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One-Pot Organocatalytic Enantioselective Domino Double-Michael Reaction and Pictet-Spengler–Lactamization Reaction. A Facile Entry to the "Inside Yohimbane" System with Five Contiguous Stereogenic Centers

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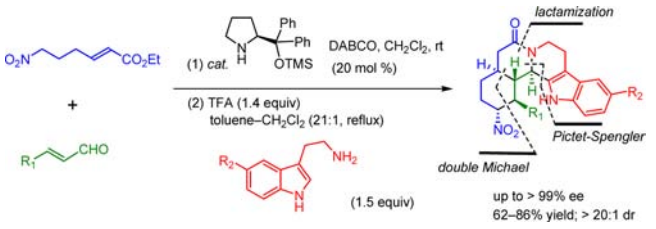
ABSTRACT



An expedited method was developed for the enantioselective synthesis of dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine containing five contiguous stereogenic centers with high enantioselectivities (>99% ee). The methodology comprises a domino organocatalytic double Michael reaction and Pictet-Spengler–lactamization reaction. The structures and absolute configurations of the appropriate products were confirmed by X-ray analysis.

The quinolizidine alkaloids represent an important class of alkaloids with a wide spectrum of biological activities and have long attracted extensive pharmacological, chemical, and synthetic interests.[1] Among these compounds, the dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine, the so-called "inside yohimbane", emerged as a preeminent member of this alkaloid category. Examples of natural and synthetic compounds bearing the dodecahydrobenz-[*a*]indolo[3,2-*h*]quinolizine skeleton have shown various biological activities (Figure 1). Manadomanzamine A and manadomanzamine B have anti HIV, antifungal, antimycobacterial, and cytotoxic activities;[2] 21a-homo-14-nor-yohimba-15,17,19-triene has high affinity for the α1 adrenergic receptors;[3] 2,3,4,4a*β*,5,6,7,8,13,13b*β*-decahydro-1*H*-6a,13-diazaindeno[1,2-*c*]phenanthren-13c*β*-ol has high affinity for the α2C-adrenoceptor;[4] pentacyclic benzindoloquinolizine has been reported to have antiserotoninergic effects.[5] The inside α-yohimbine intermediates have been prepared following the method for the total synthesis of reserpine and α-yohimbane.[6] Although several synthetic approaches toward the "inside yohimbane" skeleton have

(1) For a review, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, 139–165 and the proceeding 11 reviews in the series of indolizidine and quinolizidine alkaloids by Michael cited therein.

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been reported,[7] the construction of this pentacyclic ring system with five stereogenic centers in a cascade strategy with high enantioselectivity remains elusive. An efficient synthetic methodology toward this system with suitable functionality is certainly attractive and would be useful for discovering pharmaceutical lead compounds.

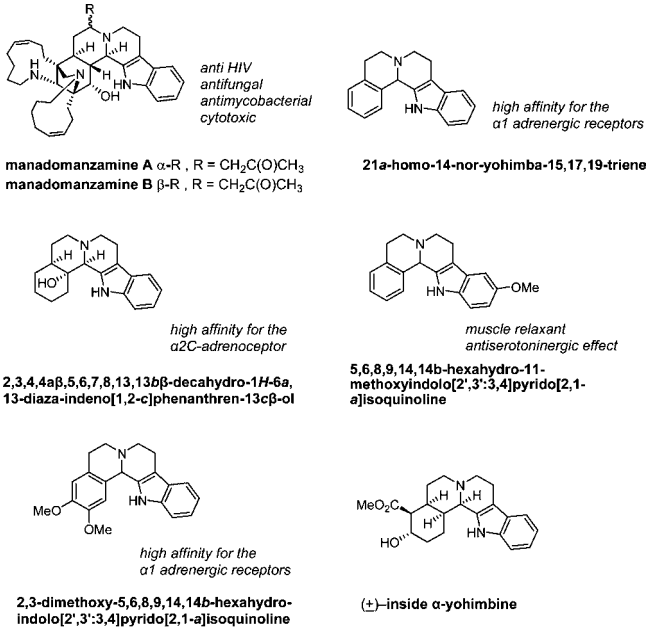


Figure 1. Select examples of the biologically active natural products and synthetic compounds with dodecahydrobenz[*a*]indolo-[3,2-*h*]quinolizine skeleton.

