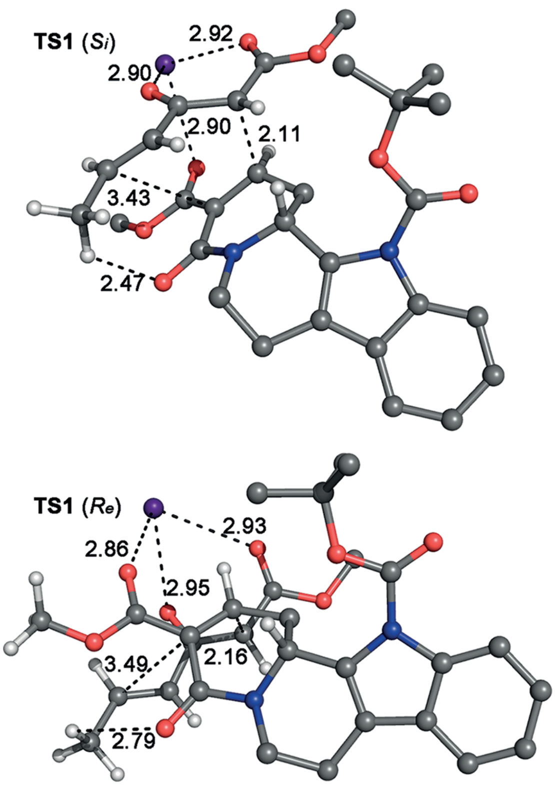

Figure 9. Representation of the transition state (TS1) formed in the first Michael addition of the Cs^+···**4** complex to lactam **8c**. The approach occurs through the *Si* (top; *pro-R* face of **4**), and *Re* (bottom; *pro-S* face of **4**) faces of the lactam. For clarity, only selected hydrogen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

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 is presumably 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 through the *Re* and *Si* addition of Cs^+···**4** to lactam **8c** indicate that the cation release from

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the intermediate is favored by 4.6 kcal/mol in the two cases, as expected from the charge transfer from **4** to **8c**.

$$\textbf{Pre-RC} \qquad Cs^+\cdots\mathbf{4}^- \text{- - -} \mathbf{8c} \xrightarrow{\Delta G_{Pre\text{-}RC}} Cs^+ + \mathbf{4}^- \text{- - -} \mathbf{8c}$$

$$\textbf{I1} \qquad Cs^+\cdots\mathbf{4} - \mathbf{8c}^- \xrightarrow{\Delta G_{I1}} Cs^+ + \mathbf{4} - \mathbf{8c}^-$$

$$\Delta\Delta G = \Delta G_{I1} - \Delta G_{Pre\text{-}RC}$$

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**.

Based on the preceding discussion, the free-energy profile leading from 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 from 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 with the reaction with the coordinated Cs^+ cation, this represents a 13-fold increase in the stereoselectivity of the annulation reaction.

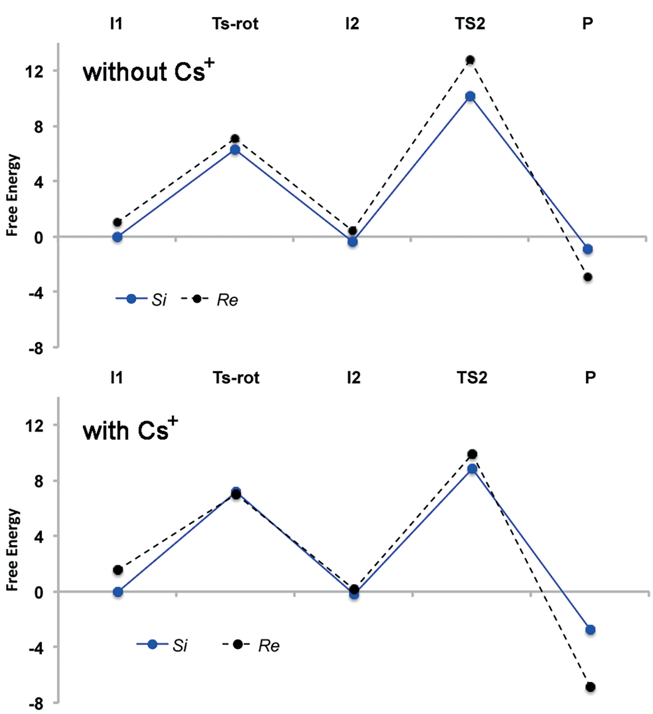

Figure 10. Free energy [kcal/mol] profile for the second Michael addition of the anionic species of Nazarov reagent **4** to lactam **8c** in the absence (top) and presence (bottom) of coordinated Cs^+ cation derived from M062X/6-31G(d) calculations in CH_2Cl_2.

