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Domino Rh-catalyzed hydroformylation–double cyclization of *o*-amino cinnamyl derivatives: applications to the formal total syntheses of physostigmine and physovenine†

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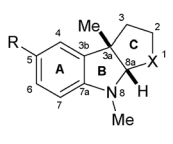
A parallel, versatile and efficient route to synthesis of pyrrolidinoindoline and tetrahydrofuranoindoline alkaloids from cinnamyl derivatives has been developed, featuring a domino Rh-catalyzed hydroformylation–double cyclization sequence. This method can be applied to the syntheses of anti-Alzheimer drugs such as physostigmine and physovenine.

The pyrrolidinoindoline alkaloid family possesses a wide range of important pharmacological activities (Fig. 1).[1] For example, physostigmine, a reversible inhibitor of acetyl- and butyryl-cholinesterase, has been used for treatment of glaucoma, myasthenia gravis and Alzheimer's disease.[2,3] Phenserine, a synthetic analogue of physostigmine, is an effective and selective inhibitor of acetylcholinesterase, but with little effect on butyryl-cholinesterase.[4] Moreover, phenserine has been recognized to inhibit β-amyloid plaque deposition, and thus used for treatment of Alzheimer's disease.[3c,5] Eseroline exhibits morphine-like potent analgesic properties.[6] Pyrrolidinoindoline alkaloids bearing a trifluoromethylsulfanyl group (CF_3S–), a group with extremely large Hansch lipophilicity parameters, at the C-**3a** position show high cytotoxicity against three cancer cell lines.[7] The physiological activities of **3a**-substituted pyrrolidinoindoline derivatives have prompted many synthetic chemists to develop various elegant approaches.[7,8]

Here we report an efficient and diverse synthesis of pyrrolidinoindolines using a domino Rh-catalyzed hydroformylation–double cyclization reaction, a general strategy to synthesize these alkaloids with flexibility for variation in pyrrolidinoindolines and tetrahydrofuranoindolines. We take advantage of the special regio-selectivity found in hydroformylation of styrene derivatives, which produce exclusive α-formylated products due to the coordination nature of the aromatic group.[9] We have also employed theoretical DFT calculations to explain the observed selectivity.

Our synthesis commenced with the preparation of carbamate derivatives **2**, obtained by a series of functional group transformations from *o*-nitro cinnamyl alcohol **1** (Scheme 1). Reduction of the aryl nitro group to the aryl amine with Fe(II), followed by protection with methyl chloroformate provided carbamate **2a** in 84% yield. Alcohol **2a** was treated with PBr_3 to provide the corresponding bromide, followed by azide substitution to introduce the nitrogen functionality, and then reduction with PPh_3 to a free amine. The resulting amine was treated with methyl chloroformate in the presence of base to obtain dicarbamate **2b** in 83% yield over 4 steps. It is noteworthy to point out that the crude products mentioned above could be used directly without further purification.

With dicarbamate **2b** in hand, we have investigated the key hydroformylation–double cyclization reaction conditions, and the results have been summarized in Table 1. Treatment of dicarbamate **2b** under the cyclized conditions, *i.e.* 2 mol% of $Rh(acac)(CO)_2$ and 8 mol% of $P(OPh)_3$ catalyst under 80 atm of CO and H_2 (1 : 1) in



R	X = NMe	X = O
H-	Desoxyeseroline	-
HO-	Eseroline	Physovenol
MeO-	Esermethol	-
PhHNCOO-	Phenserine	Phensvenine
MeHNCOO-	Physostigmine	Physovenine

Fig. 1 Substituted pyrrolidinoindoline and tetrahydrofuranoindoline.

