Synthesis of the Indolo[2,3-*a*]quinolizidine Ring through the Addition of 2-Siloxyfurans to Imines and Intrinsic Reaction Coordinate Calculations

Yaneris Mirabal-Gallardo,[a] Maria D. P. C. Soriano,[a] Julio Caballero,[b] Jans Alzate-Morales,[b] Mario J. Simirgiotis,[c] Leonardo S. Santos*[a]

[a] Laboratory of Asymmetric Synthesis, Chemistry Institute of Natural Resources, Talca University, P.O. Box 747, Talca, Chile
Fax +56(71)200448; E-mail: lssantos@utalca.cl

[b] Centre for Bioinformatics and Molecular Simulations, School of Bioinformatics, Talca University, P.O. Box 747, Talca, Chile

[c] Laboratory of Natural Products, Department of Chemistry, Faculty of Basic Sciences, University of Antofagasta, P.O. Box 170, Antofagasta, Chile

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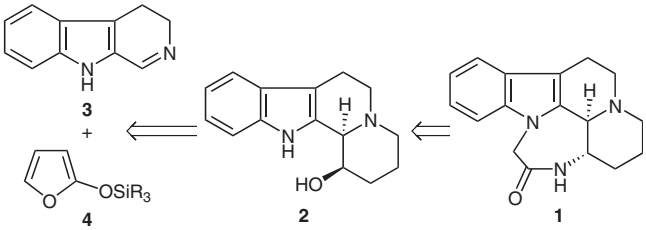
Abstract: A concise asymmetric diastereoselective strategy for the synthesis of indolo[2,3-*a*]quinolizidine derivative **1** was developed using diastereoselective addition of 2-siloxyfurans **4** to imine **3** through chiral auxiliary induction. The addition of an ionic liquid as additive in the reaction favored the *anti* configuration in the major adduct. The stereochemical outcome of the *anti*/*syn* (*threo*/*erythro*) selectivity was rationalized based on transition state and IRC calculations at DFT (B3LYP) and MP2 theories. MP2 calculations was shown to be the method of choice in these systems, which orbital desymmetrizations were observed in the *anti* transition state of the addition of **4** to **3** and secondary orbital interactions allowed us to rationalize the production of the major *anti*-adduct **6**. Furthermore, the work also suggested that 2-(triisopropylsiloxy)furan (**4a**) was the nucleophile of choice in this kind of Mannich reaction. Moreover, the strategy features the use of the Mitsunobu reaction to insert an amino group with the correct configuration into amine **2**, key intermediate to achieve **1**. The synthetic route can also be applied in the total synthesis of promising aza-β-carboline compounds.

Key words: azaeburnane, β-carbolines, chiral auxiliary, Mitsunobu reaction, intrinsic reaction coordinate calculations

Chirality in β-carboline molecules plays an important role in medicine, and activity is governed by the asymmetry in molecules. However, even after modern developments in synthetic organic chemistry, there are still few asymmetric methodologies available to prepare these chiral compounds. One methodology is the Pictet–Spengler cyclocondensation.[1] In this context, we have pursued efficient synthetic routes for novel chemotypes when selectivity is required. Over the last few years, 2-(trialkylsiloxy)furans[2] have been used as versatile reagents for the construction of several enantiomerically pure compounds of biological interest.[3] We have investigated the nucleophilic addition of carbon nucleophiles to cyclic acyliminium ions and found that the *N*-acyliminium ring size plays an important role in the stereochemical outcome of the reaction.[4] As studies involving the intermolecular nucleophilic addition of 2-(trialkylsiloxy)furans **4** to cyclic *N*-acyliminium ions are so far restricted to pyrrolidine and piperidine *N*-acyliminium ion rings, isoquinolines and mainly to *N*-benzyloxycarbonyl derivatives,[3] we decided to extend these studies to dihydro-β-carboline iminium precursor such as **3** (Scheme 1).



Scheme 1 Retrosynthetic analysis for the construction of indolo[2,3-*a*]quinolizidine ring system **2** obtained from the addition of **4** to **3** and its azaeburnane analogue **1**

As part of our efforts in the field of biologically relevant carbolines, we turned our attention towards an alternative synthetic route for chiral indolo[2,3-*a*]quinolizidine ring systems, via addition of 2-siloxyfuran **4** to key iminium precursor **3**. Recently, we reported enantioselective total syntheses of hydrastine alkaloids, (–)-quinolactacin B antibiotic, and PDE5 inhibitors.[4] Structurally, **1**[5] comprises a carboline framework containing a common quinoline core.[6] The retrosynthetic analysis for the basic framework of **1** is depicted in Scheme 1 and features the diastereoselective addition of 2-siloxyfuran **4** to the iminium ion derived from **3** as the key step. Although demonstrated to be a useful synthetic method, these asymmetric additions remain to be fully explored in the area of total syntheses of alkaloid natural products.

