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Asymmetric Synthesis of Octahydroindoles via a Domino Robinson Annulation/5-*Endo* Intramolecular Aza-Michael Reaction

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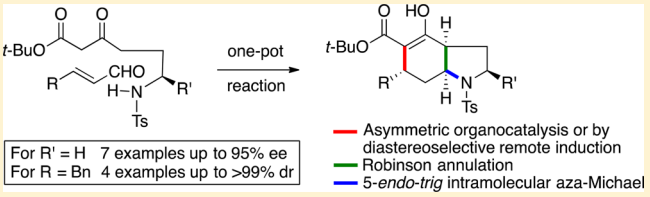
Supporting Information

ABSTRACT: A straightforward, two-step asymmetric synthesis of octahydroindoles has been developed on the basis of two complementary strategies: (i) an organocatalyzed Michael reaction followed by a tandem Robinson−aza-Michael double cyclization catalyzed by PS-BEMP, and (ii) a diastereoselective cyclization, which formally constitutes a remote 1,6 asymmetric induction mediated by PS-BEMP. This allowed the construction of complex octahydroindoles with up to four stereocenters, excellent enantioselectivities (up to 95% ee), and complete diastereoselective control in a single-pot operation. DFT calculations were performed to understand the origin of this effect.



INTRODUCTION

The organocatalyzed construction of highly functionalized polycyclic nuclei in a one-pot operation from simple acyclic precursors has the potential to greatly shorten a synthetic sequence targeting complex natural products.[1] Previously, we have developed an organocatalytic strategy toward decahydroquinolines that allowed the synthesis of an advanced common building block for a number of lycopodium alkaloids, such as lycoposerramine Z[2] and cermizine B.[3] In both cases, the tandem reaction was instrumental in enabling highly efficient syntheses of these natural products. Looking to expand the potential of this methodology, it soon became apparent that the principles[4] behind the reaction sequence, namely a *β*-keto ester, a tethered sulfonamide, and an enal engaging in a tandem Robinson aza-Michael reaction (see Figure 1), could be more general in scope, providing access to a range of different important nitrogen bicyclic nuclei in enantiopure form. Indeed, this proved to be the case and allowed us to achieve the first efficient synthetic entry to the morphan nucleus using organocatalysis from simple acyclic precursors.[5] Here, we expand the scope of this strategy to include the octahydroindole unit,[6] another privileged scaffold found in an extensive and diverse range of compounds (Figure 2). These include natural products such as aeruginosin 298-A,[7] lycorine,[8] daphniyunnine D,[9] neotuberostemonine,[10] pharmaceutical products such as perindopril,[11] and a number of proline analogue organocatalysts.[12]

While a number of methods have been developed to synthesize octahydroindoles in enantiopure form, using the chiral pool approach[13] or asymmetric metal-catalyzed reactions,[14] there are few previous approaches using aminocatalysis.[15]

Detailed herein is the development of an organocatalysis-mediated synthesis of octahydroindoles from a noncyclic

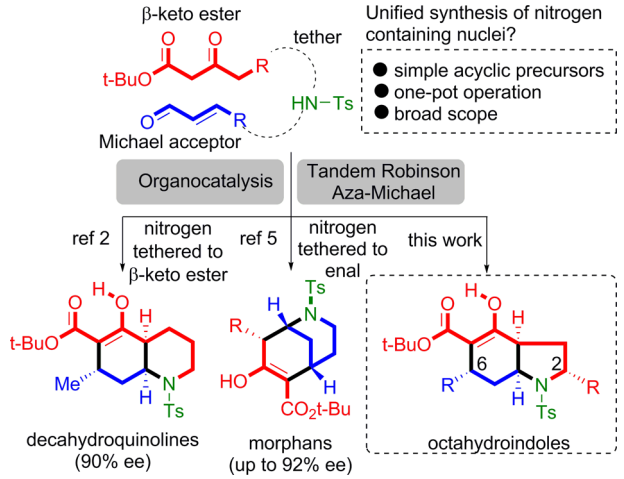


Figure 1. Unified strategy to important nitrogen-containing nuclei using an organocatalysis-initiated tandem Robinson aza-Michael reaction.

precursor. Notably, the process constitutes a rare example of an intramolecular aza-Michael reaction through a 5-*endo-trig* cyclization,[16] the latter process being disfavored according to Baldwin's rules.[17]

RESULTS AND DISCUSSION

Preparation of the required starting material was achieved in a one-step manner by ring opening of the commercially available tosyl aziridines via the dianion of *tert*-butyl acetoacetate[18] (eq

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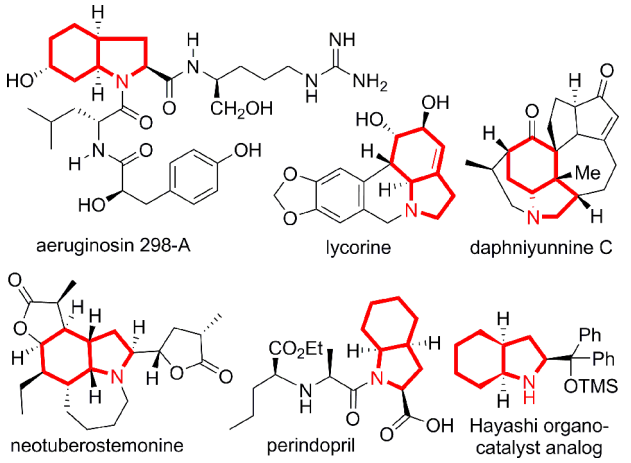
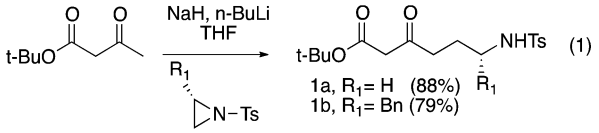


Figure 2. Diverse nitrogen-containing heterocycles with an embedded octahydroindole ring.

1). With the starting material **1a** in hand, the nonasymmetric version of the tandem cyclization reaction was initially

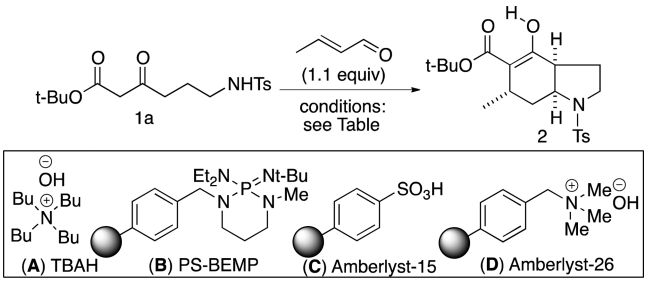


investigated. The key results are outlined in Table 1. Satisfactorily, using the optimal conditions (crotonaldehyde $LiOH{\cdot}H_2O$, *i*-PrOH, H_2O) developed for the decahydroquinoline series gave the desired analogous octahydroindole product **2a**, which maintained the *all-cis* stereochemistry (Table 1, entry 1). The moderate yield led us to evaluate other conditions[4] such as *t*-BuOK in *t*-BuOH[19] (entry 2), which gave just 15% of **2a**, with the rest (40%) recovered as the uncyclized cyclohexenone. The use of *n*-Bu_4NOH/KOH[20] gave similar results, but it was found that if the reaction was lengthened to 72 h the desired product could be obtained in moderately good yield (entry 3). We also evaluated the use of PS-BEMP with Amberlyst-15 (**B** and **C**, Table 1) under the concept of site-isolated reactivity using the conditions reported by Dixon.[21] However, only traces of the Michael product were observed (entry 4). Increasing the amount of PS-BEMP to 1 equiv gave a good yield, but significant quantities of the transesterification products were also isolated, presumably catalyzed by the acid resin (entry 5). Switching the solvent to *t*-BuOH gave a slightly less efficient conversion, but with no transesterification side products (entry 6). However, using PS-BEMP alone in *i*-PrOH gratifyingly gave **2a** in moderate yield (entry 7), while extending the reaction to 72 h gave the best yield so far of 68% (entry 8). Reducing the amount of PS-BEMP to catalytic quantities was feasible, albeit at a cost of slightly reducing the yield (entry 9). We also evaluated the more economical Amberlyst-26 resin, but this did not perform so well, with the yield dropping to 43% (entry 10).[22]