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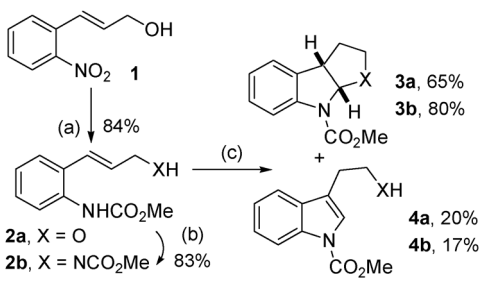
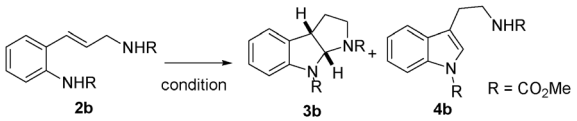
† Electronic supplementary information (ESI) available: Experimental procedure, ^1H, ^{13}C NMR spectra, stereochemistry assignment and calculated geometry coordinates. See DOI: 10.1039/c3cc43257b



Scheme 1 Preparation of cinnamyl derivatives and the results of double cyclization. (a) (i) $FeSO_4$, NH_4OH, MeOH. (ii) MeOCOCl, $NaHCO_3$, acetone. (b) (i) PBr_3, Et_2O; (ii) NaN_3, acetone, H_2O; (iii) PPh_3, THF, H_2O; (iv) MeOCOCl, K_2CO_3, acetone. (c) $Rh(acac)(CO)_2$ (2 mol%), $P(OPh)_3$ (8 mol%), CO (40 atm), H_2 (40 atm), MeCN, 95 °C.

Table 1 Optimization for the double cyclization of dicarbamate **2b**



2b **3b** **4b**

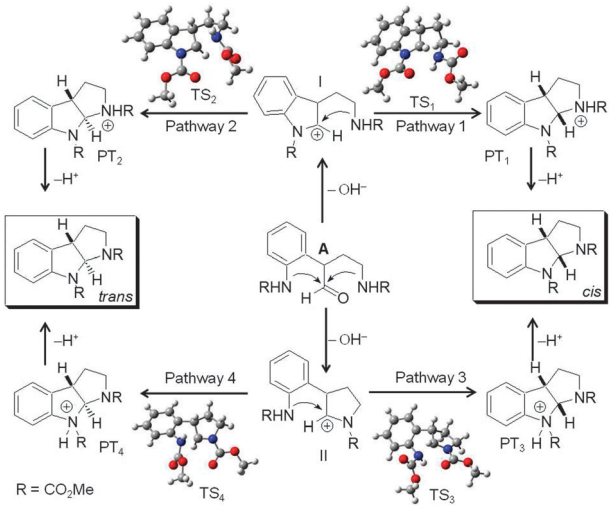
Entry[a]	Solvent	T (°C)	**3b**[b] (%)	**4b**[b] (%)
1	Toluene	75	—	91
2[c]	Toluene	75	—	87
3	Dioxane	75	65	20
4	Dioxane	95	73	20
5	Dioxane	115	74	25
6	Dimethoxyethane	95	37	59
7	THF	95	41	47
8	CH_3CN	95	80	17
9	CH_3COOH	95	—	93
10	CH_3OH	95	—	87
11[d]	CH_3CN	95	64	27

[a] All reactions were run with 1.0 mmol of **2b** (0.05 M in 20 mL solvent), $Rh(acac)(CO)_2$ (2 mol%), and $P(OPh)_3$ (8 mol%) for 16–20 h, CO (40 atm), H_2 (40 atm). [b] Isolated yield. [c] Additives of PTSA (10 mol%) used. [d] $Rh(acac)(CO)_2$ (0.5 mol%) and $P(OPh)_3$ (2 mol%) used.

toluene at 75 °C, did not afford the desired cyclized product **3b** but only tryptamine derivative **4b** in 91% yield (entry 1). Addition of a catalytic amount of PTSA (10 mol%) as a proton source did not yield the desired product either (entry 2). Use of dioxane as the solvent led to the formation of cyclized product **3b** in 65% yield, as well as tryptamine **4b** in 20% yield (entry 3). A higher reaction temperature of 95 °C improved the yield to 73%, while a reaction temperature of 115 °C did not bring significant change (entries 4 and 5). Thus, we set the optimized reaction temperature to 95 °C. Moreover, employment of CH_3CN slightly increased the yield to 80%, with appearance of side product **4b** in 17% yield (entry 8). Reaction in DME and THF as solvents produced product **3b**, but accompanied by more tryptamine side product **4b** (entries 6 and 7). Reaction in AcOH and MeOH gave only tryptamine derivative **4b** (entries 9 and 10). In addition, reaction proceeded with lower catalytic loading (0.5 mol%, entry 11), producing cyclized product **3b** in 64% isolated yield. Thus, we concluded that both dioxane and acetonitrile are used as suitable solvents for the formation of cyclized product **3b**, while acidic conditions or a protic solvent favors the formation of tryptamine product **4b**.