We first explored the reaction of different 2-siloxyfurans **4a–d**, which are readily available from furfuraldehyde,[7] and iminium precursor **3**. Imine **3** was obtained by refluxing ethyl formate (17 h) with commercial available tryptamine affording the corresponding formamide in 98% yield. Bischler–Napieralski cyclization of the formamide with phosphoryl chloride in acetonitrile at 0 °C for four hours gave **3** in 80% yield. Having prepared imine **3**, the next stage was set for model studies involving the addition of 2-siloxyfurans **4a–d** to the iminium ion intermediates obtained from **3** and **5a**,**b** (Scheme 2, Table 1).

Thus, the scope of the addition of **4a** to imine **3** mediated by chiral auxiliaries **5a** and **5b** with and without additives under different conditions was investigated (Table 1). The

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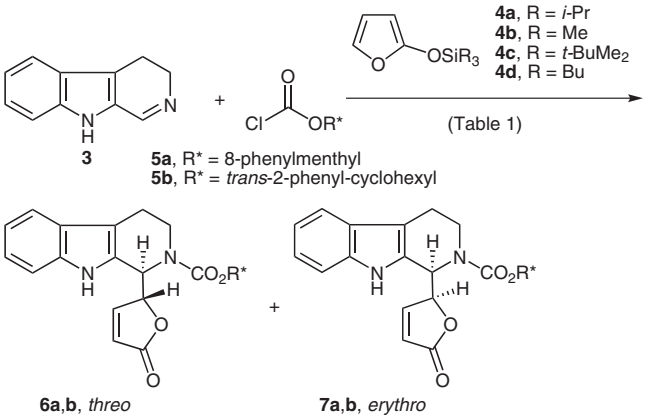


Scheme 2 Model study for the addition of **4** to iminium ion intermediate obtained from **3** and chiral auxiliaries the chloroformate of (–)-8-phenylmenthol (**5a**) or *trans*-2-phenylcyclohexanol (**5b**)

N-acyl derivatives synthesized by quaternization of imine **3** with **5a** by in situ formation of the *N*-acyliminium ion and subsequent addition of nucleophile **4a** in the absence of additives afforded *anti*-isomer **6a** in diastereomeric ratios ranging from 4.1–5.4:1 (*anti*/*syn*, entries 1 and 7). Chiral auxiliary **5b** resulted in a lower diastereomeric ratio (*anti*/*syn*, **6b/7b**, 3.5–3.8:1, entries 4 and 10) for the addition of **4a** to **3** in the absence of additives. Furthermore, without additives, the reactions required longer reaction times and resulted in moderated yields (55–65%) depending on the nature of the solvents employed (Table 1).

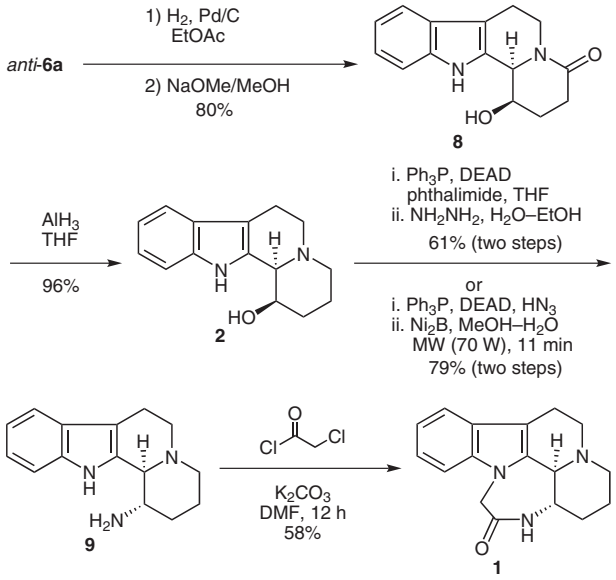
Different salts, such as metal fluorides (e.g., CsF,[8a,b] KF,[8c] CuF_2[8d]), lithium alkoxides,[8e] and imidazolium hydroxide,[8f] have been successfully used to catalyze nonstereoselective additions of trimethylsilyl cyanide to iminium ions. As the activation of R_3SiNu by a Lewis base is primarily due to the affinity of silicon for fluorine or oxygen, facilitating the formation of a reactive pentacoordinate or hexacoordinate silicon intermediate, we employed cesium fluoride and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) in an attempt to improve the nucleophilicity and stereospecificity of **4**. Thus, the role of the addition of cesium fluoride was studied as an additive (entries 2, 5, 8, and 11), and diastereoselections were obtained favoring the *anti* isomer (*anti*/*syn* 3.6–7.3:1) in shorter reaction times. Best results were obtained when **5a** was employed as a chiral auxiliary. Next, we tested the addition of [bmim][BF_4] (entries 3, 6, 9, and 12) as an additive.[9] Ionic liquid [bmim][BF_4] showed selectivity improvement when **5a** and tetrahydrofuran–dichloromethane were employed (entry 9). Finally, to study the influence of the R group (Me, *t*-$BuMe_2$, Bu) on the diastereoselectivity, **3**, **5a**, and [bmim][BF_4] were reacted with siloxyfurans **4b–d** in tetrahydrofuran–dichloromethane. In fact, the preference for the *syn*-isomer **7a** increased (entry 13) when **4b** (R = Me) was employed, compared with **4a** (R = *i*-Pr). When **4c** and **4d** were used (entries 14 and 15), the preference for *anti*-isomer **6a** was modestly lower than **4a** (entry 9). The diastereomeric ratios of **6/7** obtained were determined by isolated products and confirmed by HPLC analysis. The relative stereochemistry of compounds **6** and **7** could be deduced principally by comparison of their ^{13}C NMR spectra since it was noted that the ^{13}C chemical shifts of C5′ and C9 in the *anti* isomer are, respectively, further downfield and higher upfield than those of the corresponding carbons of the *syn* isomer.