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 vs. 2.18 Å in the absence and presence of the Cs^+ cation, respectively; see Figure 11), as well as in the larger pyramidalization of the respective carbon atoms (close to 19° in the absence of the Cs^+ cation vs. 15° with the coordinated Cs^+ cation). Let us note that the addition from the *Si* face yields the experimental stereochemistry characterized by *trans* 3-H/15-H and *cis* C19-Me/C20-CO_2Me relationships (Figure 11).

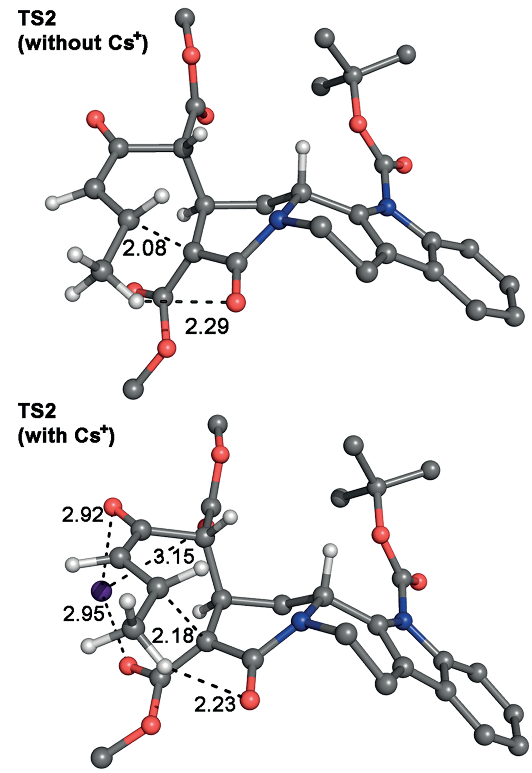

Figure 11. Representation of the transition state (TS2) formed in the second Michael addition of the anionic species of Nazarov reagent **4** to lactam **8c** in the absence (top) and presence (bottom) of a coordinated Cs^+ cation. The approach occurs from the *pro-R* face of **4** and the *Si* face of the lactam. For 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 are available in the Supporting Information.

Overall, the present results suggest that coordination of the Cs^+ cation to the carbonyl oxygen atoms 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, 20 h) 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 smaller ionic radius of Li^+, which would perturb the structural

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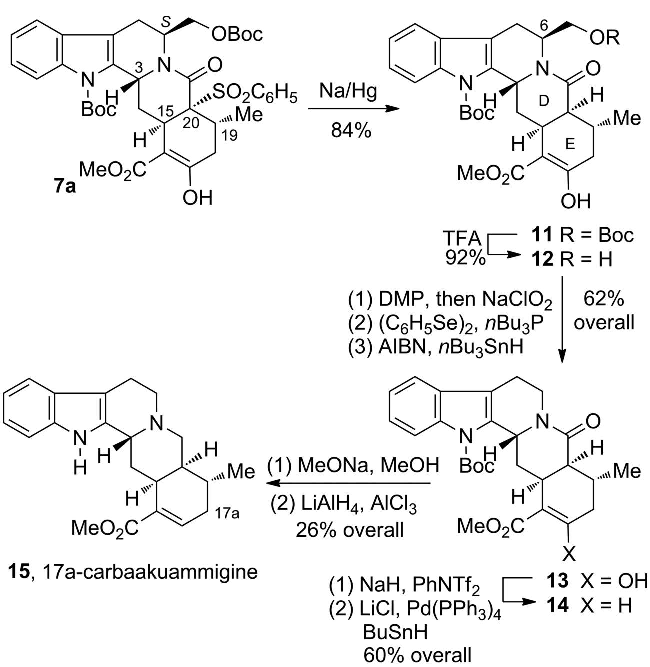
and energetic features of the Cs^+-coordinated reactive complex. Thus, theoretical calculations revealed that the intrinsic stability of the TS (TS1) for the first Michael addition is penalized by around 4 and 7 kcal/mol upon replacement of the Cs^+ cation by K^+ and Li^+, respectively. A significant 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.