Reaction of monocarbamate **2a** under the same conditions also yielded cyclized product **3a** in 65% yield, as well as tryptophol **4a** in 20% yield. The relative configurations of both tetrahydrofuranoindoline **3a** and pyrrolidinoindoline **3b** were clearly assigned as a *cis* configuration due to nOe signals observed between two methines (see ESI†).

To explain the observed *cis* selectivity, we have considered the whole reaction process as follows: the double cyclization commences with hydroformylation of the cinnamyl derivatives to yield α-aldehyde **A** (Scheme 2). One of the two carbamates (*i.e.* N-1 and N-8) is able to undergo intramolecular condensation with the aldehyde to afford either indolinium intermediate **I**, or pyrrolinium intermediate **II**. Subsequent intramolecular addition of the other carbamate to the iminium intermediate furnishes the second cyclization to give either *cis* (pathways 1 and 3) or *trans* (pathways 2 and 4) adducts, which also dominates the diastereoselectivity.[10] There are 4 possible transition states in the process to form the last ring and determine the



Scheme 2 Four possible double cyclization pathways 1–4 from α-aldehyde **A** and the corresponding transition state geometries in CH_3CN.

selectivity outcome, followed by deprotonation of these adducts to give the final *cis* or *trans* tricyclic product and completes the whole double cyclization process. Although it is known that cyclization to a 5,5-fused ring system prefers a *cis* fusion due to the highly strained nature of *trans* fusion. We believe that these 4 transition state geometries in the pathways 1–4 will provide more mechanistic information about the *cis* selectivity. Thus, we have carried out the DFT calculations to obtain four transition state geometries at the level of B3LYP/6-31++G** in the gas phase, as well as those in the acetonitrile solvent using the CPCM model (see ESI†). The geometries have been shown in Scheme 2 and the results have been summarized in Table 2.[11]

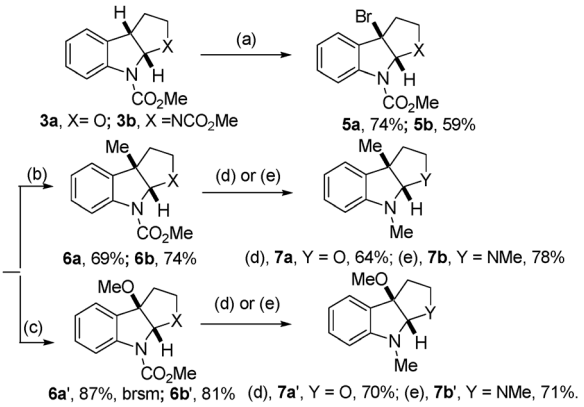
The results in Table 2 have disclosed that the stabilities of four transition states appear to be concerned with a trajectory angle (*i.e.* Bürgi–Dunitz angle[12]), which is the angle of the nitrogen nucleophile to the iminium bond. More precisely, the positions of the TSs are in respect to the deviation of the angle from the typical Bürgi–Dunitz angle (∼105°). A smaller angle difference also implies a smaller activation energy barrier. There is a small difference in the Bürgi–Dunitz angle in the TS_1, which implies that pathway 1 is preferred. In addition, the calculations also display that the *cis* tricyclic product is more stable than the *trans* tricyclic product by 23.0 kcal mol^{-1} (see ESI†). Thus, the results provide substantial theoretical corroboration to rationalize the *cis* selectivity. Since the *cis* product has been thermodynamically and kinetically favored, it is anticipated that products retain the *cis* configuration in the subsequent reactions.