Table 1 Addition of 2-Siloxyfurans **4a–d** to Iminium Ions Derived from Imine **3** and Chiral Auxiliaries **5a**,**b**

Entry	Solvent	5	4	Additive	Ratio[a] **6/7**[a]	Yield[b] (%)
1	CH_2Cl_2	**5a**	**4a**	–	4.1:1, **6a/7a**	55[c]
2	CH_2Cl_2	**5a**	**4a**	CsF	4.8:1, **6a/7a**	65
3	CH_2Cl_2	**5a**	**4a**	[bmim][BF_4]	5.9:1, **6a/7a**	72
4	CH_2Cl_2	**5b**	**4a**	–	3.5:1, **6b/7b**	58[c]
5	CH_2Cl_2	**5b**	**4a**	CsF	4.9:1, **6b/7b**	68
6	CH_2Cl_2	**5b**	**4a**	[bmim][BF_4]	5.0:1, **6b/7b**	70
7	THF–CH_2Cl_2	**5a**	**4a**	–	5.4:1, **6a/7a**	60[c]
8	THF–CH_2Cl_2	**5a**	**4a**	CsF	7.3:1, **6a**:**7a**	65
9	THF–CH_2Cl_2	**5a**	**4a**	[bmim][BF_4]	8:1, **6a/7a**	66
10	THF–CH_2Cl_2	**5b**	**4a**	–	3.8:1, **6b/7b**	65[c]
11	THF–CH_2Cl_2	**5b**	**4a**	CsF	3.6:1, **6b/7b**	72
12	THF–CH_2Cl_2	**5b**	**4a**	[bmim][BF_4]	4.6:1, **6b/7b**	70
13	THF–CH_2Cl_2	**5a**	**4b**	[bmim][BF_4]	4.3:1, **6a/7a**	74
14	THF–CH_2Cl_2	**5a**	**4c**	[bmim][BF_4]	7:1, **6a/7a**	66
15	THF–CH_2Cl_2	**5a**	**4d**	[bmim][BF_4]	7.2:1, **6a/7a**	63

[a] Diastereomeric ratio [dr (%)] calculated based on HPLC.
[b] Yields of *anti*/*syn* isomer mixtures. All reactions were performed at –78 °C to –20 °C, 12 h.
[c] Reaction time ca. 48 h.

Hydrogenation reaction of *anti*-isomer **6a** followed by removal of chiral auxiliary with sodium methoxide in methanol gave the 1-hydroxylactam **8** in 80% yield and >98% ee after spontaneous lactamization (Scheme 3). The enantiomeric excess of **8** was determined by chiral HPLC (Welk-01 column, hexanes–*i*-PrOH–*i*-Pr_2NH, 90:10:0.1; 0.8 mL/min, λ = 262 nm). The chiral auxiliary 8-phenyl-



Scheme 3

menthol was recovered in 85% yield and continuously used without loss of induction. Then, reduction of the carbonyl group of **8** with freshly prepared aluminum hydride solution (AlH_3)[4c,10] in tetrahydrofuran afforded **2** in 96% yield {$[\alpha]_D$ –32.0 (*c* 0.7, MeOH)}.[11] Next, the inversion of configuration of the (*R*)-hydroxy group in **2** to give **9** was achieved using the Mitsunobu reaction. The N-alkylation of 1*H*-indole through an intermolecular reaction when using classical Mitsunobu reaction conditions, i.e. triphenylphosphine and diethyl azodicarboxylate, was not a problem.[12a] Furthermore, the NH moiety of indolyl compounds is weakly acidic, and competitive processes showed that indolyl N-alkylation proceeded smoothly compared with other NH groups.