The relative stereochemistry of *rac*-**2**, which is the same for all compounds synthesized in this series (see below), was elucidated by 2D NMR spectra (COSY, HSQC, NOESY). Octahydroindole **2a** shows a preferred conformation in which the C7–C7a bond of the carbocyclic ring adopts an axial disposition with respect to the nitrogen-containing ring to avoid the allylic strain with the sulfonamide group. The key evidence for the structure depicted in Figure 3 was found in the ^1H NMR coupling pattern for H-7ax, which appears as a triplet of doublets (J = 12.8, 5.2 Hz). This coupling pattern is only compatible with an axially disposed location of the methyl group at C-6. Moreover, the axial proton H-7a is strongly coupled with only one adjacent axial proton. Hence, its resonance signal appears deceptively as a doublet (J = 12.8 Hz) of other doublets (J = 8.0, 4.8 Hz). This structural elucidation is fully confirmed by the NOE contacts observed for H-7a (Figure 3).

In order to render the initial Michael addition step in the tandem Robinson/aza-Michael reaction enantioselective, we applied the conditions developed in the decahydroquinoline series[2] (using the Hayashi–Palomo catalyst **3**,[23] LiOAc as an additive, and toluene as a solvent) to see if the octahydroindole series followed the same reactivity pattern. A brief solvent

Table 1. Screening of Tandem Cyclization Conditions Leading to Octahydroindole 2a



entry	base (equiv)	solvent	time (h)	yield[a] (%)
1	$LiOH{\cdot}H_2O$ (1)[b]	*i*-PrOH	24	44
2	*t*-BuOK (0.3)	*t*-BuOH	24	15[c]
3	**A**[d] (0.3), KOH (aq)	Et_2O/THF	72	57
4	**B**[e] (0.1), **C** (2)	CH_2Cl_2	72	
5	**B** (1), **C** (2)	*i*-PrOH	24	56[f]
6	**B** (1), **C** (2)	*t*-BuOH	24	45
7	**B** (1)	*i*-PrOH	24	42
8	**B** (1)	*i*-PrOH	72	68
9	**B** (0.1)	*i*-PrOH	72	54
10	**D** (1)	*i*-PrOH	24	43

[a]Yield refers to the products isolated by flash chromatography. [b]10 equiv of H_2O added. [c]Significant amounts of the noncyclized cyclohexenone were also obtained (~40%). [d]TBAH refers to 40% *n*-Bu_4NOH in H_2O. [e]PS-BEMP refers to polymer-supported 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine. [f]Isolated as a mixture of esters by a solvent transesterification process.

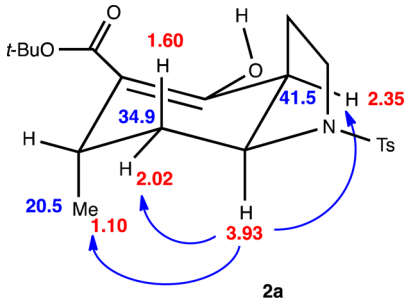


Figure 3. Characteristic NMR data and selected NOEs of hydroindole **2a**.

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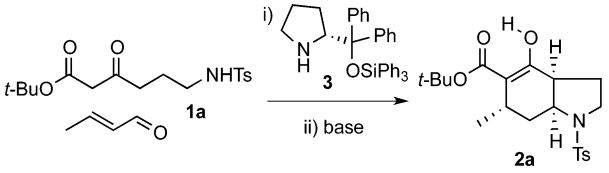
screen for the organocatalytic step proved this to be the case, so toluene was again selected as the solvent of choice based on ee and yield. With the organocatalytic step sufficiently optimized, the use of different cyclization conditions for the tandem reaction were then evaluated. With no clear winner for the base for the cyclization step, we decided to test all the conditions that had given good results (see Table 1).

The use of LiOH gave 82% ee (Table 2, entry 1), which was increased to 87% by lowering the reaction temperature (entry 5). We were surprised to observe that the choice of base was indeed crucial for obtaining good enantioselectivities. Compared to LiOH, the use of *t*-BuOK resulted in a quite considerable reduction of the ee to 73% (entry 6), while the use of KOH with TBAH under biphasic conditions gave an improved ee of 94% (entry 7). The treatment with PS-BEMP (1 equiv) performed almost equally well, giving 90% ee (entry 8). Using catalytic PS-BEMP conditions, the ee dropped slightly to 87%, and the yield was significantly reduced (entry 9). The use of the Amberlyst A26 resin resulted in a moderate 84% ee and also a moderate yield. While the KOH, TBAH conditions (entry 7) were the best in terms of enantioselectivity, we chose PS-BEMP (entry 8) as the optimum conditions based on the following criteria: (i) the reaction setup and work was significantly easier, requiring simple addition and filtration, and (ii) we observed that KOH, TBAH was less effective when the enal substituent was not a methyl group. The absolute configuration proposed for octahydroindole (+)-**2a** is based on the accepted mechanism of organocatalyzed Michael addition of *β*-keto esters upon enals[24] as well as the absolute stereochemistry reported in the related process leading to enantiopure decahydroquinolines.[3]

To test the scope of the reaction, a range of enals were examined (Scheme 1). It should be noted that in cases where the enal was not volatile, it was necessary to reduce any excess material by hydrogenation before adding the base to initiate the tandem cyclization reaction. Aliphatic enals gave the corresponding octahydroindoles **2b** and **2c** with good enantioselectivities (87% and 92% ee, respectively). The enal bearing a free hydroxyl group efficiently gave **2d** under racemic conditions but did not evolve under organocatalysis due to the formation of a stable heminal species. The reaction also generally performed well when enals with a *β*-aromatic substituent were used, giving **2e** (phenyl group), **2f** (*p*-chlorophenyl) or **2g** (*p*-methoxyphenyl), the latter bearing an electron-donating substituent, and all with excellent enantioselectivities.

