Diastereoselective Syntheses of Indoloquinolizidines by a Pictet–Spengler/Lactamization Cascade

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ABSTRACT

Arising from asymmetric organocatalysis

22 examples
up to 90% yield
up to 99% ee
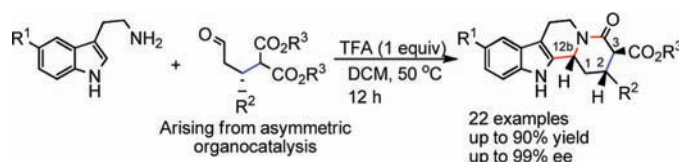
An expedient diastereoselective synthesis of highly functionalized indolo[2,3-α]quinolizidines adopting a *cis* H2/H12b geometry has been realized by a Pictet–Spengler/lactamization cascade sequence. The absolute stereochemistry at C2, C3, and C12b was governed by the originally created chirality of the Michael adduct through organocatalyzed conjugate addition of dialkyl malonates to α,β-unsaturated aldehydes.

The indolo[2,3-α]quinolizidine ring system is of great interest and significance since this structural subunit is found in numerous natural alkaloids. The stereochemical diversity and structural complexity of such natural products have rendered them interesting synthetic targets.[1]

Conventionally, optically pure indoloquinolizidines are prepared from the chiral pool.[2] However, this strategy often requires multistep functional group transformations and laborious protecting group operations. Therefore, more efficient diastereoselective methods to access these compounds would be highly desired. In addition, although numerous asymmetric catalytic syntheses of indoloquino-lizidines have been developed recently,[3,4] relatively few utilized a cascade strategy.[4]

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(1) (a) *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol 50. (b) Szántay, C.; Honty, K. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley: New York, 1994; Vol. 25, pp 161–216. (c) Baxter, E. W.; Mariano, P. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer: New York, 1992; Vol 8, pp 197–319.

(2) For selected examples of quinolizidine syntheses based on starting materials from the chiral pool, see: (a) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79. (b) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827. (c) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541. (d) Amat, M.; Pérez, M.; Managlia, A. T.; Casamitjana, N.; Bosch, J. *Org. Lett.* **2005**, *7*, 3653. (e) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255. (f) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193. (g) Ma, J.; Yin, W. Y.; Zhou, H.; Cook, J. M. *Org. Lett.* **2007**, *9*, 3491.

(3) Examples of quinolizidine syntheses by asymmetric catalysis: (a) Santos, L. S.; Pilli, R. A.; Rawal, V. H. *J. Org. Chem.* **2004**, *69*, 1283. (b) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058. (c) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646. (d) Szawkalo, J.; Czarnocki, S. J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z.; Drabowicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 406. (e) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (f) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745. (g) Jana, C. K.; Studer, A. *Chem.—Eur. J.* **2008**, *14*, 6326. (h) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533. (i) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (j) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267. (k) Jiang, J.; Qing, J.; Gong, L. Z. *Chem.—Eur. J.* **2009**, *15*, 7031.

(4) (a) Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787. (b) Zhang, W.; Franzén, J. *Adv. Synth. Catal.* **2010**, *352*, 499. (c) Wu, X. Y.; Dai, X. Y.; Nie, L. L.; Fang, H. H.; Chen, J.; Ren, Z. J.; Cao, W. G.; Zhao, G. *Chem. Commun.* **2010**, *46*, 2733.

Recently, we and Franzén et al. reported an efficient synthesis of highly functionalized indoloquinolizidines by organocatalyzed[5] enantioselective cascade reactions between α,β-unsaturated aldehydes and active methylene compounds.[6] Good to excellent yields and excellent enantioselectivities have been achieved. The relative stereochemistry of the major isomers was revealed to be a *trans* H2/H12b geometry (Scheme 1).[4] Among the challenges to be addressed in the