Thus, reaction of **2** with phthalimide, triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran followed by hydrazine treatment in water–ethanol as solvent afforded **9** in overall yields around 61%.[12f,13] Then, testing Mitsunobu reaction of **2** with diethyl azodicarboxylate, triphenylphosphine, and hydrazoic acid[14] gave the corresponding azide, which was reduced (without further purification) with nickel boride (freshly prepared)[15] to afford **9** in 79% yield under microwave-assisted irradiation (70 W) in a sealed vessel at 39 °C.[16] Finally, chloroacetic acid was converted into the respective acyl chloride using thionyl chloride, and 1.01 equivalents reacted with **9** using potassium carbonate in a highly dilute concentration in *N*,*N*-

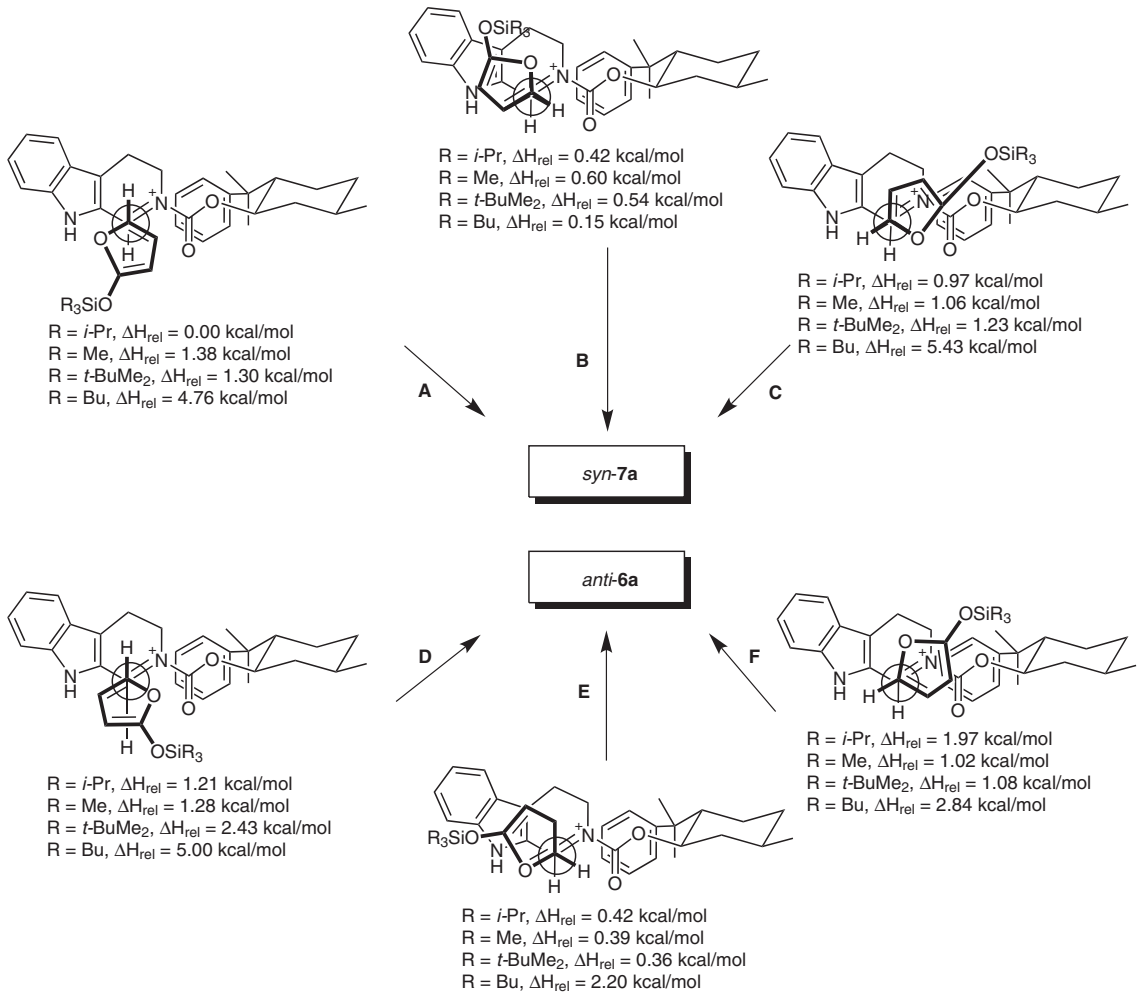


Figure 1 Calculated energies (B3LYP/6-31G*) for the transition-state models for the production of *syn*-isomer **7a** (*erythro*) and *anti*-isomer **6a** (*threo*) adducts

dimethylformamide as solvent (10^{-5} M) afforded compound **1** in 58% yield.[17]

The stereochemical outcome of the above reaction did not come as a surprise to us as previous results with 2-siloxyfurans led us to predict the preferential formation of the *anti* isomer.[4] However, in an attempt to predict the best 2-siloxyfuran (R = *i*-Pr, Me, $BuMe_2$, Bu) in this kind of reaction, theoretical calculations of the transition-state geometries associated with the addition of 2-siloxyfurans **4a–d** to the iminium ion derived from **3** at DFT level (B3LYP/6-31G*) and MP2 were carried out. Theoretical calculations of the transition-state geometries associated with the addition of 2-siloxyfuran **4a** (R = *i*-Pr) to the iminium ion derived from **3** at DFT level (B3LYP/6-31G*) showed that arrays which lead to formation of *syn* product (A, B, and C) are lower in energy than arrays leading to formation of *anti* isomer (D, E, and F). Specifically, array A showed (relative energy: 0.0 kcal/mol), expected to be the lowest energy transition state, displaying an synclinal approach of the π systems of the nucleophile and iminium ion was indeed lower in energy than array C (relative energy: 0.97 kcal/mol), as depicted in Figure 1.

