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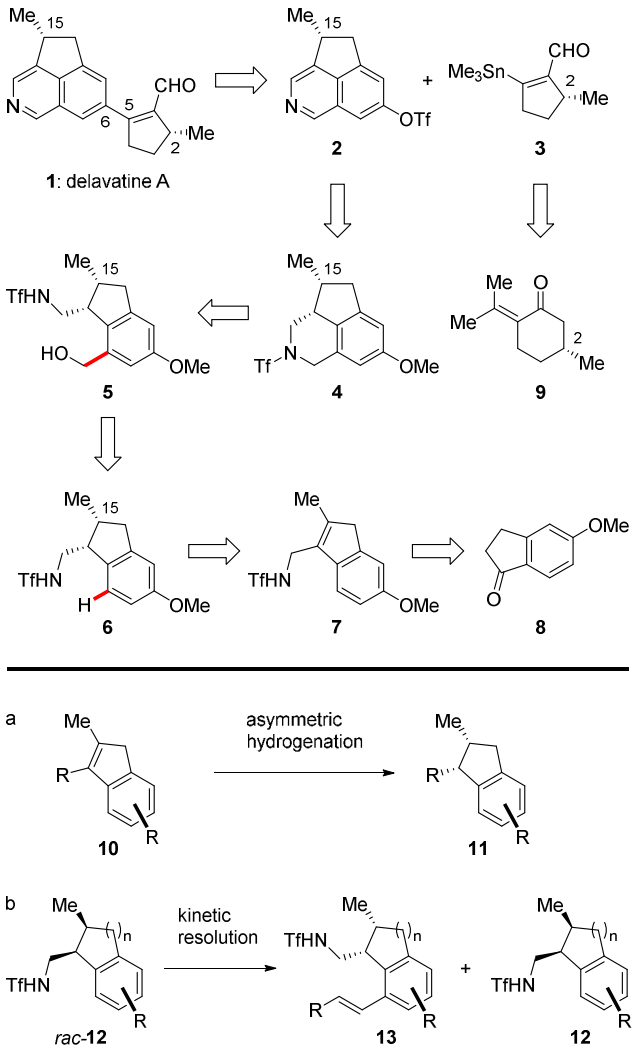
ABSTRACT: Delavatine A (**1**) is a structurally unusual isoquinoline alkaloid isolated from *Incarvillea delavayi*. The first and gram-scale total synthesis of **1** was accomplished in 13 steps (the longest linear sequence) from commercially available starting materials. We exploited an isoquinoline construction strategy and developed two reactions, namely Rh-catalyzed asymmetric hydrogenation of indene-type tetrasubstituted olefins and kinetic resolution of β-alkyl phenylethylamine derivatives through Pd-catalyzed triflamide-directed C−H olefination. The substrate scope of the first reaction covered unfunctionalized olefins and those containing polar functionalities such as sulfonamides. The kinetic resolution provided a collection of enantioenriched indane and tetralin-based triflamides, including those bearing quaternary chiral centers. The selectivity factor (*s*) exceeded 100 for a number of substrates. These reactions enabled two different yet related approaches to a key intermediate **28** in excellent enantiopurity. In the synthesis, the triflamide served as not only an effective directing group for C−H bond activation but also a versatile functional group for further elaborations. The relative and absolute configurations of delavatine A were unambiguously assigned by the syntheses of the natural product and its three stereoisomers. Their cytotoxicity against a series of cancer cell lines were evaluated.

Introduction

Plant-derived natural products are an important source of therapeutic agents.[1,2] *Incarvillea delavayi* is a mountain flowering plant native to Southwest China and has long been used in Chinese herbal medicine. Recently, we discovered a number of structurally intriguing and biologically active compounds from this species.[3] Among them, delavatine A (**1**, Scheme 1) possessing an unusual cyclopenta[*de*]isoquinoline core with a cyclopentenyl substituent at C6 displays promising anticancer properties.[4] Although its structural connectivity was established by spectroscopic studies, the stereochemical configuration of **1** remained uncertain.[4] Herein, we report the first and asymmetric total synthesis of **1**, which assigns its configuration and provides a sufficient quantity of materials for further biological studies. The methodological development for the synthesis is described as well.

Scheme 1. A Retrosynthetic Analysis of Delavatine A and Two Key Reactions in the Synthesis Plan.



We abandoned the conventional strategy of sequential functionalization of a commercially available isoquinoline derivative, considering the regio- and stereo-selectivity issues. Instead, an isoquinoline construction strategy was envisioned, which was conceptually related to the arene construction strategies exploited in our recent syntheses of daphenylline, rubriflordilactones A and B, pseudopteroxazole, ileabethoxazole, clostrubin, xiamycin A, oridamycins A and B, tubingensin A, aflavazole, deschloro 12-*epi*-fischerindole W nitrile, and mycoleptodiscin A.[5] A retrosynthetic analysis was undertaken on the basis of this strategy (Scheme 1). The initial disconnection at the C5−C6 bond led to aryl triflate **2** and alkenyl stannane **3**. Assembling the isoquinoline core of **2** may rely on a sequence of Mitsunobu annulation and oxidative aromatization, which could be viewed as a counterpart of the electrocyclization-aromatization process frequently used by our group.[5a–i] Tetrahydroisoquinoline **4** was

considered as a suitable intermediate in this sequence, which was traced back to benzylic alcohol **5** as an immediate precursor. Yu and coworkers demonstrated that triflamide could effectively direct Pd(II)-catalyzed C−H functionalization,[6] which inspired us to simplify **5** to compound **6**. A C−H olefination reaction[6a,7] would be optimal for introducing the new C−C bond in this case, compared with other indirect approaches such as C−H halogenation. Asymmetric hydrogenation of tetrasubstituted olefin **7** would solve the stereochemical problem at C15. An alternative route from **7** to enantioenriched **5** may require the development of kinetic resolution of racemic **6** through C−H olefination. Compound **7** could be prepared from a commercially available indanone **8**. The stannane segment **3** was expected to arise from (+)-pulegone (**9**) through Favorskii ring contraction and further elaborations; the C2 stereogenic center was inherited from the chiral pool. Notably, we could also synthesize the three stereoisomers of **1** by using the enantiomerically opposite chiral ligands and chiral pool, which would ultimately assign the configuration of the natural product.