Scheme 1. Organocatalyzed Asymmetric Syntheses of Highly Substituted Indoloquinolizidines
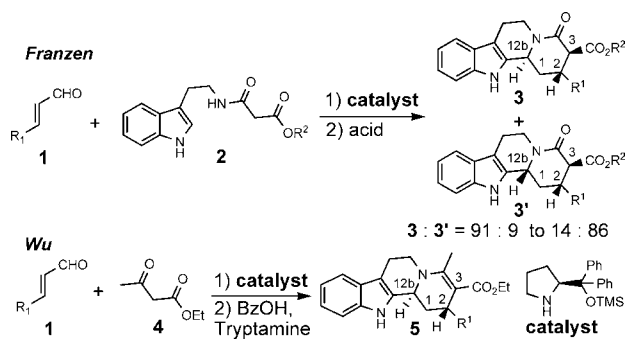
syntheses of natural alkaloids containing indoloquinolizidine motifs is the control of C2 and C12b chirality, which usually prefers the *cis* H2/H12b diastereomer.[1,2] Herein we describe a new development of our work leading to indolo[2,3-α]-quinolizidines with *cis* H2/H12b conformation. This method employs an efficient cascade reaction of two components: tryptamines **6** and conjugate adducts **7**. Aldehydes **7** were obtained from an asymmetric organocatalyzed Michael addition of dialkyl malonates to α,β-unsaturated aldehydes (Figure 1).[6a]

Our proposed cascade is shown in Figure 1. The acid-promoted Pictet−Spengler reaction of tryptamine **6** and aldehyde **7** leads to the amine intermediate **8** as a mixture of diastereomers,[7] which undergoes lactamization to afford multi-tiring compound **3** and/or **9**. Undoubtedly, the chiral-labile stereocenter C3 should adopt the thermodynamically stable *trans*

(5) For selected reviews on organocatalysis, see: (a) *Acc. Chem. Res.* **2004**, *37* (8), special issue on organocatalysis. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2004. (c) *Chem. Rev.* **2007**, *107* (12), special issue on organocatalysis. (d) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (f) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (g) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chem.* **2010**, *2*, 167.

(6) (a) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305. (b) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (c) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928. (d) Rueping, M.; Sugiono, E.; Merino, E. *Chem.−Eur. J.* **2008**, *14*, 6329. (e) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (f) Zu, L. S.; Li, H.; Xie, H.-X.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732.

(7) For examples of catalyzed asymmetric Pictet−Spengler reactions: (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (c) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. (d) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (e) Also see ref 3f and ref 3i.
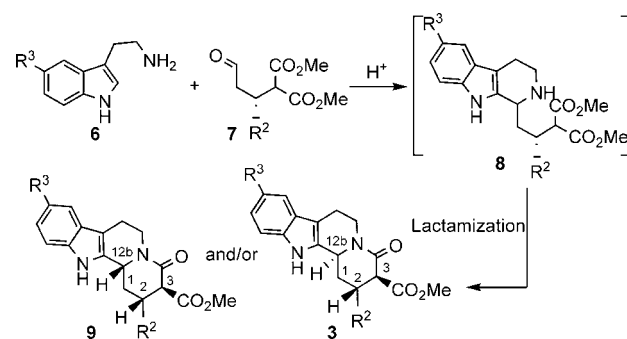
Figure 1. Concept of the Pictet−Spengler/lactamization cascade.

configuration with respect to C2 in the δ-lactam ring.[4a,b] Although numerous examples of substrate control of C12b chirality have been reported,[2f,8] to our knowledge using **7** or similar substrates as the source of chirality has yet to be reported.

To test the feasibility of this cascade, a model reaction between tryptamine **6a** and conjugate adduct **7a** was examined under a broad set of conditions (Table 1). A careful screen of