The same analysis can be performed for the *anti* energies of transition states (arrays D and F). For remaining 2-siloxyfurans **4b**,**c**,**d** the arrays B and E were lower in energy, both leading to *syn* and *anti* products, respectively. Transition-state calculations suggest that formation of *syn* intermediates is generally faster, which means it is kinetically controlled. In order to check if thermodynamic control favors the formation of the *anti* isomer, we performed intrinsic reaction coordinate (IRC) calculations[18] on each array of 2-siloxyfuran **4a** to the iminium ion derived from **3** (Figure 2). IRC calculations were performed at the same level used to characterize the transition-state structures, and they required between 30 and 40 points to reach energy convergence. The step size along the reaction path, leading to products, was set up to 10. The results showed that *syn* product, in each array, was lower in energy that *anti* product, indicating that *syn* isomers are also favored by thermodynamic control of the reaction when DFT theory was employed, as depicted in Figure 2.

Martin and co-workers have found a similar result for the transition-state calculations (RHF/3-21G*) in the addition of 2-methoxyfuran to a five-membered *N*-acyl-*N*-(methoxycarbonyl)iminium ion.[19] Generally, it is observed that the *anti* adduct is formed in the addition of 2-siloxyfurans to iminium ions as the major species.[2,4] However, for several years, we have not been able to rationalize the reversal of the stereochemical outcome observed when 2-siloxyfurans are employed in the addition to iminium ions, the unexpected preference for the *syn* adduct by *ab initio* and DFT calculation models.[4a,7,19] With the aim to elucidate the disagreement in the experimental and theoretical data when **4a** was used, we performed single point energy calculations at MP2 level, using 6-31G* basis set, on last points in previous IRC curves to the lowest energy transition state described by arrays A (R = *i*-Pr, *syn*) and D (R = *i*-Pr, *anti*). MP2 results afforded the picture for the stereochemical outcome in this Mannich reaction, which the *anti* transition state presented energy 0.29 kcal/mol lower than the *syn* transition state, as depicted in Figure 3. Additionally, we analyzed the LUMO orbitals for both transition states in order to interpret the gain in stabilization energy of the *anti* adduct. We figure that in the *anti* transition state a secondary orbital interaction of indolic nitrogen electrons lone pair to the transient π^*_{allyl} siloxyfuran system, during the production of the C–C bond, should have a higher contribution than the transition state stabilized by the π_{CO} shown in array A, Figure 3. This result suggests that, at least, the MP2 level of calculation is

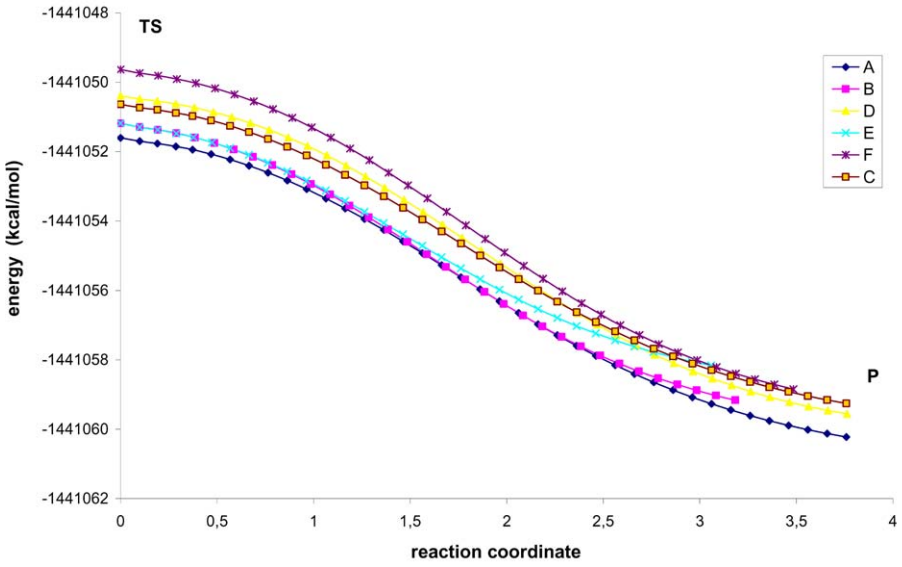


Figure 2 DFT energy profile along the optimized reaction coordinate going from transition state (TS) to products (P). The different curves correspond to possible arrays A–F adopted by 2-siloxyfuran **4a** during the attack to the iminium ion derived from **3** to form *syn*-**7a** and *anti*-**6a** products.