Our synthesis plan relied on two key reactions, namely asymmetric hydrogenation of tetrasubstituted olefins (the transformation from **10** to **11**, Scheme 1) and kinetic resolution through C−H olefination (the process from *rac*-**12** to **13** and enantioenriched **12**, Scheme 1). Tetrasubstituted olefins, particularly unfunctionalized ones, have long been challenging substrates for asymmetric hydrogenation.[8] The groups of Buchwald and Pfaltz made breakthroughs in this area, respectively.[9] The former developed a chiral zirconocene catalyst,[9a] and the latter exploited the catalytic system of Ir and chiral phosphine-oxazoline ligands, for highly enantioselective hydrogenation of unfunctionalized tetrasubstituted olefins.[9b] Despite of numerous chiral ligands and catalytic systems available, the progress in this particular area has been rather slow and mostly limited to Ir catalysis.[10,11] Rh catalysis attracted considerable attention in asymmetric hydrogenation of functionalized tetrasubstituted olefins, such as dehydroamino acid derivatives.[8a] C2-symmetric DuPhos and BPE[12] and non-C2-symmetric Josiphos[13] ligands performed well in these transformations. However, the Rh catalytic systems did not have an impressive record in asymmetric hydrogenation of unfunctionalized olefins,[14] until Mashima et al. reported excellent results on styrene-type trisubstituted olefin substrates in 2016.[15] Recently, Tang and

coworkers developed a series of powerful C2-symmetric bisphosphane ligands for asymmetric catalysis.[16] The discovery inspired us to investigate the Rh-catalyzed enantioselective hydrogenation of unfunctionalized tetrasubstituted olefins, which was unexplored to our knowledge.

The recent development of C−H functionalization reactions brought a tremendous opportunity for natural product synthesis.[17–21] On the basis of the remarkable versatility of Pd catalysis, the asymmetric C−H functionalization promoted by Pd complexes bearing chiral ligands provided a strategically new avenue of solving the connectivity and selectivity problems in complex molecule synthesis.[22,23] In 2008, Yu and coworkers developed Pd(II)-catalyzed enantioselective desymmetrizing C−H functionalization using readily available monoprotected amino acids (MPAA) as chiral ligands,[24] which represented a significant breakthrough in this field. A stream of asymmetric C−H functionalization reactions were further developed on the basis of this catalytic system, most of which involved desymmetrization of prochiral substrates.[25–28] Recently, Yu and others took an important step toward the methylene C(sp^3)−H functionalization by varying the chiral ligands.[29–31] Meanwhile, kinetic resolution through Pd(II)-catalyzed C−H functionalization emerged as an interesting synthetic tool.[32] Yu and colleagues reported the kinetic resolution of α-alkyl benzylamine derivatives through sulfonamide-directed C−H iodination[32a] and arylation with boronic acids[32c], respectively. However, β-alkyl phenylethylamine derivatives bearing a fused bicyclic scaffold (e.g. *rac*-**12**) have not been studied for kinetic resolution through C−H olefination to our knowledge. The resolution would enable an expedient access to both enantiomers of isoquinoline segment **2**. The enantioenriched cinnamate ester products (e.g. **13**) may find further use in the synthesis of pharmaceutically interesting compounds, such as the dopamine receptor D_1 ligands, the α_2 adrenergic receptor and 5-HT_{1A} receptor ligands, and the poly(ADP-ribose) polymerase (PARP) inhibitors.[33]

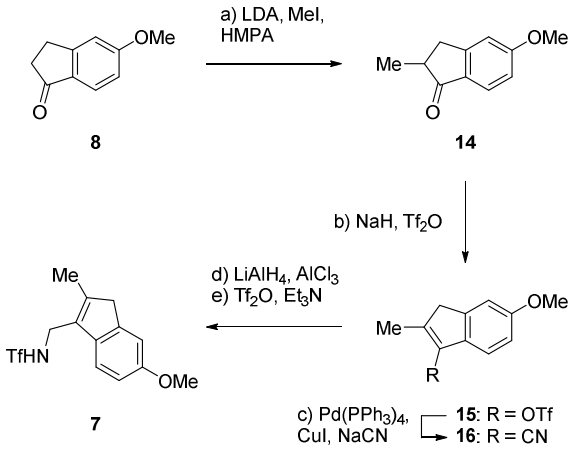
Results and discussion.

Preparation of tetrasubstituted olefin 7.

The synthesis commenced with the preparation of tetrasubstituted olefin **7** (Scheme 2). Treatment of indanone **8** with LDA and MeI in the presence of HMPA afforded *α*-methyl ketone **14** in 79% yield,

which was converted to triflate **15** in 92% yield upon exposure to NaH and Tf_2O. A variety of conditions for homologation of **15** was examined. Pd-catalyzed methoxycarbonylation gave a non-conjugate ester, presumably through a sequence of γ-deprotonation and α-protonation under basic conditions, and Stille−Migita coupling between this sterically demanding triflate and Bu_3SnCH_2OH proved to be inefficient. Under Anderson's cyanation conditions [$Pd(PPh_3)_4$, CuI, NaCN],[34] α,β-unsaturated nitrile **16** was obtained in 92% yield; C═C bond migration was not observed in this case, presumably because of the weak acidity of the γ-proton. 1,2-Reduction with AlH_3 generated *in situ* from $LiAlH_4$ and $AlCl_3$ followed by triflating the resultant amine with Tf_2O and Et_3N[5k] furnished triflamide **7** with good overall efficiency.