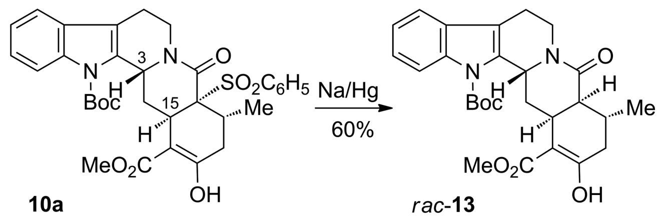
Enantioselective Synthesis of 17a-Carbaakuammigine

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] The resulting enolizable β-keto ester **13** was then converted into α,β-unsaturated ester **14** by palladium-catalyzed reductive coupling[24] of the corresponding vinyl triflate. Finally, after deprotection of the indole nitrogen atom, chemoselective alane reduction of the lactam carbonyl group 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 ^1H NMR spectroscopic analysis, from the observation of positive NOE effects between 15-H/20-H, 15-H/C19-Me, and 20-H/C19-Me in **11** and the triflate derived from **13**. Additionally, the 3-H/15-H *trans* stereochemistry in this series was unambiguously confirmed when the NMR spectroscopic 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 oxygen atoms of both the Nazarov reagent and the electron-withdrawing group in the lactam, because this determines the preferred orientation of the reactants, and ultimately the stereochemical outcome of the cyclized products. Support for the specific role of the 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 desired cyclized product. These findings open new avenues for the fine regulation of the target 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] or **8a**[8] (1 equiv.) in anhydrous THF was added at 0 °C under an inert gas to a solution of the Nazarov reagent **4** (2 equiv.) and DBU (1 equiv.) in anhydrous THF (0.02 M), and the mixture was warmed slowly to room temperature. After 20 h of stirring at room temperature, the reaction was quenched with H_2O, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with 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 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25 °C, TMS): δ = 0.97 (d, *J* = 6.8 Hz,