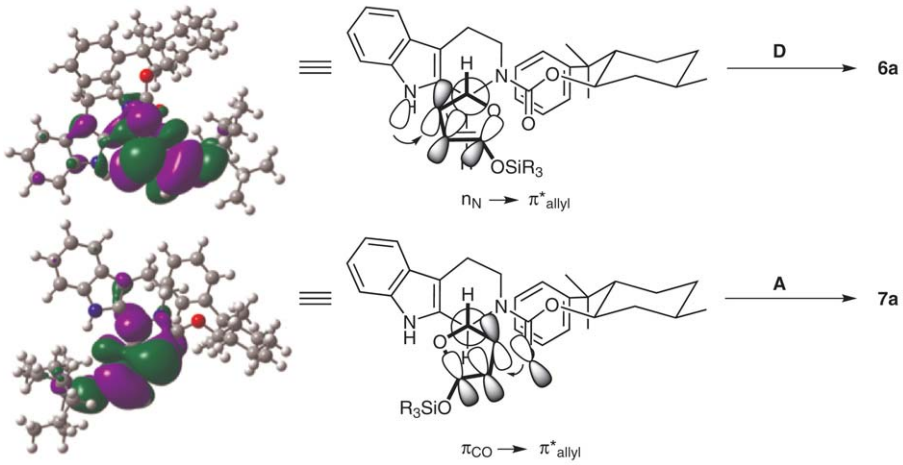


Figure 3 Proposed secondary orbital interaction stabilization for the transition state of the addition of **4a** to iminium ion derivative from **3** obtained at MP2/6-31G* level of calculation. Note that calculated energies (MP2/6-31G*) for the transition-state models for the production of *anti*-isomer **6a** and *syn*-isomer **7a** present now a difference of 0.29 kcal/mol favoring the *anti* adduct.

necessary to obtain a right representation of relative energy stabilities of isomer products in this kind of Mannich reaction. Moreover, the inclusion of exchange and correlation energy as well as the desymmetrization of molecular orbitals (Figure 3), through MP2 method, allowed us to explain the gain in energy stabilization of the *anti*-isomer product.

In conclusion, we explored an alternative and efficient route for the synthesis of azaeburnane systems. The employed method features the use of 2-siloxyfurans **4a**–**d** to imines mediated by chiral auxiliaries to introduce the chirality in **1**. The spectra data of our synthetic compounds, as well as the final products, were in accordance with those previously described.

Commercial available chemical reagents were used without further purification. HN_3, DEAD, HCO_2Et, $POCl_3$, CsF, [bmim][BF_4], NH_2NH_2, Ni_2B, $SOCl_2$, K_2CO_3, tryptamine, formamide, and chloroacetic acid were purchased from Sigma-Aldrich. (1*R*,2*S*,5*R*)-(+)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate was purchased from Aldrich and hydrolyzed to (–)-8-phenylmenthol. Ph_3P was purchased from Merck. Anhyd MeCN and THF, CH_2Cl_2, MeOH, and DMF were prepared by distillation under a N_2 atmosphere over Na/benzophenone, CaH_2, Na/P_2O_5, and CaH_2/molecular sieves, respectively, and were used for reactions. Solvents for extraction and column chromatography were distilled prior to use. NaN_3 was handled with care by wearing safety glasses, facemask, gloves, and reactions were performed in a fume hood. All microwave reactions were performed in CEM Discover LabMate equipment in a closed vessel (built-in IR sensor) with cooling system. Infrared spectra were recorded as film on KBr cells. Melting points were measured with an Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker WH Avance 300, and Varian Unity 400 MHz spectrometers using TMS as the internal standard. Mass spectra were recorded on a QTof Micro (Waters-Micromass). Column chromatography was performed using silica gel 100–200 mesh. TLC analyses were performed with silica gel plates using I_2, $KMnO_4$, and UV lamp for visualization.

***N*-Formyltryptamine**

Tryptamine (0.48 g, 3.0 mmol) and HCO_2Et (5.0 mL) were refluxed for 17 h. The solvent was evaporated under reduced pressure, and resulting the crude oil was diluted with CH_2Cl_2 (5.0 mL) and washed with 1 M HCl (5.0 mL), aq sat. K_2CO_3 soln, and brine. The organic phase was evaporated under reduced pressure, and the resulting oil dried under high vacuum for 3–4 h to give pure *N*-formyltryptamine as a colorless oil; yield: 0.553 g (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01 (t, *J* = 8.8 Hz, 2 H), 3.67 (t, *J* = 8.8 Hz, 2 H), 7.16 (t, *J* = 7.8 Hz, 1 H), 7.22 (t, *J* = 8.1 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 8.36 (s, 1 H).

4,9-Dihydro-3*H*-β-carboline (3)

N-Formyltryptamine (0.553 g, 2.94 mmol) was dissolved in MeCN (3.50 mL), and the temperature was maintained at 0 °C. Distilled $POCl_3$ (0.43 mL, 4.60 mmol) in MeCN (0.70 mL) was added over 35–40 min. The mixture was stirred at 0 °C for 3 h and then 5% HCl (20 mL) was added. The mixture was washed with Et_2O (3 × 6.0 mL). To the aqueous phase at 0 °C under vigorous stirring was added aq KOH soln [3.15 g in H_2O (6.0 mL)] dropwise; a white precipitate formed that could not be filtered off. The mixture was extracted with CH_2Cl_2 (4 × 15.0 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give imine **3** as an orange solid; yield: 0.400 g (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 8.8 Hz, 2 H), 3.95 (t, *J* = 8.8 Hz, 2 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 8.54 (s, 1 H).