Benzylic bromination of cyclized product **3b** using 1,3-dibromo-5,5-dimethylhydantoin/AIBN[13] yielded bromide **5b** in 59% yield, accompanied by tryptamine **4b** in 27% yield. Treatment of cyclized

Table 2 Relative energies, Bürgi–Dunitz angles in the 4 TS geometries[a]

	Rel E	Imag ν	θ
TS 1 (*cis*)	0.0	211	109.8
TS 2 (*trans*)	+28.3	295	131.7
TS 3 (*cis*)	+1.2	202	113.9
TS 4 (*trans*)	+23.6	251	129.4

[a] Energy in kcal mol^{-1}, imaginary frequency in cm^{-1}, Γ = ∠N–C═N in TSs.



Scheme 3 Syntheses of desoxyeseroline, CPC-1 and tetrahydrofuranoindoline analogues: (a) 1,3-dibromo-5,5-dimethylhydantoin, AIBN, CCl_4, reflux. (b) $ZnMe_2$, toluene, reflux. (c) $Ti(^iOPr)_4$ (25 mol%), MeOH, reflux. (d) (i) NaOH, microwave. (ii) HCHO, Pd/C, H_2, EtOAc, rt. (e) Red-Al, toluene, reflux.

product **3a** under the same conditions yielded bromide **5a** in a better yield of 74% and tryptamine **4a** in 21% yield. Both bromides **5b** and **5a** have been versatile building blocks for syntheses of pyrrolidinoindoline and tetrahydrofuranoindoline alkaloids. Four examples have been demonstrated for the flexibility of the synthesis (Scheme 3). Treatment of bromide **5b** with $ZnMe_2$ in toluene afforded a methylated product **6b** in 74% yield, and the reaction of bromide **5a** yielded **6a** in 69% yield. Ti-mediated methanolysis of bromide **5b** afforded ether **6b′** in 81% yield, while that of bromide **5a** took about 2 days to produce **6a′** in 56% isolated yield and recovered bromide **5a** in 35% yield. Strong nOe signals have been observed between the methyl group or the methoxy group and the methine proton (*i.e.* **8a**) in all the four cases, indicating that the *cis* configuration has been retained. Desoxyeseroline **7b** was achieved by Red-Al reduction of both two carbamate groups to methyl groups in 78% yield. Red-Al reduction of ether **6b′** provided CPC-1 **7b′** in 71% yield, a new pyrrolidinoindoline alkaloid isolated from *Chimonanthus praecox* (L.) f. concolor Makino (*Calycanthaceae*) in 2006.[14] However, Red-Al reduction of tetrahydrofuranoindolines **6a** and **6a′** to the *N*-methyl products **7a** and **7a′** resulted in the formation of a little amount of desired product, only in 10% yield and 14% yield respectively. A two-step procedure of protecting group removal–reductive methylation has been carried out: microwave-assisted basic hydrolysis of **6a** gave free amine, which was immediately treated with formalin followed by exposure to hydrogen with Pd/C to produce methyl product **7a** in 64% yield. Following the same procedure, methyl product **7a′** was obtained in 70% yield. The NMR data of **7b** and **7b′** are identical to those reported in the literature.[8f,15] Desoxyeseroline **7b** and tetrahydrofuranoindoline **7a** could be further converted into esermethole, physostigmine and physovenine according to the published reports.[15]

In conclusion, we have described a versatile synthesis of **3a**-substituted pyrrolidinoindolines and tetrahydrofuranoindolines featuring a domino Rh-catalyzed hydroformylation–double cyclization reaction. The methodology provides a flexible access to various substituted alkaloids, demonstrated as syntheses of CPC-1 and desoxyeseroline, and can be applied to synthesize pharmacological active alkaloids such as esermethole, phenserine, physostigmine and physovenine. Complete DFT calculations reveal that *cis* products are both thermodynamically and kinetically favored, and the stability guarantees a *cis* configuration in the subsequent chemical transformations. Since many efficient asymmetric hydroformylations have been developed, the methodology provides a practical way to synthesize chiral **3a**-substituted alkaloids. Subsequent investigation and extension of this methodology towards other natural products of interest are currently underway.

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