Since many octahydroindole products bear a substituent at the 2-position, we were interested in examining the effect of

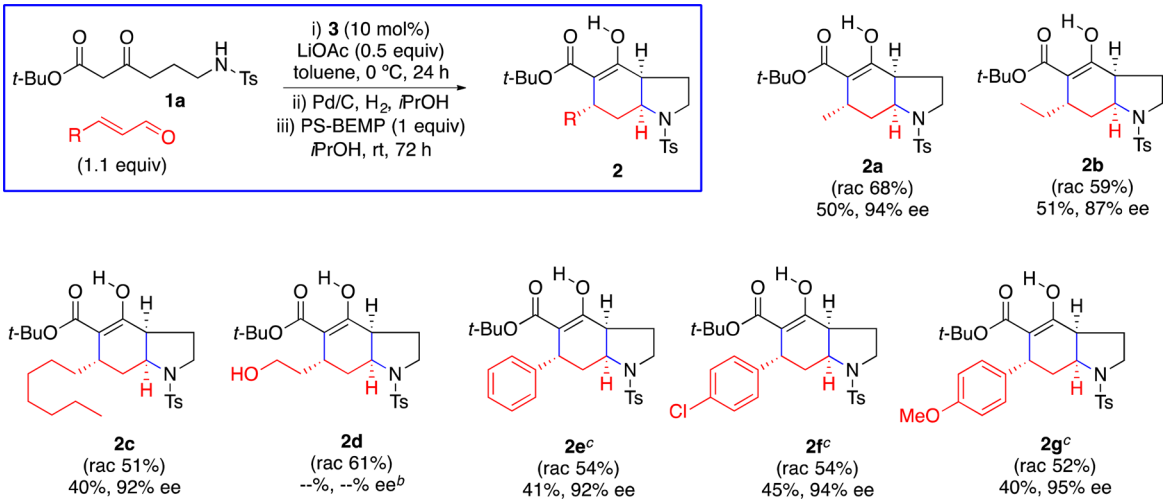
Table 2. Organocatalyzed Michael Reaction/Aldol/Intramolecular Aza-Michael Process Leading to Octahydroindole 2a



entry	solvent	temp (°C)	cyclization conditions[a]	yield[b] (%)	ee (%)
1	toluene	rt	LiOH·H_2O (T1[c]: entry 1)	51	82
2	free	rt	T1: entry 1	7	14
3	MeOH	rt	T1: entry 1	40	77
4	CH_2Cl_2	rt	T1: entry 1	27	85
5	toluene	0	LiOH·H_2O, (T1: entry 1)	55	87
6	toluene	0	*t*-BuOK (T1: entry 2)	61	73
7	toluene	0	KOH, **A**, (T1: entry 3)	51	94
8	toluene	0	**B** (T1: entry 8)	50	90
9	toluene	0	**B** (T1: entry 9)	29	87
10	toluene	0	**D** (T1:entry 10)	44	84

[a]Reactions were carried out with 1.1 equiv of crotonaldehyde and 0.5 equiv of LiOAc, as an additive, and the reaction time for the first step (i) was 24 h. The second step (ii) was carried out with the base indicated in *i*-PrOH for 72 h. [b]Yield refers to the products isolated by flash chromatography. [c]T1 refers to reaction conditions in Table 1.

Scheme 1. Scope of the Organocatalyzed Reaction[a]



[a]Each compound was prepared initially in racemic form using only the conditions of part iii of the transformation of **1a** to **2b–g**. [b]Organocatalytic conditions did not lead to any significant quantity of coupled product. [c]Excess unreacted nonvolatile enal was converted by hydrogenation to the corresponding aldehyde (see procedure C in the Experimental Section).

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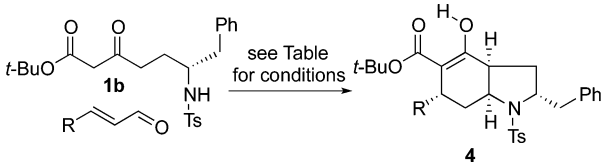
Table 3. Scope of the Domino Process from Enantiopure Acyclic β-Keto Ester 1b



entry[a]	R	compd	conditions	yield (%)
1	Me	**4a**	PS-BEMP	44
2	Me	**4a**	LiOH.H_2O	60
3	Me	**4a**	Amberlyst A-26	29
5	Me	**4a**	BEMP	24
6	Me	**4a**	**3**[b] then PS-BEMP	27
7	Me	**4a**	*ent*-**3**[b] then PS-BEMP	*c*
8	Me	**4a**	PS-BEMP (0.3)	45
9	Me	**4a**	PS-BEMP (0.3)[d]	36
10	hept	**4b**	PS-BEMP	28
11	$(CH_2)_2OH$	**4c**	PS-BEMP	30
12	Ph	**4d**	PS-BEMP[e]	43

[a]Unless otherwise stated, reactions were carried out with 1 equiv of base in *i*-PrOH for 72 h. [b]Conditions for the organocatalytic step were carried out as in Table 2, entry 8. [c]A mixture of various unidentified compounds was obtained with only traces of **4a**. [d]10 equiv of H_2O was added. [e]The use of LiOH·H_2O gave significantly lower yields when R was > Me.

placing a corresponding substituent in the β-keto ester starting material α to the nitrogen (Table 3). We began by taking α-substituted β-keto ester **1b** and reacting it under the racemic conditions (PS-BEMP, *i*-PrOH). Notably, the isolation of compound **4a** indicated that the incorporation of a stereogenic center at the α-position of the nitrogen atom (i.e., a benzyl group) caused an effective remote 1,6-asymmetric induction.[25] The stereostructure of **4a** was assigned on the basis that the set of signals in its NMR spectra (^1H and ^{13}C) showed a close correlation with those observed in **2**. Thus, considering that the pattern of chemical shifts and coupling constants for H-3a, H-6, H-7, and H-7a in **4a** was the same as in **2a**, a stereostructure analogous to that depicted in Figure 1 but having the benzyl substituent at C-2 was assigned to **4a** with the *all-cis* configuration.

To see if the above asymmetric induction was an effect unique to PS-BEMP, the previously evaluated bases were analyzed, and the product found in each case was **4a** (Table 3). The effect of using the organocatalyst **3** in the initial Michael step was then examined. While the matched organocatalyst (−)-**3** gave a similar result regarding the *all-cis* stereochemistry, *ent*-**3** failed to provide the opposite stereochemistry at C-6.

To explore the scope of the reaction, some different unsaturated aldehydes were used in the coupling reaction. As can be seen in Table 3, the reaction worked with a variety of substrates, leading to the octahydroindoles **4b**−**d** in a nonoptimized moderate yield.