Scheme 2. Preparation of Tetrasubstituted Olefin 7[a]



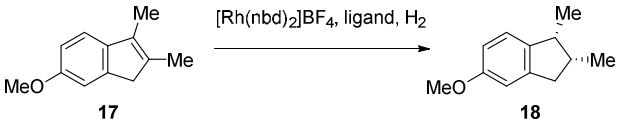
[a] Reagents and conditions: a) LDA (1.0 equiv), MeI (1.1 equiv), HMPA (2.0 equiv), THF, 22 °C, 10 h, 79%; b) NaH (1.8 equiv), Tf_2O (1.5 equiv), Et_2O, 0 °C, 30 min, 92%; c) $Pd(PPh_3)_4$ (5 mol%), CuI (11 mol%), NaCN (1.3 equiv), MeCN, 90 °C, 2 h, 92%; d) $LiAlH_4$ (1.5 equiv), $AlCl_3$ (1.5 equiv), Et_2O, 22 °C, 2 h; e) Tf_2O (0.96 equiv), Et_3N (1.2 equiv), CH_2Cl_2, −80 °C, 30 min, 85% (2 steps).

Rh-catalyzed asymmetric hydrogenation of indene-type tetrasubstituted olefin.

A series of chiral bisphosphane ligands were examined for the Rh-catalyzed hydrogenation reaction (Table 1). We used unfunctionalized tetrasubstituted olefin **17** as a testing substrate, which shared an indene core structure with intermediate **7** in the delavatine A synthesis. [Rh(bisphosphane)]BF_4 complexes were generated in situ from [$Rh(nbd)_2$]BF_4 and the corresponding ligands, and the hydrogenation reactions were performed under H_2 at a pressure of 60 bar at 60 °C. Under these

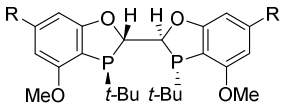
conditions, (*R*)-BINAP gave racemic **18** despite of an excellent yield (entry 1). Me-DuPhos and Me-BPE, two powerful ligands for Rh-catalyzed asymmetric hydrogenation of functionalized tetrasubstituted olefins,[12a–c,e] exhibited poor reactivity and selectivity with substrate **17** (entries 2 and 3). Josiphos-family ligands performed well in asymmetric hydrogenation of functionalized tetrasubstituted olefins as well;[13] however, (*R*,*S*)-PPF-PCy_2 [(*R*,*S*)-JOSIPHOS][13a,b] led to an unsatisfactory result in this case (entry 4). To our delight, a C2-symmetric ligand MeO-BIBOP (**19**) with a deep and well-defined chiral pocket, which was developed by Tang and colleagues for asymmetric hydrogenation of *N*-acyl enamides,[16a–c] significantly elevated the level of the enantioselectivity and yield of **18** (entry 5). A slightly modified ligand, Anthryl-MeO-BIBOP (**20**), gave the optimal ee value (94%, entry 6).

Table 1. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation[a]



17 **18**

entry	ligand	yield	ee
1	(*R*)-BINAP	99%	0%
2	(*S*,*S*)-Me-DuPhos	21%	48%
3	(*S*,*S*)-Me-BPE	14%	20%
4	(*R*,*S*)-PPF-PCy_2	40%	–27%
5	**19**	99%	92%
6	**20**	99%	94%



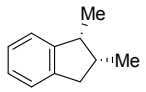
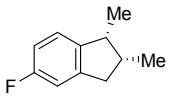
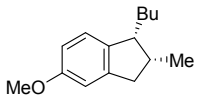
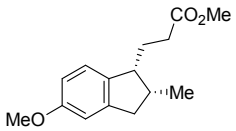
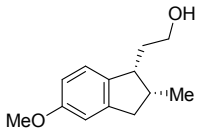
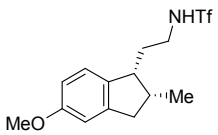
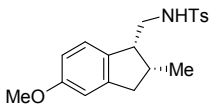
19: R = H
20: R = 9-anthryl

[a] Reactions were carried out in CH_2Cl_2 (0.05 M) under H_2 (60 bar) in the presence of 10 mol% of $[Rh(nbd)_2]BF_4$ and 12 mol% of the indicated ligand at 60 °C for 96 h. The enantiomeric excesses were determined by SFC with a chiral stationary phase.

In Table 2 was summarized the results of the asymmetric hydrogenation of a number of tetrasubstituted olefins structurally related to indene **7**. Compounds **21**–**27** were obtained in good to excellent enantiopurity; the enantiomeric excesses of **21**, **24**, and **26** reached 95%, respectively. The

isolation yields of **21** and **22** were lower than those of the others because of their volatility. Electronic property of the arenes did not influence the enantioselectivity (entries 1–3). Polar functional groups such as ester, alcohol, and sulfonamide did not interfere with the catalytic activity and asymmetric induction (entries 4–7), which indicated flexible synthetic use of this transformation. The absolute configuration of **26** was determined by X-ray crystallographic analysis (Figure 1, sulfur as a heavy atom).

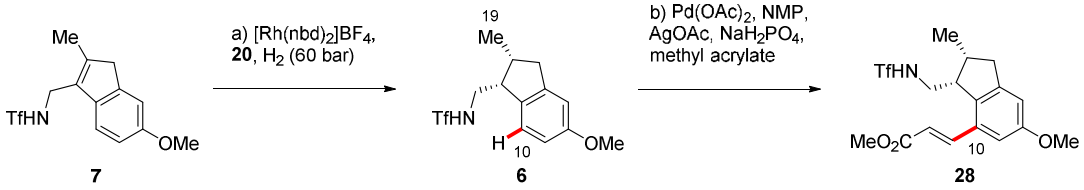
Table 2. Asymmetric Hydrogenation of Indene-Type Tetrasubstituted Olefins[a]

entry	products	yield	ee
1	 **21**	76%	95%
2	 **22**	81%	93%
3	 **23**	99%	93%
4[b]	 **24**	99%	95%
5[b]	 **25**	99%	85%
6[b]	 **26**	99%	95%
7[b]	 **27**	99%	90%

[a] Reactions were carried out in CH_2Cl_2 (0.05 M) under H_2 (60 bar) in the presence of 10 mol% of $[Rh(nbd)_2]BF_4$ and 12 mol% of **20** at 60 °C for 96 h. The enantiomeric excesses were determined by GC/SFC with a chiral stationary phase. [b] 5.0 mol% of $[Rh(nbd)_2]BF_4$ and 6.0 mol% of **20**.