Scheme 1. Retrosynthetic Analysis of Dodecahydrobenz-[*a*]indolo[3,2-*h*]quinolizine

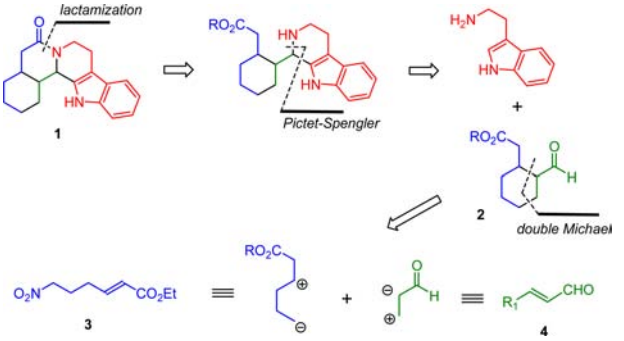
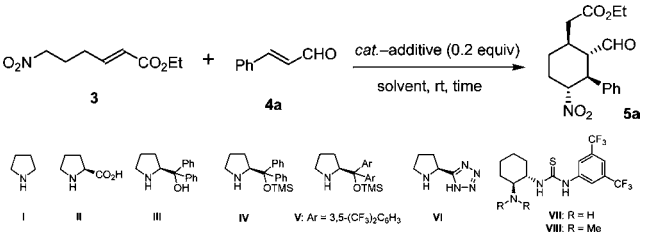


Table 1. Screening of the Catalysts, Solvents, and Reaction Conditions for the Stereoselective Double Michael Reaction[a]



entry	cat.–additive	solvent	time (h)	yield[b,c] (%)
1	**I**–DABCO	$CHCl_3$	7	84
2	**II**–DABCO	$CHCl_3$	96	50
3	**III**–DABCO	$CHCl_3$	96	nr
4	**IV**–DABCO	$CHCl_3$	44	83[d]
5	**V**–DABCO	$CHCl_3$	96	0
6	**VI**–DABCO	$CHCl_3$	96	56
7	**VII**–DABCO	$CHCl_3$	19	15
8	**VIII**–DABCO	$CHCl_3$	41	trace
9	**IV**–DABCO	toluene	96	41
10	**IV**–DABCO	CH_2Cl_2	64	89[d]
11	**IV**–DABCO	THF	72	80
12	**IV**–DABCO	EtOH[e]	10	90[d,f]
13	**IV**–DABCO	DMF	96	71
14	**IV**–DABCO	CH_3CN	61	90[d,g]
15	**IV**–DABCO	1,4-dioxane	96	59
16	**IV**–Et_3N	CH_2Cl_2	43	68
17	**IV**–NaOAc	CH_2Cl_2	39	62
18	**IV**–DBU	CH_2Cl_2	18	65
19	**IV**–2,6-lutidine	CH_2Cl_2	39	65
20	**IV**–HOAc	CH_2Cl_2	39	41

[a] Unless otherwise noted, the reactions were performed on a 0.1 mmol scale of **3a** and **4a** (1.2 equiv) using 20 mol % of the catalyst and additive at ambient temperature in a vial containing the appropriate solvent. [b] Isolated yields of **5a**. [c] Unless otherwise noted, diastereomeric ratio >20:1, determined by ^{1}H NMR of the reaction mixture. [d] >99% ee of **5a**, determined by HPLC with chiral column Chiralpak IA. [e] 99% ethanol. [f] Diastereomeric ratio 16:1. [g] Diastereomeric ratio 17:1, nr = no reaction.