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3 H, CH_3), 1.43 [s, 9 H, $(CH_3)_3C$], 1.44 (masked, 1 H, 14-H), 1.73 [s, 9 H, $(CH_3)_3C$], 2.17 (dd, J = 18.4, 0.8 Hz, 1 H, 18-H), 2.77 (ddd, J = 16.8, 6.0, 2.4 Hz, 1 H, 6-H), 2.87 (dt, J = 16.8, 1.6 Hz, 1 H, 6-H), 3.05 (m, 1 H, 19-H), 3.14–3.21 (m, 2 H, 18-H, 14-H), 3.67 (dd, J = 10.8, 5.2 Hz, 1 H, CH_2O), 3.85 (dd, J = 10.8, 8.8 Hz, 1 H, CH_2O), 3.92 (s, 3 H, CH_3O), 3.96 (m, 1 H, 15-H), 5.14 (dd, J = 10.4, 2.0 Hz, 1 H, 3-H), 5.49 (m, 1 H, 5-H), 7.23 (td, J = 7.6, 1.2 Hz, 1 H, H_{AR}), 7.29 (td, J = 6.8, 1.2 Hz, 1 H, H_{AR}), 7.40 (dd, J = 6.8, 1.2 Hz, 1 H, H_{AR}), 7.57 (tt, J = 7.6, 0.8 Hz, 2 H, H-*m* C_6H_5), 7.67 (tt, J = 7.6, 1.2 Hz, 1 H, H-*p* C_6H_5), 7.94 (d, J = 7.6 Hz, 1 H, H_{AR}), 8.01 (dd, J = 7.6, 0.8 Hz, 2 H, H-*o* C_6H_5), 12.40 (s, 1 H, OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.8 (CH_3), 22.2 (C-6), 27.7 [$(CH_3)_3C$], 28.3 [$(CH_3)_3C$], 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 [$(CH_3)_3C$], 84.4 [$(CH_3)_3C$], 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 (2 C-*m* C_6H_5), 128.8 (C_{AR}), 131.1 (2 C-*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) ppm. IR (ATR Pike): $\tilde{\nu}$ = 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: ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25 °C, TMS): δ = 0.97 (d, J = 6.8 Hz, 3 H, CH_3), 1.42 (masked, 1 H, 14-H), 1.72 [s, 9 H, $(CH_3)_3C$], 2.17 (dd, J = 17.6 Hz, ■■ ((<=AUTHOR: 2nd coupling missing; please check!)) ■■ 1 H, 18eq-H), 2.55–2.68 (m, 3 H, 2 6-H, 5-H), 3.02–3.17 (m, 3 H, 18-H, 14-H, 19-H), 3.88 (m, 1 H, 15-H), 3.92 (s, 3 H, CH_3O), 4.84 (m, 1 H, 5-H), 5.12 (dd, J = 10.0, 2.4 Hz, 1 H, 3-H), 7.23 (td, J = 7.6, 1.2 Hz, 1 H, H_{AR}), 7.28 (td, J = 6.8, 1.2 Hz, 1 H, H_{AR}), 7.39 (dd, J = 6.8, 1.2 Hz, 1 H, H_{AR}), 7.56 (tt, J = 7.6, 0.8 Hz, 2 H, H-*m* C_6H_5), 7.65 (tt, J = 7.6, 1.2 Hz, 1 H, H-*p* C_6H_5), 7.91 (d, J = 7.6 Hz, 1 H, H_{AR}), 7.99 (dd, J = 7.6, 0.8 Hz, 2 H, H-*o* C_6H_5), 12.45 (s, 1 H, OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.9 (CH_3), 21.6 (C-6), 28.3 [$(CH_3)_3C$], 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 [$(CH_3)_3C$], 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 (2 C-*m* C_6H_5), 128.6 (C_{AR}), 130.9 (2 C-*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) ppm. IR (ATR Pike): $\tilde{\nu}$ = 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 gas 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 warmed 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: Obtained in 9:1 enol/keto ratio; m.p. 98–100 °C; $[\alpha]_D^{22}$ = +20.5 (c = 0.7 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25 °C, TMS): δ = 1.20 (d, J = 6.4 Hz, 3 H, CH_3), 1.41 [s, 9 H, $(CH_3)_3C$], 1.69 [s, 9 H, $(CH_3)_3C$], 1.95 (dd, J = 18.0, 1.6 Hz, 1 H, 18-H), 2.25 (ddd, J = 14.0, 12.0, 3.2 Hz, 1 H, 14-H), 2.56 (d, J = 16.4 Hz, 1 H, 6-H), 2.69 (ddd, J = 16.4, 4.4, 2.4 Hz, 1 H, 6-H), 2.81 (m, 2 H, 18-H, 19-H), 3.16 (app dt, ■■ ((<=AUTHOR: OK?)) ■■ J = 14.0, 3.2, 3.2 Hz, 1 H, 14-H), 3.80 (m, 1 H, CH_2O), 3.81 (s, 3 H, CH_3O), 4.08 (m, 2 H, 15-H, CH_2O), 4.94 (d, J = 11.2 Hz, 1 H, 3-H), 5.63–5.71 (m, 1 H, 5-H), 7.20–7.60 (m, 6 H, H_{AR}), 7.87 (dd, J = 8.0, 1.2 Hz, 1 H, H_{AR}), 8.00 (dd, J = 8.0, 1.2 Hz, 2 H, H_{AR}), 12.2 (s, 1 H, OH) ppm. ^{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) ppm. IR (film): $\tilde{\nu}$ = 1728, 1640 cm^{-1} (C=O). HRMS (ESI): calcd. for $[C_{39}H_{46}N_2O_{11}S + H]^+$: 751.2895; found: 751.2892. $C_{39}H_{46}N_2O_{11}S$ (750.86): calcd. C 62.38, H 6.17, N 3.73; found C 62.15, H 6.34, N 3.36.