We turned our attention back to the delavatine A synthesis (Scheme 3). A gram-scale asymmetric hydrogenation of **7** using 1.0 mol% of $[Rh(nbd)_2]BF_4$ and 1.3 mol% of Anthryl-MeO-BIBOP (**20**) delivered compound **6** in 98% yield and 91% ee. This sample was recrystallized from EtOAc/hexanes (1:5) to reach an excellent level of enantiopurity (> 99% ee, 82% yield). The absolute configuration of **6** was verified by X-ray crystallographic analysis (Figure 1, sulfur as a heavy atom).

Scheme 3. Conversion of Tetrasubstituted Olefin 7 into Enantioenriched 28[a]



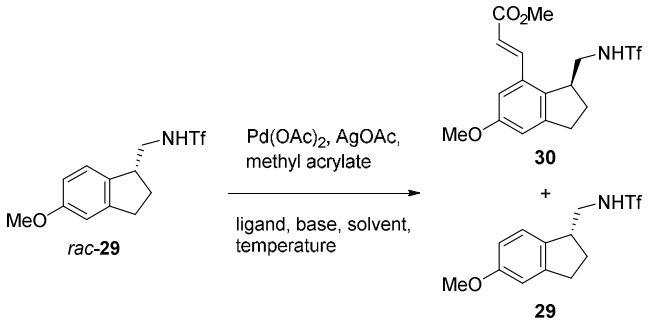
[a] Reagents and conditions: a) $[Rh(nbd)_2]BF_4$ (1.0 mol%), Anthryl-MeO-BIBOP (**20**, 1.3 mol%), H_2 (60 bar), 60 °C, 96 h, 98%, 91% ee; b) $Pd(OAc)_2$ (20 mol%), AgOAc (2.5 equiv), methyl acrylate (5.0 equiv), NaH_2PO_4 (1.0 equiv), NMP/toluene (1:30), 100 °C, 12 h, 64% (56% on a decagram scale).

Pd-catalyzed C−H olefination of enantioenriched triflamide 6.

With enantioenriched triflamide **6** in hand, we investigated the C−H functionalization at C10 (Scheme 3). Two potential challenges were posed by this substrate. First, the indane scaffold may increase the ring strain of the presumed palladacycle intermediate. Second, undesired C19−H bond activation concerned us because of the proximity of the C19 methyl and the triflamide.[35] To our delight, under Yu′s standard conditions[6a] [methyl acrylate, $Pd(OAc)_2$, AgOAc, NaH_2PO_4, DMF] but with toluene instead of 1,2-dichloroethane as a solvent, the desired product **28** was obtained in 49% yield. Interestingly, Jia′s protocol[7] withdrawing DMF as an additive resulted in a poor yield (ca. 10–15%) in this particular case. NMP was found to be a superior additive to DMF, which improved the efficiency of this transformation to a synthetically useful level (64% yield of **28**, along with 30% of recovered **6**).[6b] The reaction was reliably performed on a decagram scale.

Kinetic resolution of β-alkyl phenylethylamine derivatives through Pd-catalyzed triflamide-directed C−H olefination.

Table 3. Optimization of Conditions of the Kinetic Resolution[a]



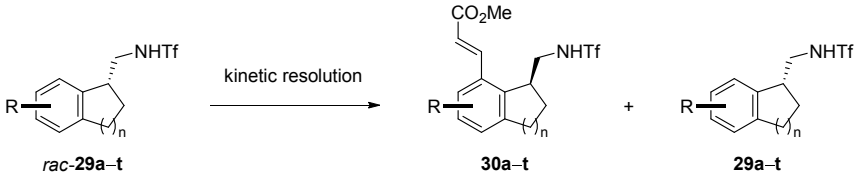
entry	conditions	yield of **30**	ee of **30**	yield of **29**	ee of **29**
1	Boc-L-Val-OH, NaH_2PO_4, toluene/NMP (3:1), 100 °C	52%	40%	43%	52%
2	Boc-L-Val-OH, NaH_2PO_4, *t*-AmOH/NMP (3:1), 60 °C	38%	85%	58%	50%
3	Boc-L-Val-OH, K_2CO_3, *t*-AmOH/NMP (3:1), 60 °C	38%	96%	56%	57%
4	Boc-L-*t*-Leu-OH, K_2CO_3, *t*-AmOH/NMP (3:1), 60 °C	41%	98%	54%	76%
5[b]	Boc-L-*t*-Leu-OH, K_2CO_3, *t*-AmOH/NMP (3:1), 60 °C	46%	97%	51%	83%

[a] Reactions were carried out in the indicated solvent (0.075 M) at the indicated temperature for 12 h, in the presence of 20 mol% of $Pd(OAc)_2$, 40 mol% of the indicated MPAA ligand, 2.0 equiv. of methyl acrylate, 2.5 equiv. of AgOAc, and 2.5 equiv. of the indicated inorganic base. The enantiomeric excesses were determined by HPLC with a chiral stationary phase. [b] 10 mol% of $Pd(OAc)_2$ and 20 mol% of the indicated MPAA ligand, 48 h.