Table 1. Screen of Reaction Conditions[a]
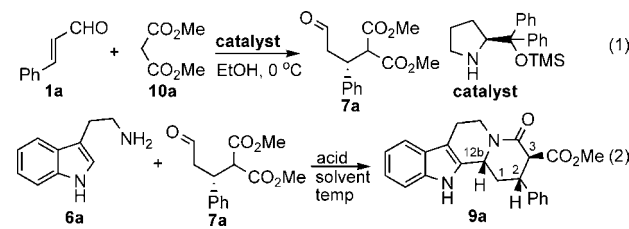
entry	acid	solvent	[7a], mM	yield %[b]	ee %[c]
1	PhCO₂H	toluene	60	23	93
2	AcOH	toluene	60	34	96
3	TFA	toluene	60	53	97
4	4-NO₂-C₆H₄CO₂H	toluene	60	48	95
5	3,5-(NO₂)₂C₆H₃CO₂H	toluene	60	39	95
6	TfOH	toluene	60	37	91
7	TsOH	toluene	60	29	90
8	HCl	toluene	60	33	93
9	TFA	toluene	20	68	97
10	TFA	toluene	10	81	97
11	TFA	DCM	10	90	98
12	TFA	CHCl₃	10	62	98
13	TFA	THF	10	68	96
14	TFA	DMSO	10	-	-
15	TFA	DMF	10	-	-
16	TFA	EtOH	10	-	-
17[d]	TFA	DCM	10	-	-

[a] General conditions of reaction 1: **1a** (1.5 equiv), **10a** (1 equiv), and catalyst (0.1 equiv) in EtOH (0.2 M) at 0 °C for 48 h. General conditions of reaction 2: crude **7a** (1 equiv), **6a** (1.5 equiv), and acid (1 equiv) at 50 °C. [b] Yield referred to isolated pure product. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Reaction run at 20 °C.

acids (entries 1−8) revealed that TFA afforded the product in a moderate yield (entry 3). Although the enantiomeric excess

of the product was somewhat independent of the acid chosen, acids other than TFA led to lower yields. To our delight, the yields were substantially improved by lowering the substrate concentration to 10 mM in toluene (entry 10).[9] A brief screen of solvents revealed that the reaction was quite solvent dependent. DCM proved to be the best (entry 11).

Chloroform and THF provided the product with good yield, albeit inferior to DCM (entries 12 and 13). In more polar solvents, such as DMSO, DMF, and EtOH, no or trace formation of the product was detected (entries 14−16). No product was observed when the temperature was lowered to 20 °C (entry 17).

The *cis* H2/H12b configuration was determined by comparison of the ^{1}H NMR spectrum of **9a** with the previous work of Franzén et al.[4b] To our pleasure, no *trans* diastereoisomer was observed; this was confirmed by HPLC and TLC tests of the product **9a** with a *trans* sample obtained by Franzén's method.

After the optimized reaction conditions were obtained (entry 11, Table 1), the scope of this cascade reaction was next examined. We first investigated the one-pot cascade sequence employing tryptamine **6a** and aldehydes **7b−l** obtained from asymmetric conjugate addition of dimethyl malonate **10a** to the corresponding α,β-unsaturated aldehydes **1b−l**. As shown in Table 2, the cascade reaction proceeded

Table 2. Cascade Reaction of Tryptamine **6a** and Aldehydes **7b−l**[a]
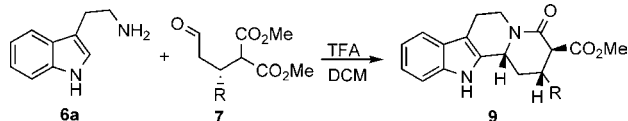
entry	R	7	9	yield %[b]	ee %[c]
1	4-Br-C$_6$H$_4$	**7b**	**9b**	64	97
2	4-F-C$_6$H$_4$	**7c**	**9c**	85	98
3	2,4-(Cl)$_2$-C$_6$H$_3$	**7d**	**9d**	67	98
4	4-Me-C$_6$H$_4$	**7e**	**9e**	73	97
5	2-MeO-C$_6$H$_4$	**7f**	**9f**	85	95
6	4-MeO-C$_6$H$_4$	**7g**	**9g**	72	96
7	2-Br-C$_6$H$_4$CH=CH	**7h**	**9h**	43	98
8	4-F-C$_6$H$_4$CH=CH	**7i**	**9i**	54	92
9	Me	**7j**	**9j**	42	88
10	Et	**7k**	**9k**	41	93
11	*n*-Pr	**7l**	**9l**	41	93

[a] See footnote a in Table 1. [b] Yield referred to isolated pure product. [c] Enantiomeric excess was determined by chiral HPLC analysis.

well for aromatic-substituted aldehydes **7b−g** bearing electron-donating or electron-withdrawing substituents on the aryl

ring, providing the products in good yields and excellent enantioselectivities as single diastereoisomers (entries 1−6). Styrenyl-substituted aldehydes **7h-i** and aliphatic-substituted aldehydes **7j−l** also gave only one diastereomer and excellent enantioselectivities (entries 7−11); however, the yields of products **9h−l** were much lower than those of the aromatic analogues.