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl *anti*-1-(2,5-Dihydro-5-oxofuran-2-yl)-4,9-dihydro-3*H*-β-carboline-2-carboxylate (6a)

To a soln of imine **3** (306 mg, 1.80 mmol) in anhyd CH_2Cl_2–THF (1:1, 10.0 mL) and (–)-8-phenylmenthyl chloroformate (**5a**, 530 mg, 1.80 mmol) at –78 °C was added [bmim][BF_4] (0.020 mL, 1.80 mmol) and the mixture was stirred for 30 min under an argon atmosphere, followed by slow addition of 2-(triisopropylsiloxy)furan (**4a**, 460 mg, 1.80 mmol) in CH_2Cl_2–THF (1:1, 1.00 mL). After 12 h, sat. aq NH_4Cl (10.0 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude diastereomeric mixture (8:1) was submitted to flash column chromatography purification (hexane–EtOAc, 2:1) affording pure *anti*-isomer **6a** (543 mg, 1.06 mmol,

59%) and *syn*-isomer **7a** (64.0 mg, 0.126 mmol) contaminated with **6a**.

$[\alpha]_D$ –64 (*c* 1.0, $CHCl_3$).

FTIR (film): 3088, 3060, 2956, 2921, 2869, 2850, 1760, 1696, 1682, 1457, 1427 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6, 360 K): δ = 0.83–0.90 (m, 1 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 1.10–1.42 (m, 9 H), 1.47–1.67 (m, 2 H), 1.75–1.86 (m, 2 H), 1.99–2.06 (m, 1 H), 2.45–2.50 (m, 1 H), 2.45–2.73 (m, 4 H), [3.97–4.11/4.66–4.75 (m, m, 1 H)], [4.95–5.10/5.25–5.28 (m, m, 1 H)], 5.61 (br d, *J* = 6.3 Hz, 1 H,), 6.99 (d, *J* = 6.3 Hz, 1 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 6.04 (t, *J* = 7.4 Hz, 1 H), 7.23–7.38 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 17.5 (2 ×), 21.8, 27.2, 28.7, 31.4, 34.7, 39.2, 49.7, 50.9, 60.4, 75.3, 84.2, 110.8, 118.0, 118.2, 119.4, 121.7, 124.3, 124.8, 125.5, 126.6, 128.0, 128.4, 134.8, 135.8, 151.7, 153.4, 155.6, 155.3, 173.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{37}N_2O_4$: 513.2753; found: 513.2750.

(1*R*,12b*R*)-1-Hydroxy-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (8)

To a soln of *anti*-isomer **6a** (1.20 mmol) in EtOAc (12.0 mL) was added 10% Pd/C (38 mg) and the mixture was stirred under H_2 (1 atm) overnight. The mixture was then filtered through Celite, and the pad was rinsed with EtOAc–MeOH (4:1, 200 mL). The organic layer was concentrated under reduced pressure. Then, a soln of 1.1 M NaOMe in MeOH (5.2 mL) was added to the crude at 0 °C, and the mixture was stirred at r.t. After 2 h, 2 M HCl–MeOH soln (10.0 mL) was carefully added. The organic layer was concentrated under reduced pressure, purified by flash chromatography (silica gel) providing **8** as a colorless oil (246 mg, 0.96 mmol, 80%). The enantiomeric excess of **8** was determined by HPLC analysis using a Welk-01 column [eluent: hexanes–*i*-PrOH–*i*-Pr_2NH (90:10:0.1); flow rate: 0.8 mL/min; λ = 262 nm]: t_R (major) = 7.5 min, t_R (minor) = 9.1 min, 99:1 ratio (>98% ee).

$[\alpha]_D$ –102.0 (*c* 1.0, MeOH).

FTIR (film): 3440, 2910, 1622 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.74–1.77 (m, 1 H), 1.88–1.91 (m, 1 H), 2.42–2.47 (m, 1 H), 2.59–2.62 (m, 1 H), 2.68–3.00 (m, 4 H), 3.34 (br s, 1 H, OH), 4.11 (d, *J* = 10.0 Hz, 1 H), 4.75 (m, 1 H), 7.10 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.15 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 7.9 Hz, 1 H), 9.65 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 31.5, 32.8, 40.2, 54.1, 66.6, 109.0, 111.0, 118.5, 119.7, 122.1, 126.8, 133.4, 136.0, 169.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found: 257.1294.

(1*R*,12b*R*)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-ol (2)

To a soln of **8** (65.5 mg, 0.256 mmol) in anhyd THF (4.3 mL) was added 1.55 M AlH_3 in THF (0.330 mL, 0.512 mmol) at r.t. After 10 min, the reaction was quenched with sat. aq Na_2SO_4 soln (1.0 mL) and filtered. The solids were washed with CH_2Cl_2 (50 mL), and the filtrate was dried (Na_2SO_4), evaporated, and concentrated under vacuum. Purification of the residue by column chromatography (10% $CHCl_3$–MeOH) afforded a colorless oil (59.4 mg, 0.2458 mmol, 96%).