Compound 7b: Obtained in >9:1 enol/keto ratio. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25 °C, TMS): δ = 1.26 (d, J = 11.2 Hz, 3 H, CH_3), 1.45 [s, 9 H, $(CH_3)_3C$], 1.68 [s, 9 H, $(CH_3)_3C$], 2.01 (m, 1 H, 14-H), 2.10 (masked, 1 H, 14-H), 2.40 (m, 1 H, 19-H), 2.65 (d, J = 16.4 Hz, 1 H, 6-H), 2.68–2.79 (m, 2 H, 18-H), 2.76–2.90 (ddd, J = 16.4, 6.4, 2.4 Hz, 1 H, 6-H), 3.49 (m, 1 H, 15-H), 3.83 (s, 3 H, CH_3O), 3.96 (t, J = 10.4 Hz, 1 H, CH_2O), 4.11 (dd, J = 10.4, 7.2 Hz, 1 H, CH_2O), 4.94 (dm, J = 8.4 Hz, 1 H, 3-H), 5.11 (d, J = 12.4 Hz, 1 H, $CH_2C_6H_5$), 5.17 (d, J = 12.4 Hz, 1 H, $CH_2C_6H_5$), 5.74 (m, 1 H, 5-H), 7.19–7.36 (m, 7 H, H_{AR}), 7.39 (d, J = 7.6, 1.2 Hz, 1 H, H_{AR}), 7.94 (d, J = 7.6, 1.2 Hz, 1 H, H_{AR}), 12.2 (s, 1 H, OH) ppm. ^{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, 3 CO) ppm. IR (film): $\tilde{\nu}$ = 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: ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25 °C, TMS): δ = 1.18 (d, J = 6.8 Hz, 3 H, CH_3), 1.69 [s, 9 H, $(CH_3)_3C$], 2.00 (dd, J = 18.4, 2.0 Hz, 1 H, 18-H), 2.27 (ddd, J = 14.4, 11.6, 2.6 Hz, 1 H, 14-H), 2.48–2.61 (m, 3 H, 2 6-H, 18-H), 2.74 (m, 2 H, 19-H, 5-H), 3.25 (dt, J = 14.4, 4.0 Hz, 1 H, 14-H), 3.93 (s, 3 H, CH_3O), 3.99 (br. s, 1 H, 15-H), 4.99 (m, 2 H, 3-H, 5-H), 7.21–7.29 (m, 2 H, H_{AR}), 7.37–7.42 (m, 3 H, H_{AR}), 7.53 (tt, J = 8.0, 1.2 Hz, 1 H, H_{AR}), 7.89 (dd, J = 8.0, 1.2 Hz, 1 H, H_{AR}), 8.00 (dd, J = 8.0, 1.2 Hz, 2 H, H_{AR}), 12.40 (s, 1 H, OH) ppm. ^{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) ppm.

Compound 10b: ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, enol form, 25 °C, TMS): δ = 1.18 (br. s, 3 H, CH_3), 1.67 [s, 10 H, $(CH_3)_3C$, 14-H], 2.00–2.40 (m, 2 H, 14-H, 19-H), 2.45–2.90 (m, 5 H, 2 6-H, 5-H, 2 18-H), 3.38 (br. s, 1 H, 15-H), 3.82 (s, 3 H, CH_3O), 4.97–6.05 (m, 2 H, 5-H, 3-H), 5.07 (d, J = 12.8 Hz, 1 H, $CH_2C_6H_5$), 5.13 (d, J = 12.8 Hz, 1 H, $CH_2C_6H_5$), 7.12–7.31 (3m, 7 H, H_{AR}), 7.40 (d, J = 7.6 Hz, 1 H, H_{AR}), 7.95 (d, J = 7.6 Hz, 1 H, H_{AR}) ppm. ^{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, 3 CO) ppm. IR (ATR Pike): $\tilde{\nu}$ = 1652, 1728 cm^{-1} (C=O). HRMS (ESI): calcd. for $[C_{35}H_{38}N_2O_8 + H]^+$ 615.2701; found 615.2701.

When the reaction from **5a** was carried out at 0 °C for 2 h, intermediate **D** was isolated (23 %) by flash chromatography (9:1, hexane/EtOAc).