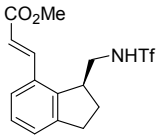
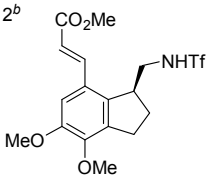
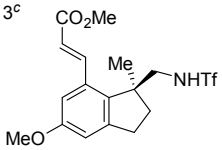
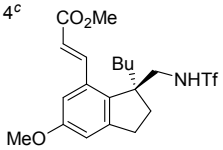
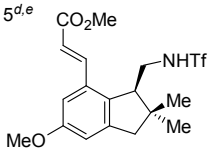
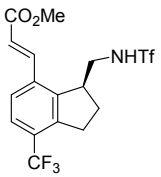
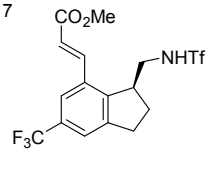
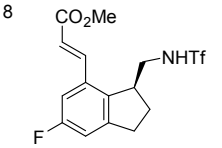
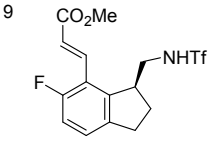
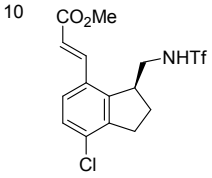
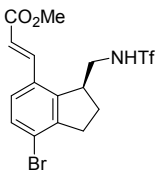
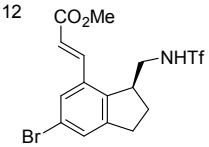
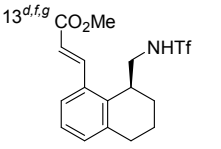
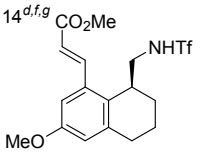
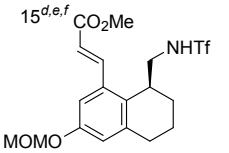
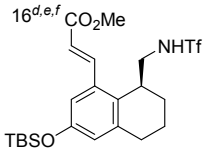
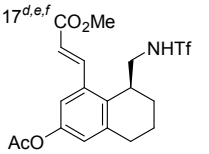
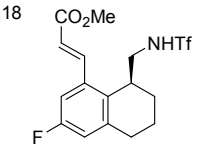
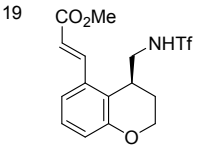
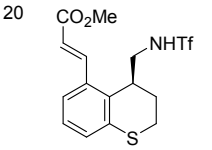
Encouraged by the results of the triflamide-directed C−H olefination, we turned our attention to the kinetic resolution of racemic **6**-type compounds through Pd-catalyzed C−H olefination, which would address the enantioselectivity and connectivity issues in a single step. Readily available *rac*-**29** was employed as a model substrate for studying the kinetic resolution, and the tested conditions was summarized in Table 3. To our delight, the addition of *N*-Boc-L-valine (Boc-L-Val-OH) as a chiral ligand under our initial C−H olefination conditions resulted in a resolution of *rac*-**29**, leading to **30** in 40% ee and 52% yield along with **29** in 52% ee and 43% yield (entry 1). The ee value of **30** significantly increased to 85% when the reaction temperature decreased to 60 °C, although its yield dropped to 38% due to a slow reaction rate (entry 2). K_2CO_3 was found to be a superior base to NaH_2PO_4 for the kinetic resolution; **30** and **29** were obtained in 96% and 57% ee, respectively (entry 3). The more bulky ligand *N*-Boc-L-*tert*-leucine (Boc-L-*t*-Leu-OH) further enhanced the enantiopurity of the two products (entry 4,

98% ee for **30** and 76% ee for **29**). The reaction proceeded smoothly with reduced $Pd(OAc)_2$ loading (10 mol%) upon prolonged reaction times (48 h) to afford **30** in 97% ee and 46% yield and **29** in 83% ee and 51% yield (entry 5); the selectivity factor[36] (*s*) was 171.6 (C = 46%) in this case. The absolute configurations of the compounds obtained from the kinetic resolution were determined by X-ray crystallographic analysis of **30** (Figure 1, sulfur as a heavy atom).

Table 4. Kinetic Resolution of β-Alkyl Phenylethylamine Derivatives through Pd-Catalyzed Triflamide-Directed C−H Olefination[a]



rac-**29a**–**t** **30a**–**t** **29a**–**t**

entry					
1	2[b]	3[c]	4[c]	5[d,e]
				
30a: 44% yield, 97% ee **29a**: 48% yield, 76% ee C = 44%, *s* = 151.2	**30b**: 46% yield, 93% ee **29b**: 51% yield, 82% ee C = 47%, *s* = 70.4	**30c**: 46% yield, 93% ee **29c**: 45% yield, 77% ee C = 45%, *s* = 64.3	**30d**: 47% yield, 93% ee **29d**: 46% yield, 73% ee C = 44%, *s* = 60.4	**30e**: 44% yield, 90% ee **29e**: 47% yield, 78% ee C = 46%, *s* = 45.0
6	7	8	9	10
				
30f: 38% yield, 96% ee **29f**: 58% yield, 66% ee C = 41%, *s* = 97.5	**30g**: 46% yield, 98% ee **29g**: 39% yield, 77% ee C = 44%, *s* = 231.9	**30h**: 45% yield, 97% ee **29h**: 46% yield, 79% ee C = 45%, *s* = 159.1	**30i**: 44% yield, 95% ee **29i**: 45% yield, 77% ee C = 45%, *s* = 91.1	**30j**: 50% yield, 95% ee **29j**: 43% yield, 96% ee C = 50%, *s* = 153.9
11	12	13[d,f,g]	14[d,f,g]	15[d,e,f]
				
30k: 45% yield, 94% ee **29k**: 41% yield, 93% ee C = 50%, *s* = 110.5	**30l**: 40% yield, 97% ee **29l**: 43% yield, 63% ee C = 39%, *s* = 125.8	**30m**: 43% yield, 90% ee **29m**: 46% yield, 90% ee C = 50%, *s* = 58.4	**30n**: 38% yield, 90% ee **29n**: 48% yield, 97% ee C = 52%, *s* = 79.6	**30o**: 40% yield, 92% ee **29o**: 47% yield, 94% ee C = 50%, *s* = 85.2
16[d,e,f]	17[d,e,f]	18	19	20
				
30p: 37% yield, 90% ee **29p**: 45% yield, 91% ee C = 50%, *s* = 60.2	**30q**: 41% yield, 95% ee **29q**: 52% yield, 80% ee C = 46%, *s* = 96.0	**30r**: 44% yield, 90% ee **29r**: 51% yield, 88% ee C = 49%, *s* = 55.3	**30s**: 42% yield, 92% ee **29s**: 41% yield, 94% ee C = 50%, *s* = 85.2	**30t**: 42% yield, 95% ee **29t**: 43% yield, 83% ee C = 47%, *s* = 101.7

[a] Reactions were carried out in *t*-AmOH/NMP (3:1, 0.075 M), in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% of Boc-L-*t*-Leu-OH, 2.0 equiv. of methyl acrylate, 2.5 equiv. of AgOAc, and 2.5 equiv. of