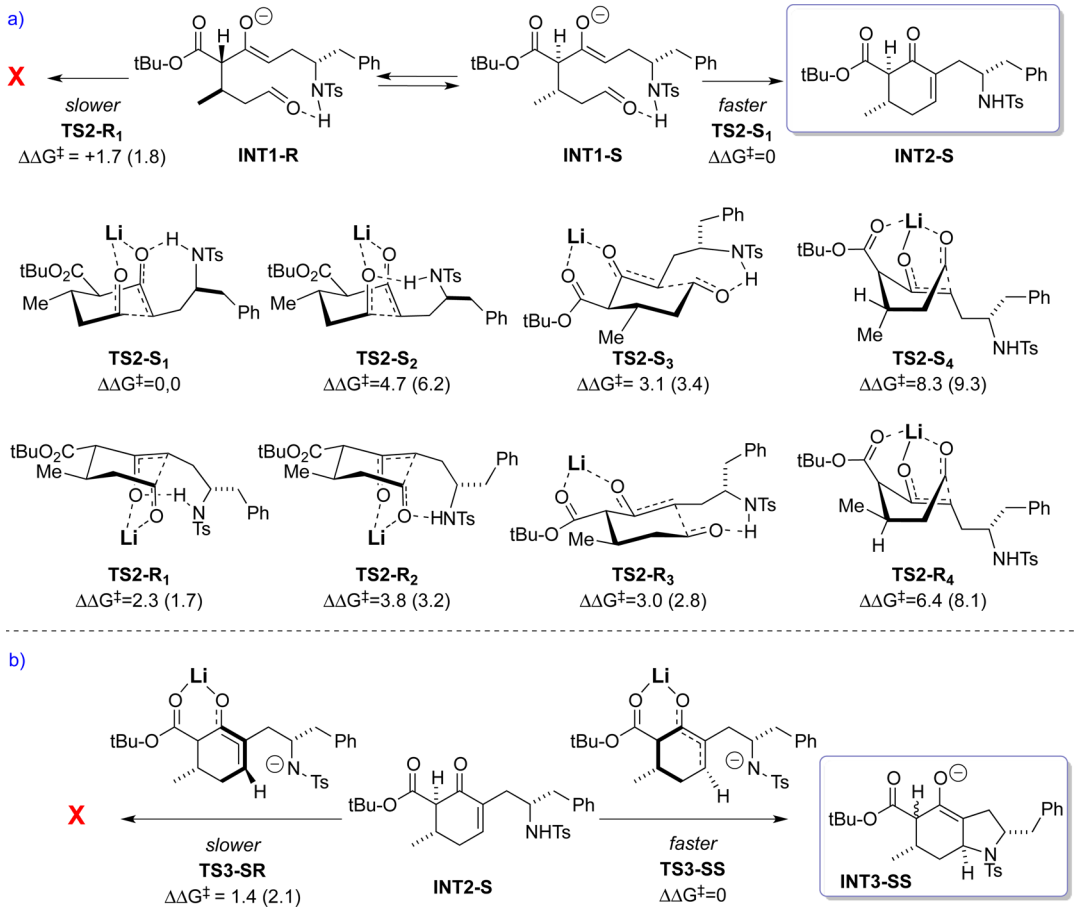


Figure 4. Proposed mechanism for the diastereoselective synthesis of enantiopure octahydroindoles **4**: (a) Robinson annulation; (b) intramolecular aza-Michael. Relative activation Gibbs Free energies computed at M062x/6-311+G** (CPCM = water) level of theory. Value in parentheses corresponds to wB97xD/6-311+G** (water) single points.

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Next, we conducted DFT calculations[26] in order to shed light on the unexpected complete diastereoselectivity exerted by the benzyl substituent on the bicycle formation. At first sight, any of the C−C or C−N bond-forming processes is a potential candidate to be the stereodetermining transformation. We thus considered all possibilities, starting with the initial Michael addition of the dicarbonylic compound to cronotaldehyde (**TS1**, see the SI), to form **INT1-R** and **INT1-S** (Figure 4), which, as expected, turned out to be nonselective. The absence of interaction between the forming C−C bond and the stereogenic center α to the nitrogen atom might be behind the observed lack of stereocontrol. The fact that **TS1** is nonselective undoubtedly means that **INT1-R** and **INT1-S** must be in equilibrium (Curtin−Hammett conditions) prior to the stereodetermining step, which we hypothesized to be **TS2** (Figure 4a). A number of **TS2** structures were located, showing different Li cation and H-bond (TsNH) activation modes of the ring formation process. Gratifyingly, the transition state lowest in energy (**TS2-S$_1$**) corresponds to the formation of the *S* epimer, which is the one experimentally observed. In this structure (**TS2-S$_1$**), the lithium atom is bonded to the two reacting oxygen units (enolate and aldehyde) and the NH of the tosyl group is hydrogen bonding the enolate oxygen. Any other Li/NH bond combination (**TS2-S$_2$** to **TS2-S$_4$**, Figure 4a) is not so favorable in terms of energy. Similar activation modes can be found in the transition states leading to the *R* epimer, **TS2-R$_1$** being the lowest one, but their energies are at least 1.7−2.0 kcal/mol larger than those of the *S* isomer, in agreement with the experimental selectivity data. We hypothesized that the reason for the energy difference between **TS2-S$_1$** and **TS2-R$_1$** might be the tight character of these *tricyclic* structures, where the steric interaction of the benzyl group with the rest of the molecule gains significance.

We also studied the diastereoselectivity of the second ring formation by attack of the nitrogen atom to **INT2-S**. The most favorable transition states located were **TS3-SR** and **TS3-SS** (Figure 4b), and the comparison of their relative Gibbs free energies is again in agreement with the experimental results, predicting the formation of the *SS* adduct. In both diastereoisomers, the lithium cation is bonded to the oxygens of the dicarbonylic system, activating the enone (**INT2-S**) toward the nucleophilic attack of the tosylamine.

In conclusion, an effective, enantioselective, organocatalytic route to polyfunctionalized octahydroindoles was developed using a one-pot sequence, further expanding the potential scope of the organocatalyzed Robinson/aza-Michael reaction for the rapid construction of important natural product nuclei. The further application of this methodology to synthesize other azabicyclic scaffolds and its use in total synthesis is currently in progress in our laboratory. Moreover, a diastereoselective route starting from commercially available enantiopure aziridine was developed, in which a 1,6-remote control induction was observed in a process leading to enantiopure 2,4,5,6-tetrasubstituted hydroindoles.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography was performed on SiO_2 (silica gel 60 F_{254}), and the spots were located with 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60 ACC, 35−75 μm, 230−240 mesh). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments are supported by gCOSY and gHSQC experiments. The triphenylsilyl catalyst **3** was prepared by a literature procedure.[23]

*tert-Butyl 6-(4-Methylphenylsulfonamido)-3-oxohexanoate (**1a**).*[16] THF (40 mL) was added to NaH (60% in mineral oil) (0.37 g, 9.22 mol), and the resulting suspension was cooled 0 °C. *tert*-Butyl acetoacetate (0.73 g, 4.61 mmol) was added dropwise, and the colorless solution was stirred at 0 °C for 10 min. Then *n*-butyllithium (1.9 mL, 2.6 M in hexanes, 4.94 mmol) was added dropwise, and the resulting orange solution was stirred at 0 °C for an additional 10 min. *N*-Tosylaziridine (1.00 g, 5.07 mmol) in THF (5 mL) was added (the color of the dianion faded on addition of the aziridine), and the reaction mixture was stirred at room temperature for 15 min. The mixture was quenched with aqueous NH_4Cl (2 mL) plus 5 mL of water (5 mL) and diluted with Et_2O (15 mL). The organic phase was washed with water, dried, and concentrated. Purification by chromatography (hexane to hexane/EtOAc 1:1) gave β-keto ester **1a** (1.44 g, 88%) as a light colored oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H, CH_3), 1.75 (qd, J = 6.4, 0.8 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.54 (td, J = 6.8, 1.2 Hz, 2H, CH_2), 2.92 (qd, J = 6.8, 1.2 Hz, 2H, CH_2), 3.31 (s, 2H, CH_2), 4.76 (br, 1H, NH), 7.28 (d, 2H, *m*-ArH), 7.71 (d, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 ($ArCH_3$), 23.1 (C-5), 27.8 (CH_3), 39.4 (C-4), 42.2 (C-6), 50.4 (C-2), 82.1 (C), 127.1 (*o*-Ar), 129.7 (*m*-Ar), 136.9 (*p*-Ar), 143.3 (*ipso*-Ar), 166.6 (C-3), 202.9 (CO); HRMS (ESI-TOF) m/z [M + NH_4]$^+$ calcd for $C_{17}H_{29}N_2O_5S$ 373.1792, found 373.1798.