To further illustrate the power of this diastereoselective cascade reaction, the substituted tryptamines **6b−c** and conjugate adducts **7m−p** arising from diethyl malonate and dibenzyl malonate were also examined. The results are listed in Table 3. Except in the case of entry 7, all of the substrates

Table 3. Further Expansion of Substrate Scope
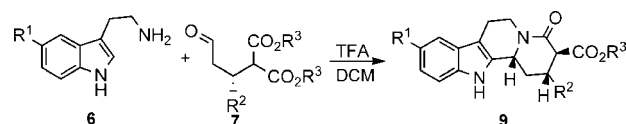
entry	R^1, **6**	R^2, R^3	7	9	yield %	ee %
1	Br, **6b**	C$_6$H$_5$, Me	**7a**	**9m**	86	99
2	Br, **6b**	4-Br-C$_6$H$_4$, Me	**7b**	**9n**	62	96
3	Br, **6b**	4-F-C$_6$H$_4$, Me	**7c**	**9o**	79	99
4	MeO, **6c**	C$_6$H$_5$, Me	**7a**	**9p**	75	98
5	MeO, **6c**	4-F-C$_6$H$_4$, Me	**7c**	**9q**	78	98
6	H, **6a**	C$_6$H$_5$, Et	**7m**	**9r**	52	98
7	Br, **6b**	C$_6$H$_5$, Et	**7m**	**9s**	27	99
8	H, **6a**	4-Br-C$_6$H$_4$, Et	**7n**	**9t**	65	77
9	H, **6a**	2-Br-C$_6$H$_4$CH=CH, Et	**7o**	**9u**	42	87
10	H, **6a**	C$_6$H$_5$, Bn	**7p**	**9v**	52	97

employed afforded the products in moderate to good yields. Conjugate adducts arising from diethyl malonate or dibenzyl malonate generally led to lower yields as compared to those from dimethyl malonate (entries 1−5 vs entries 6−10).

The collective results shown above (Tables 2 and 3) indicated that this cascade sequence could tolerate a broad spectrum of substrates. On the basis of the fact that *cis* H2/H12b relative configuration and highly substituted indolo[2,3-α]quinolizidine diastereoisomer were obtained, this method should be useful in both library syntheses and total syntheses alike.

The relative configuration of the cyclized product **9h** was unambiguously determined to be 2*S*, 3*S*, and 12b*R* by single-crystal X-ray diffraction analysis (Figure 2). The stereochemistry at C2 of **9h** originated from **7h** by asymmetric conjugate addition of dimethyl malonate to unsaturated aldehyde **1h** catalyzed by (*S*)-prolinol TMS ether. The selective formation of C3 and C12b stereochemistry was induced by C2 chirality during the lactamization procedure.

The excellent diastereoselectivities in all of the cascade reactions are notable and deserve further comment.[10] It is well documented that the stereogenic center formed in the

(8) For selected examples of substrate-controlled selective formation of quinolizidines: (a) Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661. (b) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357. (c) Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J. *Eur. J. Org. Chem.* **2005**, 4179. (d) Allin, S. M.; Duffy, L. J.; Page, P. C. B.; McKee, V.; Edgar, M.; McKenzie, M. J.; Amat, M.; Bassas, O.; Santos, M. M. M.; Bosch, J. *Tetrahedron Lett.* **2006**, *47*, 5713. (e) Amat, M.; Santos, M. M. M.; Gómez, A. M.; Jokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907.