Prompted by the above background and in the context of our ongoing investigations in organocatalyzed annulations,[8,9] we envisioned that the lactamization and Pictet–Spengler[10] transformation of the "inside yohimbane" system

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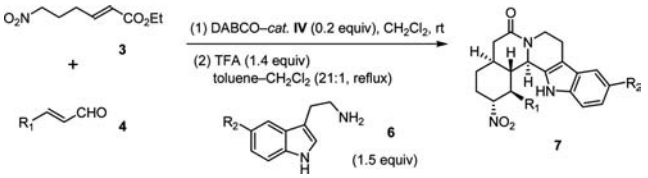
1 would lead to the precursor, cyclohexylcarbaldehyde **2**, which could be efficiently prepared via a domino organocatalyzed double Michael reaction[11] of the suitable nitro alkenoate **3** and α,β-unsaturated aldehyde **4** (Scheme 1). We report herein the development of a one-pot organocatalytic enantioselective domino double-Michael reaction and Pictet–Spengler–lactamization reaction sequence leading to dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizines in good yields and excellent diastereoselectivities and enantioselectivities (up to >99% ee).

Table 2. Scope of Organocatalytic Double-Michael–Pictet–Spengler Reactions[a]



entry	R_1	R_2	time[b] (h)	yield[c,d] (%)	ee[e] (%)
1	**7a**, C_6H_5	H	34	77	>99
2	**7b**, 4-FC_6H_4	H	36	82	>99
3	**7c**, 4-ClC_6H_4	H	25	83	>99
4	**7d**, 4-BrC_6H_4	H	36	62	>99
5	**7e**, 4-$NO_2C_6H_4$	H	26	77	>99
6	**7f**, 4-$MeOC_6H_4$	H	36	82	>99
7	**7g**, 4-$NMe_2C_6H_4$	H	31	84	>99
8	**7h**, 2-MeC_6H_4	H	168	76	>99
9	**7i**, 4-MeC_6H_4	H	25	83	>99
10	**7j**, 2-furyl	H	44	65	>99
11	**7k**, C_6H_5	OMe	38	86	>99

[a] Unless otherwise noted, the reactions were performed on a 0.2 mmol scale of **3** and **4**, in a ratio of 1:1.2, using 20 mol % of the catalyst **IV** and DABCO at room temperature in a vial containing the appropriate solvent. [b] Time required for 1st–double Michael reaction. [c] Isolated yield of **7**. [d] Diastereomeric ratio >20:1, determined by ^1H NMR of crude reaction mixture. [e] The ee of **7**, determined by HPLC with Chiralpak IA.

Initially, the double Michael reaction of nitroalkenoate **3** and cinnamaldehyde **4a** was performed with pyrrolidine (**I**)–DABCO in $CHCl_3$ at ambient temperature for 7 h and provided the cyclohexylcarbaldehyde **5a** in 84% yield (Table 1, entry 1). After the reactions were screened with other catalysts, e.g., **II**–**VIII**, the best result was obtained with the condition of **IV**–DABCO for 44 h reaction to give 83% yield of **5a** with >99% ee (Table 1, entry 4). The reactions with other catalysts afforded much lower yield, or there was no observation of product **5a** (Table 1, entries 1–8). Further optimization of the double-Michael reaction with **IV**–DABCO in various solvents was conducted, and the optimal yield of **5a** was obtained in 89% yield with >99% ee for the reaction in CH_2Cl_2 (Table 1, entries 9–15 and entry 10). The reactions in 99% EtOH or CH_3CN gave slightly lower diastereoselectivity (Table 1, entries 12 and 14). Reactions performed with catalysts **IV** and other additives were not promising and provided lower yields (Table 1, entries 16–20).