*tert-Butyl (S)-6-((4-Methylphenyl)sulfonamido)-3-oxo-7-phenylheptanoate (**1b**).* THF (10 mL) was added to NaH (60% mineral oil, 113 mg, 2.84 mmol), and the resulting suspension was cooled to 0 °C. *tert*-Butyl acetoacetate (144 mg, 0.949 mmol) was added dropwise, and the colorless solution was stirred at 0 °C for 10 min. Then *n*-butyllithium (385 μL of 2.6 M in hexanes, 1.00 mmol) was added dropwise, and the orange solution was stirred at 0 °C for an additional 10 min. (*S*)-(+)-2-Benzyl-1-(*p*-tolylsulfonyl)aziridine (1.04 mmol, 300 mg) in THF (1 mL) was added (the color of the dianion faded immediately on addition of the aziridine), and the reaction mixture was stirred at room temperature for 15 min. The mixture was quenched with aqueous NH_4Cl (1 mL) plus water (3 mL) and diluted with Et_2O (7 mL). The organic phase was washed with water, dried, and concentrated. Purification by chromatography (hexane to hexane/EtOAc 1:1) gave β-keto ester **1b** (334 mg, 79%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H, CH_3), 1.51−1.61 (m, 1H, H-5), 1.78−1.86 (m, 1H, H-5), 2.41 (s, 3H, CH_3), 2.52−2.65 (m, 4H, $2CH_2$), 3.29 (dd, J = 3.2 Hz, 2H, CH_2), 3.40−3.49 (m, 1H, H-6), 4.63 (br, 1H, NH), 6.94 (dd, J = 7.6, 2.8 Hz, 2H, Ph), 7.17−7.20 (m, 3H, Ph), 7.24 (d, J = 8.4 Hz, 2H, *m*-ArH), 7.64 (d, J = 8.4 Hz, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 ($ArCH_3$), 27.9 (C-5), 28.0 (CH_3), 38.9 (C-4), 41.8 (CH_2), 50.5 (C-2), 54.3 (C-6), 81.9 (C), 126.7 (*p*-Ph), 126.9 (*o*-Ph), 128.5 (*o*-Ar), 129.3 (*m*-Ph), 129.7 (*m*-Ar), 136.6 (*p*-Ar), 137.7(*p*-Ph), 143.3 (*ipso*-Ar), 166.6 (C-3), 203.3 (CO); HRMS (ESI-TOF) m/z [M + NH_4]$^+$ calcd for $C_{24}H_{35}N_2O_5S$ 463.2261, found 463.2254.

Representative Experimental Procedures for the Intermolecular Michael/Aldol Cyclization/Intramolecular Aza-Michael Reaction. *General Procedure A.* PS-BEMP (1.0 equiv) was added to a solution of the β-keto ester (1.0 equiv) and Michael acceptor (1.1 equiv) in *i*-PrOH (4 mL/mmol), and the resulting mixture was stirred at room temperature for 72 h. Filtration, evaporation of the solvent, and chromatography gave the corresponding octahydroindole product.

General Procedure B. To β-keto ester (1.0 equiv) and Michael acceptor (1.1 equiv) in toluene at 0 °C was added LiOAc (0.5 equiv) followed by pyrrolidine **3** (0.1 equiv), and the resulting mixture was stirred at 0 °C for 24 h. The solvent was removed in vacuo and the residue dissolved in *i*-PrOH (4 mL/mmol). PS-BEMP (1.0 equiv) was added, and the resulting mixture was stirred at room temperature for 72 h. Filtration, concentration, and chromatography gave the corresponding enantioenriched octahydroindole product.

General Procedure C. To β-keto ester (1.0 equiv) and Michael acceptor (1.1 equiv) in toluene at 0 °C was added LiOAc (0.5 equiv)

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followed by catalyst **3** (0.1 equiv), and the resulting mixture was stirred at 0 °C for 24 h. The solvent was removed and the residue dissolved in *i*-PrOH (4 mL/mmol). Pd/C (20% w/w) was added, and the flask was fitted with a hydrogen balloon and hydrogenated until no enal was observed. The mixture was filtered through Celite, and the solvent was evaporated in vacuo. PS-BEMP (1.0 equiv) was then added, and the resulting mixture was stirred at room temperature for 72 h. Filtration of the resin and chromatography gave the corresponding enantioenriched octahydroindole product.

*rac-(3aR,6R,7aR)-tert-Butyl 4-Hydroxy-6-methyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**rac-2a**).* Prepared according to general procedure A using crotonaldehyde (26 μL, 0.309 mmol), β-keto ester **1a** (100 mg, 0.281 mmol), PS-BEMP (130 mg, 0.286 mmol), and *i*-PrOH (1 mL). Purification by chromatography (hexane to hexane/EtOAc 3:1) gave octahydroindole ***rac*-2a** (78 mg, 68%) as a white solid: mp 131−132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 3H, CH_3), 1.50 (s, 9H, CH_3), 1.60 (td, *J* = 12.8, 5.2 Hz, 1H, H-7ax), 1.90 (qd, *J* = 12.0, 8.0 Hz, 1H, H-3β), 2.02 (ddd, *J* = 13.0, 5.0, 2.4 Hz, 1H, H-7eq), 2.26 (dt, *J* = 12.0, 6.0 Hz, 1H, H-3α), 2.35 (ddd, *J* = 12.0, 8.0, 7.2 Hz, 1H, H-3a), 2.44 (s, 3H, $ArCH_3$), 2.72 (qdd, *J* = 7.2, 2.8, 2.0 Hz, 1H, H-6eq), 3.06 (ddd, *J* = 12.0, 8.0, 6.0 Hz, 1H, H-2α), 3.58 (t, *J* = 8.0 Hz, 1H, H-2β), 3.93 (ddd, *J* = 12.8, 8.0, 4.8 Hz, 1H, H-7a), 7.35 (d, 2H, *m*-ArH), 7.75 (d, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_3), 21.5 ($ArCH_3$), 27.5 (C-6), 28.2 (CH_3), 29.3 (C-3), 34.9 (C-7), 41.5 (C-3a), 47.9 (C-2), 55.0 (C-7a) 81.5 (C), 104.2 (C-5), 127.4 (*o*-Ar), 129.8 (*m*-Ar), 134.4 (*p*-Ar), 143.5 (*ipso*-Ar), 169.0 (C-4), 171.9 (CO); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{30}NO_5S$ 408.1839, found 408.1848.

*(3aR,6R,7aR)-tert-Butyl 4-Hydroxy-6-methyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**2a**).* Prepared according to general procedure B using β-keto ester **1a** (100 mg, 0.281 mmol), crotonaldehyde (22 mg, 0.309 mmol), catalyst **3** (14 mg, 0.028 mmol), LiOAc (9 mg, 0.141 mmol), and toluene (1.0 mL) at 0 °C for 24 h followed by cyclization with PS-BEMP (128 mg, 0.281 mmol) and *i*-PrOH (1 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **2a** (57 mg, 50%) as a white solid: $[\alpha]_D$ +110.9 (*c* 1, $CHCl_3$). For analysis data, see the procedure for rac-2a.