$[\alpha]_D$ –32.0 (*c* 0.7, MeOH).

FTIR (film): 3505, 2070, 1425 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.54–1.72 (m, 3 H), 1.92–2.00 (m, 2 H), 2.46 (br t, *J* = 7.9, 1.1 Hz, 1 H), 2.67–2.73 (m, 2 H), 2.90–3.00 (m, 2 H), 3.04 (br s, 1 H, OH), 3.55 (br s, 1 H), 4.19 (br s, 1 H), 7.10–7.11 (m, 2 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 7.46 (d, *J* = 7.9 Hz, 1 H), 8.12 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 21.4, 28.3, 34.0, 47.2, 48.7, 53.1, 56.0, 56.9, 66.7, 111.1, 112.2, 127.1, 128.3, 145.3, 147.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1497; found: 243.1500.

(1*S*,12b*R*)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-amine (9)

DEAD (0.30 mL, 1.88 mmol) was added dropwise to soln of **2** (115.7 mg, 0.48 mmol), 2.7 M HN_3 in toluene (0.78 mL, 2.18 mmol), Ph_3P (498 mg, 1.90 mmol), and THF (7.0 mL) at 0 °C over 15 min using a syringe pump. After an additional 30 min, hexanes (9.0 mL) were added, and Ph_3PO was filtered off. The crude mixture was dissolved in MeOH (6.0 mL), and then Ni_2B (114 mg, 1.47 mmol) and 1 M HCl (1.5 mL) were added. The reaction was subjected to microwave-assisted irradiation at 70 W using CEM Discover LabMate equipment in a closed vessel with the temperature monitored by a built-in infrared sensor for 11 min at 39 °C with cooling. The resulting mixture was filtered, and then the MeOH was evaporated under vacuum. Sat. $NaHCO_3$ soln (15 mL) was added to the mixture, which was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and rotaevaporated under reduced pressure to afford pure **9** as a white solid; yield: 91.4 mg (79%); mp 133.0–135.0 °C.

$[\alpha]_D$ +3.7 (*c* 1.0, MeOH).

FTIR (film): 3345, 3269, 2920, 2805, 2740, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.27 (m, 1 H), 1.67–1.91 (m, 4 H), 2.05–2.10 (m, 1 H), 2.35 (dt, *J* = 11.4, 3.0 Hz, 1 H), 2.53–2.75 (m, 2 H), 2.82 (dt, *J* = 10.3, 4.0 Hz, 1 H), 2.89–3.14 (m, 4 H), 7.06 (t, *J* = 7.0 Hz, 1 H), 7.12 (t, *J* = 7.0 Hz, 1 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 10.54 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 25.1, 39.2, 53.2, 54.2, 55.8, 66.0, 107.8, 111.5, 118.3, 119.0, 121.1, 127.4, 135.9, 136.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}N_3$: 242.1657; found: 242.1661.

trans-(+)-14-Oxo[1,12]iminoethano-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (1)

To a solution of **9** (50.0 mg, 0.207 mmol) in DMF (3.0 mL) under vigorous stirring was added chloroacetyl chloride (0.016 mL, 0.209 mmol) at r.t. followed by K_2CO_3 (0.057 mg). After 12 h of reaction, H_2O (10.0 mL) was added, and intensive stirring was continued for an additional 10 min. The mixture was kept at 5 °C, and after 6 h a colorless precipitate was obtained, collected by filtration, and washed twice with H_2O (2 × 0.1 mL). Drying under high vacuum afforded a solid, which was dissolved in hot MeOH (6.0 mL) and fumaric acid (11.4 mg, 0.10 mmol) was added. After 20 min, colorless crystals of pure **1** were obtained and filtered off; yield: 33.7 mg (58%); mp 255–258 °C.

$[\alpha]_D$ +8.1 (*c* 1, pyridine).

FTIR (film): 1695 cm^{-1}.

^1H NMR (400 MHz, pyridine-d_5): δ = 1.61–1.82 (m, 3 H), 2.09–2.25 (m, 2 H), 2.49–2.52 (m, 1 H), 2.67 (dd, *J* = 14.2, 5.3 Hz, 1 H), 2.85 (dd, *J* = 12.3, 3.2 Hz, 1 H), 2.94–3.12 (m, 2 H), 3.13 (d, *J* = 10.7 Hz, 1 H), 3.78 (ddd, *J* = 10.7, 10.0, 5.0 Hz, 1 H), 4.74 (d, *J* = 2.2 Hz, 1 H), 5.14 (d, *J* = 2.2 Hz, 1 H), 7.24 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.32 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.50 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.58 (dd, *J* = 8.0, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, pyridine-d_5): δ = 22.1, 24.5, 31.2, 50.1, 51.2, 54.2, 54.8, 66.7, 107.3, 110.5, 118.8, 120.2, 122.2, 128.5, 134.9, 135.8, 169.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}N_3O$: 282.1606; found: 282.1610.

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