The Pictet–Spengler reaction and lactamization was achieved by the reaction of **5a**, isolated from the reaction depicted in Table 1, and 1.5 equiv of 2-(1*H*-indol-3-yl)-ethanamine (**6a**) with 1.4 equiv of trifluoroacetic acid (TFA) in refluxing toluene for 1 h to give 73% yield of **7a**. Notably, the domino reaction sequence, the double-Michael, and the Pictet–Spengler reactions could be achieved in one pot without the need to isolate the double Michael adducts **5a**. The one-pot reaction strategy was achieved via the addition of toluene in the reaction mixtures after the completion of double Michael reaction in CH_2Cl_2, followed by treatment with **6a** and TFA, to provide 77% yield of **7a** with >99% ee. In addition, the one-pot process provided a slightly better yield than that obtained with the isolation of **5a** and the resubmission sequence of the Pictet–Spengler–lactamization reaction (Table 2, entry 1). With the optimized conditions in hand, the one-pot domino-reaction protocol was applied in the reaction with various α,β-unsaturated aldehydes **4**, and the results were promising and general with high yields and stereoselectivities (Table 2). Usually, the reaction was completed in 2 days, but a much longer reaction time was required in the case with **4h** bearing the *ortho*-substituent. The steric bulkiness so close to the conjugate addition center may encumber the reactions (Table 2, entry 8). The structures of the adducts were assigned on the basis of the X-ray analysis of a single crystal of (−)-**7a** (Figure 1).[12] In particular, the absolute configurations of the products were unambiguously determined by the X-ray analysis of (−)-**7c** (Figure 2).[13]

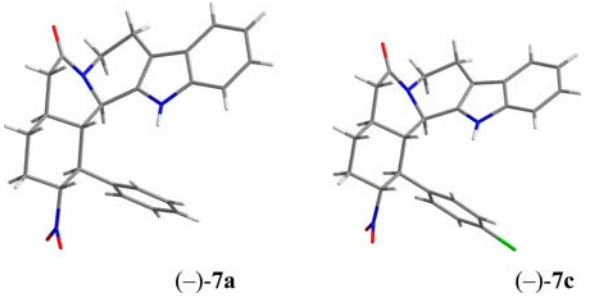


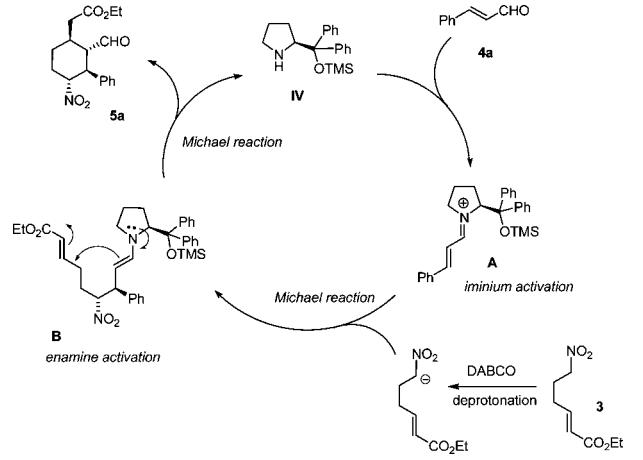
Figure 2. Stereoplots of the X-ray crystal structures of (−)-**7a** and (−)-**7c**: C, gray; O, red; N, blue; Cl, green.

(11) For recent examples, see: (a) Varga, S.; Jakab, G.; Drahos, L.; Holczbauer, T.; Czugler, M.; Soós, T. *Org. Lett.* **2011**, *13*, 5416–5419. (b) Wang, L.-L.; Peng, L.; Bai, J.-F.; Jia, L.-N.; Luo, X.-Y.; Huang, Q.-C.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2011**, *47*, 5593–5595. (c) Ma, A.; Ma, D. *Org. Lett.* **2010**, *12*, 3634–3637. (d) Zhao, G.-L.; Ibrahem, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Córdova, A. *Chem.—Eur. J.* **2008**, *14*, 10007–10011. (e) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863.