*(3aR,6R,7aR)-tert-Butyl 4-Hydroxy-6-ethyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**2b**).* Prepared according to general procedure B using *trans*-pentanal (34 mg, 0.402 mmol), β-keto ester **1a** (130 mg, 0.366 mmol), organocatalyst **3** (19 mg, 0.037 mmol), and LiOAc (12 mg, 0.183 mmol) in toluene (1.4 mL) at 0 °C for 24 h followed by cyclization with PS-BEMP (166 mg, 0.366 mmol) and *i*-PrOH (1 mL). Chromatography (hexane to hexane/EtOAc 3:1) gave octahydroindole **2b** (78 mg, 51%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, *J* = 7.4 Hz, 3H, CH_3), 1.19−1.28 (m, 1H, H6-CH_2), 1.38−1.44 (m, 1H, H-7), 1.49 (s, 9H, CH_3), 1.50−1.57(m, 1H, H6-CH_2) 1.89 (ddd, *J* = 19.6, 11.6, 7.6 Hz, 1H, H-3β), 2.20 (ddd, *J* = 4.7, 2.4 Hz, 1H, H-7eq), 2.21−2.29 (m, 1H, H-3α), 2.32−2.40 (m, 1H, H-6), 2.43 (s, 3H, $ArCH_3$), 2.41−2.48 (m, 1H, H-3a), 3.05 (ddd, *J* = 11.6, 9.6, 6.4 Hz, 1H, H-2α), 3.58 (ddd, *J* = 9.1, 7.8, 1.0 Hz, 1H, H-2β), 3.86 (ddd, *J* = 12.8, 8.2, 4.8 Hz, 1H, H-7a), 7.32 (d, *J* = 7.9 Hz, 2H, *m*-ArH), 7.72 (d, *J* = 8.3 Hz, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (CH_3), 21.6 ($ArCH_3$), 27.4 (CH_2), 28.3 (CH_3), 29.5 (C-3), 30.8 (C-7), 34.3 (C-6), 41.5 (C-3a), 48.0 (C-2), 55.1 (C-7a) 81.6 (C), 104.0 (C-5), 127.5 (*o*-Ar), 129.9 (*m*-Ar), 134.4 (*p*-Ar), 143.6 (*ipso*-Ar), 169.4 (C-4), 172.1 (CO); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{32}NO_5S$ 422.2005, found 422.1996.

*(3aS,6S,7aS)-tert-Butyl 6-Heptyl-4-hydroxy-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**2c**).* Prepared according to general procedure C using β-keto ester **1a** (100 mg, 0.281 mmol), *trans*-2-decenal (57 μL, 0.309 mmol), catalyst **3** (15 mg, 0.028 mmol), and LiOAc (9 mg, 0.140 mmol) in toluene (1 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **2c** (55 mg, 40%) as a white solid: mp 118−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.8 Hz, 3H, CH_3), 1.15−1.40 (m, 12H, H-alkyl), 1.41−1.50 (m, 1H, H-7), 1.50 (s, 9H, CH_3), 1.88 (dddd, *J* = 12.0, 12.0, 12.0, 8.0 Hz, 1H, H-3) 2.19 (ddd, *J* = 13.2, 4.4, 2.4 Hz, 1H, H-7), 2.27 (ddd, *J* = 12.4, 6.4, 6.4 Hz, 1H, H-3), 2.37 (dt, *J* = 12.0, 7.6 Hz, 1H, H-3a), 2.44 (s, 3H, $ArCH_3$), 2.49−2.57 (m, 1H, H-6), 3.06 (ddd, *J* = 11.2, 9.6, 6.4 Hz, 1H, H-2), 3.58 (dd, *J* = 8.8, 8.8 Hz, 1H, H-2), 3.86 (ddd, *J* = 12.8, 8.4, 4.8 Hz, 1H, H-7a), 7.32 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.71 (d, *J* = 8.4 Hz, 2H, *o*-ArH), 12.4 (s, 1H, enal); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3 side chain), 21.5 ($ArCH_3$), 22.7 (CH_2−alkyl), 27.8 (CH_2−alkyl), 28.2 (CH_3 *t*-Bu), 29.26 (CH_2−alkyl), 29.33 (CH_2−alkyl), 29.6 (C-3), 30.9 (C-7), 31.9 (CH_2−alkyl), 32.3 (C-6), 34.2 (CH_2−alkyl), 41.4 (C-3a), 47.9 (C-2), 54.9 (C-7a), 81.5 (C *t*-Bu), 104.0 (C-5), 127.4 (*o*-Ar), 129.7 (*m*-Ar), 134.3 (*p*-Ar), 143.5 (*ipso*-Ar), 169.2 (C-4), 172.0 (CO); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{42}NO_5S$ 492.2778, found 492.2779.

*(3aS,6R,7aS)-tert-Butyl 4-Hydroxy-6-(2-hydroxyethyl)-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**rac-2d**).* Prepared according to general procedure A using (*E*)-5-hydroxypent-2-enal[27] (17 mg, 0.171 mmol), β-keto ester **1a** (55 mg, 0.155 mmol), PS-BEMP (70 mg, 0.155 mmol), and *i*-PrOH (0.6 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole ***rac*-2d** (42 mg, 61%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H, CH_3), 1.53−1.62 (m, 2H, H-7 and H-1′), 1.71−1.79 (m, 1H, H-1′) 1.90 (ddd, *J* = 12.0, 4.0 Hz, 1H, H-3), 2.19 (ddd, *J* = 4.8, 2.4 Hz, 1H, H-7eq), 2.25−2.32 (m, 1H, H-3α), 2.37−2.42 (m, 1H, H-3a), 2.44 (s, 3H, $ArCH_3$), 2.69−2.75 (m, 1H, H-6), 3.04 (ddd, *J* = 11.2, 9.6, 6.4 Hz, 1H, H-2α), 3.58 (ddd, *J* = 9.2, 7.6, 0.8 Hz, 1H, H-2β), 3.67−3.78 (m, 2H, H-2′), 3.93 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1H, H-7a), 7.32 (d, *J* = 7.9 Hz, 2H, *m*-ArH), 7.72 (d, *J* = 8.3 Hz, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 ($ArCH_3$), 28.4 (CH_3), 29.4 (C-3), 29.5 (C-6), 32.2 (C-7), 37.6 (C-1′), 41.6 (C-3a), 48.0 (C-2), 55.1 (C-7a), 61.4 (C-2′), 82.3 (C), 103.3 (C-5), 127.6 (*o*-Ar), 129.9 (*m*-Ar), 134.3 (*p*-Ar), 143.8 (*ipso*-Ar), 170.1 (C-4), 171.9 (CO); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{32}NO_6S$ 438.1949, found 438.1945.