Major Isomer: ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C, TMS): δ = 1.42 [s, 9 H, $(CH_3)_3$], 1.73 [s, 9 H, $(CH_3)_3$], 1.74 (m, 1 H, 1-H), 1.94

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(ddd, J = 11.6, 7.2, 1.6 Hz, 3 H, CH_3), 2.54 (m, 1 H, 1-H), 2.91 (m, 2 H, 7-H), 3.61 (m, 1 H, 2-H), 3.72 (s, 3 H, CH_3O), 3.94 (tt, J = 10.8, 3.6 Hz, 1 H, CH_2O), 4.17 (ddd, J = 10.8, 6.4, 5.6 Hz, 1 H, CH_2O), 4.27 (d, J = 4.0 Hz, 1 H, 3-H), 4.32 (d, J = 6.0 Hz, 1 H, CHCOO), 5.34–5.44 (m, 2 H, 6-H, 12-Hb), 6.20–6.28 (m, 1 H, CH=), 7.07–7.14 (dq, J = 15.8, 6.8 Hz, 1 H, CH=), 7.23–7.33 (2m, 2 H, H_{AR}), 7.41 (dm, J = 8.0 Hz, 1 H, H_{AR}), 7.57 (m, 2 H, H_{AR}), 7.68 (m, 1 H, H_{AR}), 7.99 (m, 2 H, H_{AR}), 8.11 (d, J = 8.0 Hz, 1 H, H_{AR}) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 18.6 (CH_3), 21.7 (C-7), 27.7 [(CH_3)$_3$C], 28.2 [(CH_3)$_3$C], 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)$_3$*C*], 84.9 [(CH_3)$_3$*C*], 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) ppm.

Minor Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 25 °C, TMS): δ = 1.44 [s, 9 H, (CH_3)$_3$], 1.52 (m, 1 H, 1-H), 1.77 [s, 9 H, (CH_3)$_3$], 1.97 (ddd, J = 11.6, 7.2, 1.6 Hz, 3 H, CH_3), 2.72 (m, 1 H, 1-H), 2.91 (m, 2 H, 7-H), 3.70 (m, 1 H, 2-H), 3.72 (s, 3 H, CH_3O), 4.00 (m, 1 H, CH_2O), 4.02 (d, J = 6.0 Hz, 1 H, 3-H), 4.17 (m, 1 H, CH_2O), 4.45 (d, J = 6.0 Hz, 1 H, CHCOO), 5.34–5.44 (m, 2 H, 6-H, 12-Hb), 6.20–6.28 (m, 1 H, CH=), 6.92–7.05 (dq, J = 15.8, 6.8 Hz, 1 H, CH=), 7.23–7.33 (2 m, 2 H, H_{AR}), 7.41 (dm, J = 8.0 Hz, 1 H, H_{AR}), 7.57 (m, 2 H, H_{AR}), 7.68 (m, 1 H, H_{AR}), 7.99 (m, 2 H, H_{AR}), 8.15 (d, J = 8.0 Hz, 1 H, H_{AR}) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 18.5 (CH_3), 21.5 (C-7), 27.7 [(CH_3)$_3$C], 28.3 [(CH_3)$_3$C], 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)$_3$*C*], 85.1 [(CH_3)$_3$*C*], 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) ppm.

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 by 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 Gaussian 09,[36] which was used to carry out these calculations.

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Keywords: Density functional calculations · Michael addition · Nazarov reagent · Density functional calculations · Stereoselectivity

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[12] Another stereoisomer, with a 3-H/15-H *cis* stereochemistry, was isolated in 19 % yield.

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

[14] This stereochemical outcome is the same as that found in related annulations of the methyl-substituted Nazarov reagent **2** with 2-(methoxycarbonyl)-2-cyclohexenones; see refs.[6a,6b]

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Stereoselectivity

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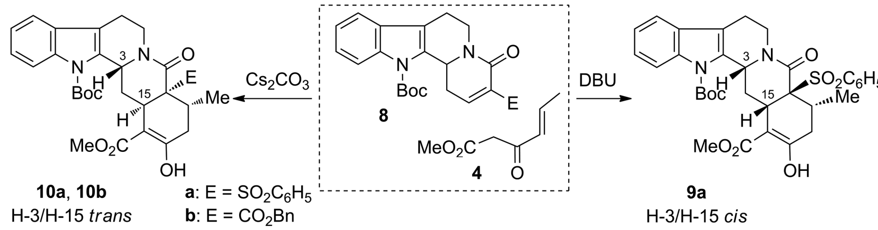
Origin of the Base-Dependent Facial Selectivity in Annulation Reactions of Nazarov-Type Reagents with Unsaturated Indolo[2,3-*a*]quinolizidine Lactams



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 17a-carbaakuammigine.

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