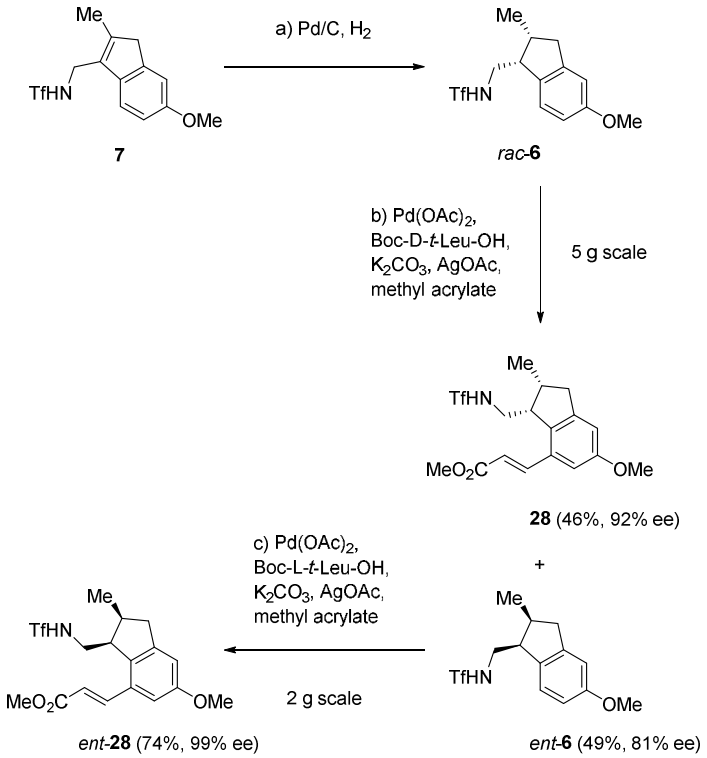
K_2CO_3, at 60 °C for 48 h. The enantiomeric excesses were determined by HPLC with a chiral stationary phase. [b] 24 h. [c] 36 h. [d] 20 mol% of $Pd(OAc)_2$ and 40 mol% of Boc-L-*t*-Leu-OH. [e] 12 h. [f] 3.0 equiv. of K_2CO_3. [g] 11 h.

We further investigated the substrate scope of the kinetic resolution. As shown in Table 4, the selectivity factor[36] (*s*) exceeded 100 for a number of substrates. Enantioenriched compounds **29a**–**t** and **30a**–**t** were obtained through the resolution. In particular, the enantiomeric excesses of **30g** and **30h** reached 98% and 97%, respectively. The reaction performed well regardless of the electronic property of the aromatic substrates, leading to good to excellent yields and enantiomeric excesses of the resolved products (entries 1–12). The adjacent quaternary carbon had little influence upon this process (entries 3–5). Notably, **30c** and **30d** bearing quaternary chiral centers were obtained in excellent enantiopurity (entries 3 and 4). The enantioenriched products containing pharmaceutically interesting CF_3, Cl, and F substituents were of potential interest as well (entries 6–10). The aryl bromides were tolerated under the C−H olefination conditions, and direct Heck reactions with methyl acrylate were not observed (entries 11 and 12). This provided an opportunity for orthogonal functionalization of the optically active multisubstituted arenes. The kinetic resolution of tetralin-based substrates proceeded with good efficiency and stereoselectivity as well (entries 13–18). Acid-labile MOM and TBS protecting groups (entries 15 and 16) and nucleophile-sensitive phenol acetate functionality (entry 17) survived under the reaction conditions. Enantioenriched heterocyclic compounds were obtained through the kinetic resolution (entries 19 and 20), and the sulfide did not interfere with the Pd catalysis (entry 20).

The kinetic resolution enabled an expedient and scalable approach to both enantiomers of **28** (Scheme 4), which would benefit the synthesis-based stereochemical assignment of delavatine A. *rac*-**6** was readily prepared from **7** by hydrogenation (Pd/C, H_2). With Boc-D-*t*-Leu-OH as a ligand, the resolution proceeded smoothly on five-gram scale to give **28** (46% yield, 92% ee) possessing the desired absolute configuration for the synthesis of delavatine A, along with *ent*-**7** (49% yield, 81% ee). The absolute configuration of **28** was confirmed by X-ray crystallographic analysis (Figure 1, sulfur as a heavy atom). *ent*-**7** so obtained was then subjected to the kinetic resolution conditions with the enantiomerically

opposite ligand Boc-L-*t*-Leu-OH to afford *ent*-**28** in 74% yield and 99% ee; this reaction was carried out on two-gram scale.

Scheme 4. An Expedient and Scalable Access to both enantiomers of 28[a]



[a] Reagents and conditions: a) Pd/C (10 mol%), H_2 (1 atm), MeOH, 22 °C, 24 h, 97%; b) methyl acrylate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), Boc-D-*t*-Leu-OH, (20 mol%), AgOAc (2.5 equiv), K_2CO_3 (2.5 equiv), *t*-AmOH/NMP (3:1), 60 °C, 36 h, **28**: 46%, 92% ee; *ent*-**6**: 49%, 81% ee; c) methyl acrylate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), Boc-L-*t*-Leu-OH (20 mol%), AgOAc (2.5 equiv), K_2CO_3 (2.5 equiv), *t*-AmOH/NMP (3:1), 60 °C, 36 h, 74%, 99% ee.