*(3aR,6R,7aR)-tert-Butyl 4-Hydroxy-1-(4-methylphenylsulfonyl)-6-phenyl-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**2e**).* Prepared according to general procedure C using cinnamaldehyde (23 mg, 0.176 mmol), β-keto ester **1a** (57 mg, 0.160 mmol), organocatalyst **3** (8 mg, 0.016 mmol), and LiOAc (5 mg, 0.080 mmol) in toluene (0.5 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **2e** (36 mg, 41%) as a white solid: mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H, CH_3), 1.89−1.97 (m, 1H, H-7ax), 1.90−1.98 (m, 1H, H-3β), 2.17−2.20 (m, 1H, H-7eq), 2.90−2.26 (m, 1H, H-3α), 2.41−2.51 (m, 1H, H-3a), 2.41 (s, 3H, $ArCH_3$), 3.08 (td, *J* = 10.1, 6.6 Hz, 1H, H-2α), 3.54−3.58 (m, 1H, H-7a), 3.58 (ddd, *J* = 12.0, 9.6, 7.6, 2.0 Hz, 1H, H-2β), 3.90 (t, *J* = 8.8 Hz, 1H, H-6eq), 7.07 (d, *J* = 7.2 Hz, 2H, *m*-Ph), 7.22 (d, *J* = 8.0 Hz, 2H, *o*-Ph), 7.28 (d, *J* = 8.0 Hz, 2H, *m*-ArH), 7.60 (d, *J* = 8.4 Hz, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 ($ArCH_3$), 27.8 (CH_3), 28.8 (C-3), 35.7 (C-7), 38.5 (C-6), 41.8 (C-3a), 48.2 (C-2), 54.7 (C-7a) 81.6 (C), 101.7 (C-5), 126.0 (*o*-Ph), 127.2 (*m*-Ph), 127.4 (*o*-Ar), 128.1 (*p*-Ph) 129.6 (*m*-Ar), 133.7 (*p*-Ar), 143.4 (*ipso*-Ar), 144.1 (*ipso*-Ph), 170.7 (C-4), 171.7 (CO); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{32}NO_5S$ 470.2001, found 470.1996.

*(3aS,6R,7aS)-tert-Butyl 6-(4-Chlorophenyl)-4-hydroxy-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**2f**).* Prepared according to general procedure C using 4-chlorocinnamaldehyde (33 mg, 0.198 mmol), β-keto ester **1a** (64 mg, 0.180 mmol), organocatalyst **3** (9 mg, 0.018 mmol), and LiOAc (6 mg, 0.090 mmol) in toluene (0.7 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **2f** (39 mg, 43%) as a white solid: mp 185−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, CH_3), 1.89−2.00 (m, 2H, H-7ax, H-3β), 2.14 (dt, *J* = 7.6, 3.6 Hz, 1H, H-7eq), 2.22 (dtd, *J* = 13.6, 8.8, 6.8 H, H-3α), 2.42 (s, 3H, $ArCH_3$), 2.44−2.52 (m, 1H, H-3a), 3.08 (dt, *J* = 10.0, 6.4 Hz, 1H, H-2α), 3.47−3.53 (m, 1H, H-6), 3.88 (t, *J* = 4.8 Hz, 1H, H-2β), 7.03 (d, *J* = 8.4 Hz, 2H, *o*-Ar), 7.25 (d, *J* = 8.8 Hz, 2H, *m*-Ar), 7.27 (d, *J* = 6.4 Hz, 2H, *o*-Ph), 7.48 (d, *J* = 8.0 Hz, 2H, *m*-Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 ($ArCH_3$), 28.0 (CH_3), 28.9 (C-3), 35.9 (C-7), 38.2 (C-6), 41.9 (C-3a), 48.3 (C-2), 54.7 (C-7a), 82.0 (C), 101.4 (C-5), 127.6 (*o*-Ar),

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128.4 (*o*-Ph), 128.7 (*m*-Ph), 129.8 (*m*-Ar), 131.9 (*p*-Ph), 133.8 (*p*-Ar), 143.0 (*ipso*-Ar), 143.8 (*ipso*-Ph), 170.9 (C-4), 171.6 (CO); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{31}ClNO_5S$ 504.1606, found 504.1609.

*(3aR,6R,7aR)-tert-Butyl 4-Hydroxy-6-(methoxyphenyl)-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**2g**).* Prepared according to general procedure C using *trans*-4-methoxycinnamaldehyde (29 mg, 0.179 mmol), β-keto ester **1a** (58 mg, 0.163 mmol), catalyst **3** (8 mg, 0.016 mmol), and LiOAc (5 mg, 0.082 mmol) in toluene (0.5 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **2g** (32 mg, 40%) as a white solid: mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, CH_3), 1.87 (td, J = 12.8, 7.6 Hz, 1H, H-7ax), 1.90−2.00 (m, 1H, H-3β), 2.16 (dt, J = 8.0, 4.0 Hz, 1H, H-7eq), 2.23 (ddd, J = 14.0, 8.4, 6.8 H, H-3α), 2.41 (s, 3H, $ArCH_3$), 2.42−2.49 (m, 1H, H-3a), 3.07 (dt, J = 10.0, 6.4 Hz, 1H, H-2α), 3.56−3.62 (m, 2H, H-6 and H-2β), 3.83 (s, 3H, CH_3), 3.86 (dd, J = 5.2, 2.8 Hz, 1H, H-7a), 6.83 (d, J = 8.8 Hz, 2H, *o*-Ph), 6.99 (d, J = 8.8 Hz, 2H, *o*-Ar), 7.23 (d, J = 8.0 Hz, 2H, *m*-Ar), 7.48 (d, J = 8.4 Hz, 2H, *m*-Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 ($ArCH_3$), 27.9 (CH_3), 28.9 (C-3), 35.9 (C-7), 37.7 (C-6), 41.7 (C-3a), 48.2 (C-2), 54.7 (C-7a), 55.3 (OCH_3), 81.6 (C), 101.8 (C-5), 113.5 (*o*-Ph), 127.4 (*o*-Ar), 128.1 (*m*-Ph), 129.6 (*m*-Ar), 133.7 (*p*-Ar), 136.2 (*p*-Ph), 143.4 (*ipso*-Ar), 157.8 (*ipso*-Ph), 170.3 (C-4), 171.7 (CO); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{34}NO_6S$ 500.2103, found 500.2101.

*(2R,3aS,6S,7aS)-tert-Butyl 2-Benzyl-4-hydroxy-6-methyl-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**4a**).* Prepared according to general procedure A using β-keto ester **1b** (190 mg, 0.426 mmol), crotonaldehyde (36 mg, 0.511 mmol), PS-BEMP (194 mg, 0.426 mmol), and *i*-PrOH (2 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **4a** (105 mg, 44%) as a colorless oil: $[\alpha]_D$ −6.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 7.2 Hz, 3H, CH_3), 1.24−1.27 (m, 1H, H-7ax), 1.47 (s, 9H, CH_3), 1.62−1.72 (m, 1H, H-3), 1.77 (ddd, J = 13.2, 4.8, 2.0 Hz, 1H, H-7eq) 1.98−2.04 (m, 1H, H-3a), 2.12−2.18 (m, 1H, H-3), 2.44 (s, 3H, $ArCH_3$), 2.61 (qdd, J = 7.2, 5.6, 2.4 Hz, 1H, H-6), 2.94 (dd, J = 13.2, 8.8 Hz, 1H, CH_2Ph), 3.40 (dd, J = 13.2, 3.2 Hz, 1H, CH_2Ph), 3.67−3.74 (m, 1H, H-2), 3.98 (ddd, J = 12.5, 7.8, 4.8 Hz, 1H, H-7a), 7.21−7.35 (m, 7H, ArH), 7.78 (d, J = 8.3 Hz, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 21.7 ($ArCH_3$), 27.5 (C-6), 28.4 (CH_3), 34.8 (C-7), 35.8 (C-3), 40.3 (C-3a), 43.1 (CH_2−Ph), 56.9 (C-7a), 62.2 (C-2), 81.7 (C), 104.0 (C-5), 126.7 (*o*-Ph), 127.6 (*o*-Ar), 128.4 (*m*-Ph), 130.0 (*m*-Ar), 130.1 (*p*-Ph), 134.6 (*p*-Ar), 137.7 (Ph), 143.9 (*ipso*-Ar), 169.3 (C-4), 172.1 (CO); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{36}NO_5S$ 498.2309, found 498.2293.