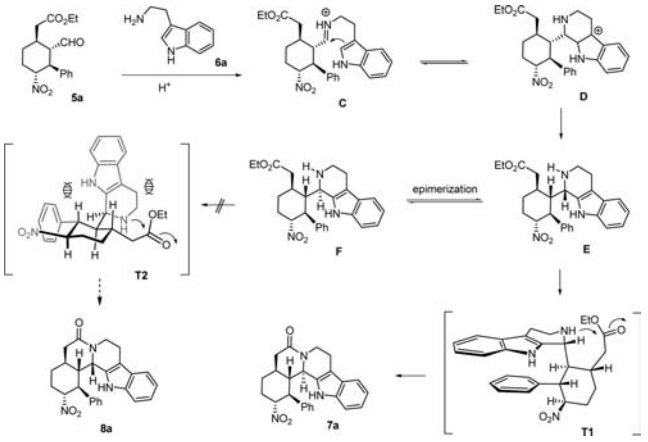
(12) X-ray crystal structure analysis of (−)-**7a**: $C_{25}H_{25}N_3O_3$, weight 415.48 g mol^{-1}, colorless crystal. CCDC-909086 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

(13) X-ray crystal structure analysis of (−)-**7c**: $C_{25}H_{24}ClN_3O_3$, weight 449.92 g mol^{-1}, colorless crystal. CCDC-909087 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Plausible Reaction Mechanism for the Double-Michael Reaction



Scheme 3. Plausible Reaction Mechanism for the Pictet–spengler Reaction



To explain the stereoselectivity of the reactions, plausible mechanisms were proposed as shown in Scheme 2 and Scheme 3. Initially, iminium formation of **4a** with catalyst **IV** provide the iminium intermediate **A**, followed by the nitro-Michael addition of the nitroalkane **3**, triggered by DABCO, from the *re* face under the control of the catalyst to give intermediate **B**, which could then undergo the subsequent Michael reaction to provide **5a** (Scheme 2).

Treatment of adduct **5a** with tryptamines **6a** and TFA afforded the Pictet–Spengler adducts (**E** or/and **F**) (Scheme 3). Since the stereogenic center formed in the Pictet–Spengler reaction is well-known to be subject to epimerization,[14] the high diastereoselectivity of the cascade Pictet–Spengler–lactamization is probably governed by the differential rates of lactamization of intermediates **E** and **F**. As such, the predominate formation of **7a** arose from **E** via the lesser sterically bulky transition state **T1**, while another pathway from **F** toward **8a** was encumbered owing to the significant steric hindrance in transition state **T2**.

In summary, we have achieved an organocatalytic double-Michael reaction and Pictet–Spengler–lactamization of (*E*)-ethyl 6-nitrohex-2-enoate, α,β-unsaturated aldehydes, and 2-(1*H*-indol-3-yl)ethanamine and provided a facile entry to the dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine system with five contiguous stereogenic centers. The mild reaction conditions at ambient temperatures as well as the one-pot operation further manifest the merit of this strategy. The highly enantioselective transformation and the highly functionalized pentacyclic benzindolo-quinolizine products render this reaction sequence as a potential protocol for future synthetic applications. The structures as well as the absolute configurations of the products were unambiguously confirmed by X-ray crystallographic analysis of the appropriate adducts. Further work is underway to elaborate the synthetic applications of this procedure.

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Supporting Information Available. Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compounds (−)-**7a** and (−)-**7c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Van Linn, M. L.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3587. (b) Fang, H.; Wu, X.; Nie, L.; Dai, X.; Chen, J.; Cao, W.; Zhao, G. *Org. Lett.* **2010**, *12*, 5366–5369. (c) Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, *352*, 499–518. (d) Shi, X. X.; Liu, S. L.; Xu, W.; Xu, Y. L. *Tetrahedron: Asymmetry* **2008**, *19*, 435. (e) Han, D. M.; Försterling, F. H.; Deschamps, J. R.; Parrish, D.; Liu, X. X.; Yin, W. Y.; Huang, S. M.; Cook, J. M. *J. Nat. Prod.* **2007**, *70*, 75. (f) Jiang, W. Q.; Sui, Z. H.; Chen, X. *Tetrahedron Lett.* **2002**, *43*, 8941. (g) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 44.

The authors declare no competing financial interest.