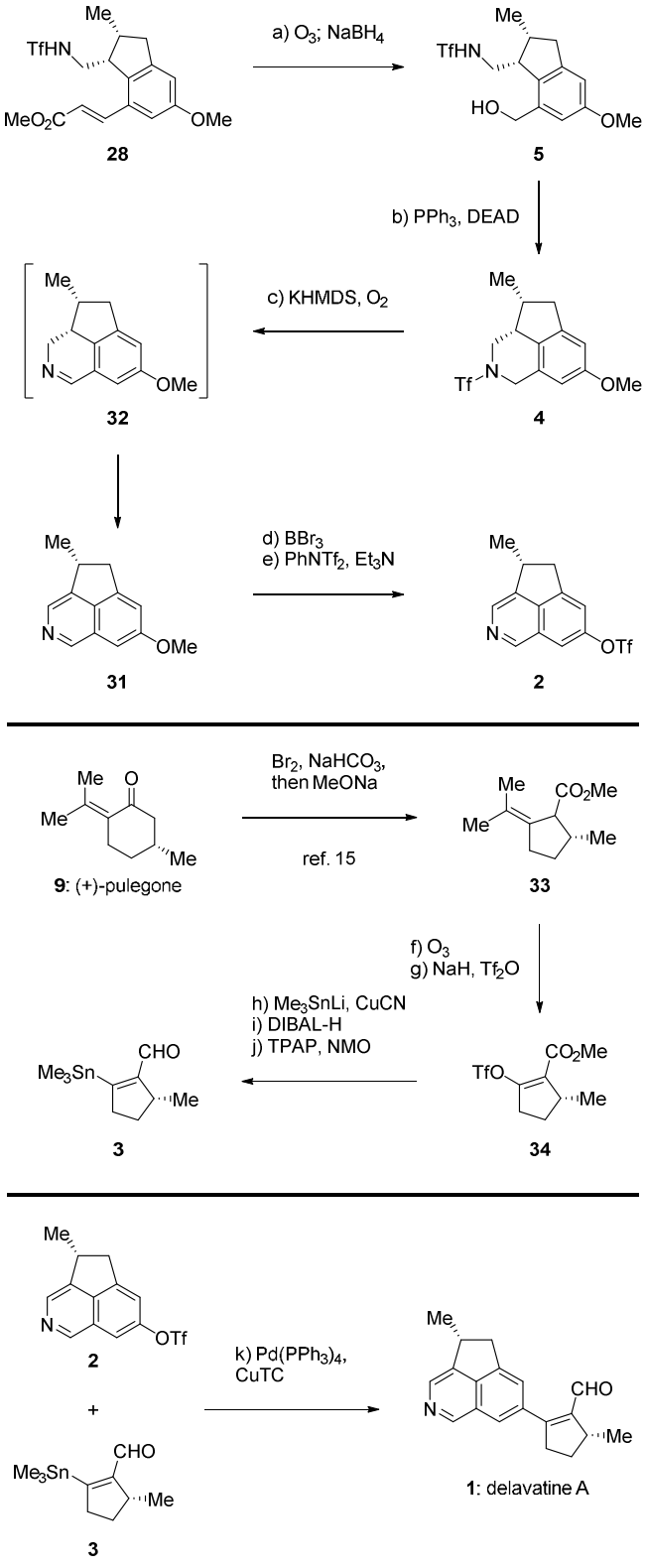
Completion of the synthesis of delavatine A.

Having established the two approaches toward enantioenriched **28**, we moved forward to construct the pyridine moiety of delavatine A through a sequence of Mitsunobu cyclization reaction and oxidative aromatization (Scheme 5). Ozonolysis of **28** followed by reductive quench with $NaBH_4$ provided benzylic alcohol **5** in 85% yield, which underwent Mitsunobu reaction (DEAD, PPh_3) to give tetrahydroisoquinoline **4** in 90% yield. The triflamide served as an excellent Mitsunobu substrate here, taking advantage of its suitable acidity. Watson reported the conversion of *N*-sulfonyl tetrahydroisoquinolines into the corresponding 3,4-dihydroisoquinolines promoted by methanolic KOH at elevated temperature.[37] Inspired by this E_{1cb} type reaction, we subjected **4** to KHMDS under an

oxygen atmosphere; isoquinoline **31** was directly obtained in 51% yield (40% on a gram scale). Skeletal decomposition was responsible for this moderate yield. This one-pot reaction may proceed through Tf elimination, benzylic deprotonation, peroxidation, and aromatization, with the intermediacy of 3,4-dihydroisoquinoline **32**. Here we exploited Tf as a good leaving group. Demethylation with BBr_3 followed by triflating the resultant phenol ($PhNTf_2$, Et_3N) afforded compound **2** in 81% overall yield.

We then prepared the right hand fragment **3** and completed the synthesis of delavatine A (Scheme 5). As reported by Wolinsky and Chan, dibromination of (+)-pulegone (**9**), followed by Favorskii rearrangement and spontaneous elimination of HBr under basic conditions,[38] furnished ester **33**. The stereochemical configuration at the carbonyl α position was inconsequential. Ozonolysis and then triflation of the resultant β-ketoester (NaH, Tf_2O) afforded compound **34** with good overall efficiency. Treatment of **34** with $(Me_3Sn)_2CuLi$[39] gave the corresponding stannane in 79% yield, presumably through 1,4-addition-elimination. DIBAL-H reduction and TPAP oxidation provided **3** in 71% yield for the two steps. The two segments **2** and **3** were forged together through Stille−Migita coupling [$Pd(PPh_3)_4$, CuTC][40] to give delavatine A (**1**) in 90% yield. Over 1 g of synthetic **1** was delivered through this route, every reaction in which can be reliably carried out on a gram scale.[41] In 2015, the Lei group reported an elegant synthesis of (–)-incarviatone A, a congener of delavatine A, using a C−H functionalization strategy.[42]

Scheme 5. Completion of the Synthesis of Delavatine A[a]



[a] Reagents and conditions: a) O_3, MeOH, −78 °C, then $NaBH_4$ (3.0 equiv), 22 °C, 30 min, 85%; b) PPh_3 (1.4 equiv), DEAD (1.2 equiv), THF, 0 °C, 30 min, 90%; c) KHMDS (5.0 equiv), O_2 (balloon), THF, 0 °C, 1.5 h, 51% (40% on a gram scale); d) BBr_3 (3.0 equiv), CH_2Cl_2, 22 °C, 4 h; e) $PhNTf_2$ (2.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 22 °C, 1 h, 81% (2 steps); f) O_3, CH_2Cl_2, −78 °C, 93%; g) NaH (1.8 equiv), Tf_2O (1.5 equiv), Et_2O, 0 °C, 30 min, 91%; h) $(Me_3Sn)_2CuLi$ (1.1 equiv), THF, 0 °C, 30 min, 79%; i) DIBAL-H (2.5 equiv), THF, 0 °C, 1 h; j) TPAP (10 mol%), NMO (1.5 equiv), 4 Å molecular sieves,

CH_2Cl_2, 22 °C, 1 h, 71% (2 steps); k) **2** (1.0 equiv), **3** (1.2 equiv), $Pd(PPh_3)_4$ (10 mol%), CuTC (1.5 equiv), NMP, 22 °C, 10 min, 90%.