*(2R,3aS,6S,7aS)-tert-Butyl 2-Benzyl-6-heptyl-4-hydroxy-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**4b**).* Prepared according to general procedure A using β-keto ester **1b** (100 mg, 0.224 mmol), *trans*-2-decenal (46 μL, 0.246 mmol), PS-BEMP (102 mg, 0.225 mmol), and *i*-PrOH (1 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **4b** (36 mg, 28%) as a colorless oil: $[\alpha]_D$ −12.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83−0.92 (m, 3H, CH_3 alkyl), 1.10−1.18 (m, 1H, H-7), 1.18−1.38 (m, 12H, CH_2 alkyl), 1.47 (s, 9H, CH_3), 1.67 (ddd, J = 12.4, 12.4, 10.4 Hz, 1H, H-3), 1.93 (ddd, J = 13.2, 4.8, 2.4 Hz, 1H, H-7),2.04 (ddd, J = 12.4, 7.6, 7.2 Hz, 1H, H-3a), 2.16 (ddd, J = 12.4, 7.2, 6.8 Hz, 1H, H-3), 2.38−2.46 (m, 1H, H-6), 2.44 (s, 3H, $ArCH_3$), 2.93 (dd, J = 13.2, 9.2 Hz, 1H, CH_2Ph), 3.42 (dd, J = 13.2, 3.2 Hz, 1H, CH_2Ph), 3.65−3.75 (m, 1H, H-2), 3.91 (ddd, J = 12.8, 8.0, 4.8 Hz, 1H, H-7a), 7.20−7.36 (m, 7H, ArH), 7.76 (d, J = 8.4 Hz, 2H, *m*-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3 alkyl), 21.5 ($ArCH_3$), 22.7 (CH_2 alkyl) 27.8 (CH_2 alkyl), 28.2 (CH_3 *t*-Bu), 29.3 (CH_2 alkyl), 29.6 (CH_2 alkyl), 30.7 (C-7), 31.9 (CH_2 alkyl), 32.2 (C-6), 34.2 (CH_2 alkyl), 35.8 (C-3), 40.0 (C-3a), 42.9 (CH_2Ph), 56.8 (C-7a), 62.0 (C-2), 81.5 (C *t*-Bu), 103.5 (C-5), 126.5, 127.5, 128.3, 129.8, 129.9, 134.5, 137.6, 143.7, 169.4 (C-4), 172.0 (CO); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{48}NO_5S$ 582.3253, found 582.3262.

*(2R,3aS,6R,7aS)-tert-Butyl 2-Benzyl-4-hydroxy-6-(2-hydroxyethyl)-1-(4-methylphenylsulfonyl)-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**4c**).* Prepared according to general procedure A using β-keto ester **1b** (56 mg, 0.126 mmol), (*E*)-5-hydroxypent-2-enal (14 mg, 0.138 mmol), PS-BEMP (57 mg, 0.126 mmol), and *i*-PrOH (0.5 mL). Purification by chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **4c** (20 mg, 30%) as a colorless oil: $[\alpha]_D$ −17.1 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−121 (m 1H, H-1′), 1.48−1.56 (m, 1H, H-3), 1.49 (s, 9H, CH_3), 1.64−1.74 (m, 1H, H-3), 1.91−1.95 (dm, 1H, H-1′), 2.04−2.10 (m, 1H, H-3a), 2.14−2.20 (m, 1H, H-7), 2.44 (s, 3H, $ArCH_3$), 2.60−2.62 (m, 1H, H-6), 2.95 (dd, J = 13.6, 8.8 Hz, 1H, CH_2Ph), 3.40 (dd, J = 13.6, 3.2 Hz, 1H, CH_2Ph), 3.61−3.75 (m, 3H, H-2, H-2′), 3.97 (ddd, J = 12.4, 7.2, 4.4 Hz, 1H, H-7a), 7.21−7.35 (m, 5H, ArH), 7.35 (d, J = 8.0 Hz, 2H, *o*-Ar), 7.77 (d, J = 8.0 Hz, 2H, *m*-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 ($ArCH_3$), 28.4 (CH_3), 29.3 (C-6), 31.9 (C-1′), 35.9 (C-7), 37.6 (C-3), 40.1 (C-3a), 42.8 (CH_2−Ph), 57.0 (C-7a), 61.4 (C-2′), 62.2 (C-2), 82.3 (C), 102.9 (C-5), 126.7, 127.6, 128.4, 130.1, 130.2, 134.4, 137.6, 144.0, 170.1 (C-4), 171.9 (CO); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{29}H_{38}NO_6S$ 528.2434, found 528.2414.

*(2R,3aS,6R,7aS)-tert-Butyl 2-Benzyl-4-hydroxy-1-(4-methylphenylsulfonyl)-6-phenyl-2,3,3a,6,7,7a-hexahydro-1H-indole-5-carboxylate (**4d**).* Prepared according to general procedure A using β-keto ester **1b** (49 mg, 0.110 mmol), cinnamaldehyde (16 mg, 0.121 mmol), PS-BEMP (50 mg, 0.110 mmol), and *i*-PrOH (0.4 mL). Chromatography (hexane to hexane/EtOAc 1:1) gave octahydroindole **4d** (26 mg, 43%) as a white solid: mp 145−147 °C; $[\alpha]_D$ −46.8 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H, CH_3), 1.49−1.55 (m, 1H, H-3), 1.71−1.81 (m, 1H, H-7) 1.88 (dt, J = 13.2, 7.2, 3.2 Hz, 1H, H-3), 2.11−2.20 (m, 2H, H-7, H-3a), 2.42 (s, 3H, $ArCH_3$), 2.96 (dd, J = 13.2, 8.8 Hz, 1H, CH_2Ph), 3.38 (dd, J = 13.2, 2.8 Hz, 1H, CH_2Ph), 3.63 (ddd, J = 12.0, 7.6, 4.4 Hz, 1H, H-7a), 3.72−3.84 (m, 2H, H-2, H-6), 7.01 (d, J = 7.6 Hz, 2H, *o*-Ar), 7.21−7.35 (m, 10H, ArH), 7.49 (d, J = 8.0 Hz, 2H, *m*-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 ($ArCH_3$), 28.0 (CH_3), 34.9 (C-7), 35.5 (C-3), 38.8 (C-6), 40.4 (C-3a), 42.9 (CH_2−Ph), 56.4 (C-7a), 62.5 (C-2), 81.7 (C), 101.2 (C-5), 126.2, 126.7 127.3, 127.6 128.2, 128.3, 128.6, 128.8, 129.8, 130.0, 130.2, 134.0, 137.7, 143.8, 144.2, 170.9 (C-4), 171.8 (CO); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{33}H_{38}NO_5S$ 560.2469, found 560.2465.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01568.

Analytical data and copies of HPLC and ^{1}H and ^{13}C NMR spectra of the new compounds; Cartesian coordinates and energies for all species considered in Figure 4 (PDF)

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Notes

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