(9) For examples of asymmetric Pictect−Spengler cyclization in low substrate concentration, see: ref 3e and ref 3i.
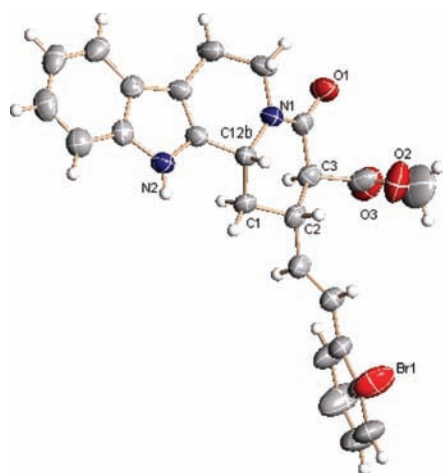
Figure 2. X-ray structure of **9h**.

Pictet−Spengler reaction is subject to epimerization.[11] No epimerization was observed when pure **9a** or the C12 epimer of **9a** was treated with TFA at 50 °C in DCM.[12] It is plausible that the diastereoselectivity of the overall cascade reaction is determined by the differential rates of lactamization of intermediate **8a** and **8a′** (Figure 3). The exclusive formation of **9a** was reasonable since far less steric interaction presents in **TS1** with all the substituents around the newly formed lactam ring adopting equatorial placement. This result is in accordance with the observed product structure. **TS2** and **TS3** are disfavored due to the presence of significant steric interaction.

In summary, we have developed an operationally simple diastereoselective cascade sequence for the preparation of

Figure 3. Proposed transition states in lactamization.

indolo[2,3-α]quinolizidines. The highly functionalized products were obtained as single diastereomers from a broad spectrum of readily available reagents in moderate to good yields and good to excellent enantioselectivities. The H2/H12b relative configuration of the products was determined to be *cis*, which is commonly adopted by a number of natural alkaloids. Further investigation to extend the applicability of this reaction to a broader range of substrates and apply this method in total syntheses of natural alkaloids is currently underway in our laboratory.

Supporting Information Available: General experimental conditions, NMR spectra, and HPLC analysis of the products; CIF of **9h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The relative configuration of **9g** and **9r** was also confirmed by comparison of ^{1}H NMR spectra with known compounds reported in ref 4b. The stereochemistry of other products was assigned by analogy.

(11) (a) 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. (b) Jiang, W. Q.; Sui, Z. H.; Chen., X. *Tetrahedron Lett.* **2002**, *43*, 8941. (c) 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. (d) Shi, X. X.; Liu, S. L.; Xu, W.; Xu, Y. L. *Tetrahedron: Asymmetry* **2008**, *19*, 435. (e) Van Linn, M. L.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3587.

(12) It is reported that harsh conditions (refluxing in TFA) were required to epimerize C12b chirality of **9a**: (a) Lounasmaa, M.; Berner, M.; Brunner, M.; Suomalainen, H.; Tolvanen, A. *Tetrahedron* **1998*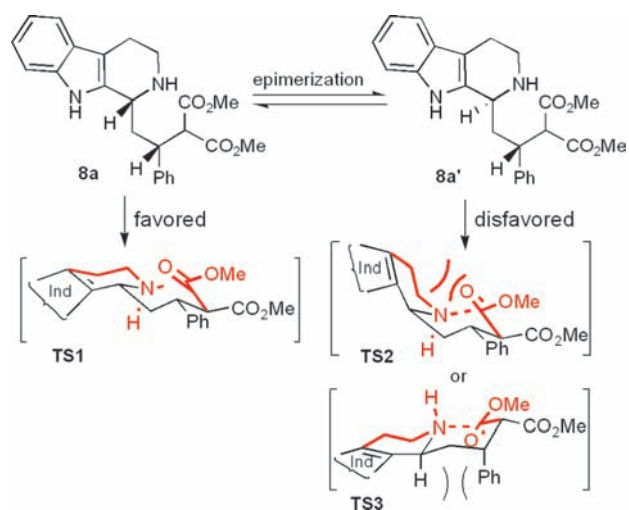*, *54*, 10205. (b) Also see ref 4b.