Stereochemical assignment of delavatine A.

The spectra and physical properties (including the optical rotation) of the synthetic sample were identical to those of the natural product. However, this consistency may not be sufficient for determining the natural product configuration; the two stereogenic centers are remote from each other, and thus all four possible stereoisomers could have identical NMR spectra. To unambiguously address the issue, we coupled racemic **2** and **3** and obtained a mixture of the four stereoisomers in a ca. 1:1:1:1 ratio. This mixture was cleanly separated by analytical HPLC with chiral column to give four individual peaks. On the other hand, we independently synthesized the three stereoisomers of **1**; the enantiomerically opposite right-hand segment was prepared from (–)-pulegone (*ent*-**9**). Under the same separation conditions, the retention times of the authentic delavatine A and synthetic **1** (2*R*,15*R*) were identical to that of the second component of the mixture, and the retention times of the (2*S*,15*R*), (2*S*,15*S*), and (2*R*,15*S*) isomers matched those of the first, third, and fourth components of the mixture, respectively (see Supporting Information). This experiment verified that **1** represents the structure of delavatine A.

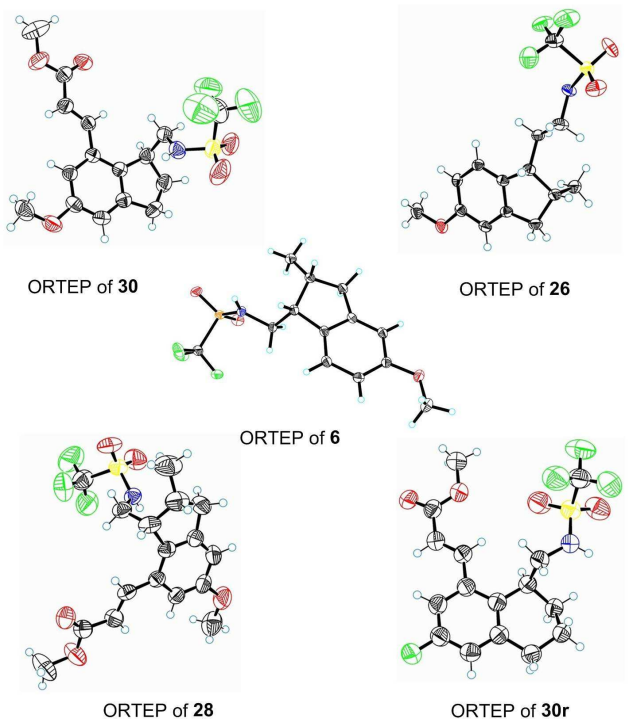


Figure 1. ORTEP drawings of compounds **6**, **26**, **28**, **30**, and **30r**.

Cytotoxicity of the synthetic delavatine A and related compounds against cancer cell lines.

With the synthetic delavatine A, its three stereoisomers, and a series of intermediates along the route in hand, we examined the effect of these compounds on cell viability of a number of cancer cell lines, such as MCF7 human breast cancer cells, HCT116 human colon cancer cells, SKOV3 human ovarian cancer cells, SMMC-7721 human liver cancer cells, and Hela human cervical cancer cells, using celastrol (also named tripterine) as a positive control. Cell viability was measured by the Cell Counting Kit-8 (CCK8) assay, and the 50% inhibitory concentrations (IC_{50}) for 24 h treatment were shown in Table S1 (see the supporting information). The synthetic delavatine A displayed considerable cellular toxicity, which was similar to the naturally occurring sample. Other stereoisomers exhibited cytotoxicity comparable to delavatine A, which implied a possible structural simplification strategy of eliminating stereocenters for further analogue synthesis. Compounds **4**, **5**, **6**, **28**, and **31** were not cytotoxic against the tested cell lines.

Conclusion

We accomplished the first, gram-scale, and asymmetric total synthesis of delavatine A, via a longest linear sequence of 13 steps. Two enantioselective transformations were developed to obtain the key intermediate of the synthesis on a large scale. The Rh-catalyzed asymmetric hydrogenation with Anthryl-MeO-BIBOP as a ligand was applicable to indene-type tetrasubstituted olefins including unfunctionalized ones and those containing sulfonamide, alcohol, and ester groups. For unfunctionalized tetrasubstituted olefin substrates, this reaction represented the first example of Rh-catalyzed hydrogenation with high enantioselectivity. The kinetic resolution of β-alkyl phenylethylamine derivatives was achieved by using Pd-catalyzed triflamide-directed C−H olefination with commercially available *N*-Boc-*tert*-leucine as a chiral ligand. This functionality-tolerated process delivered a variety of fused bicyclic triflamides including those possessing quaternary chiral centers in good to excellent enantiopurity. The selectivity factor (*s*) of the kinetic resolution exceeded 100 for a number of substrates. In addition to its initial role as a directing group, the triflamide was strategically used as a versatile functional group for constructing the isoquinoline moiety. The stereochemical configuration of

delavatine A was assigned by the syntheses of the natural product and its three stereoisomers. Their cytotoxicity against a number of cancer cell lines were evaluated.

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Supporting Information. Experimental procedures and compound characterization (cif, pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

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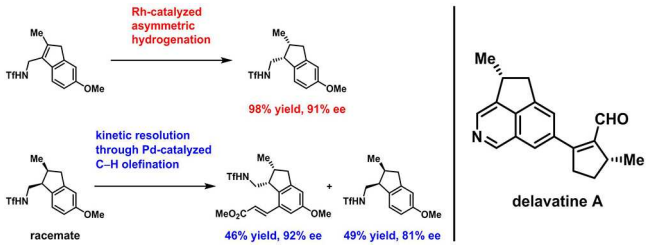
TOC Graphic


Rh-catalyzed
asymmetric
hydrogenation
98% yield, 91% ee
kinetic resolution
through Pd-catalyzed
C–H olefination
racemate
46% yield, 92% ee
49% yield, 81% ee
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