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Diastereoselective Multicomponent Cascade Reaction Leading to [3.2.0]-Heterobicyclic Compounds

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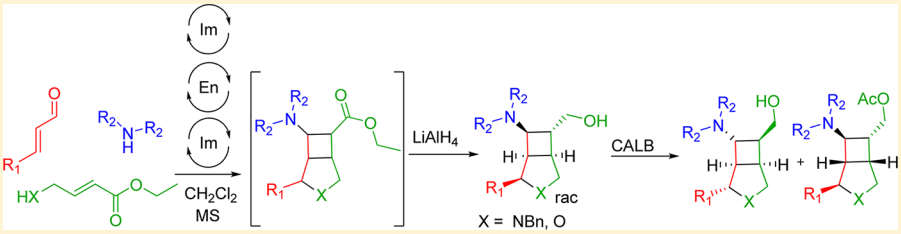
Supporting Information



ABSTRACT: A general three-component triple cascade reaction through an iminium−enamine−iminium sequential activation initiated by a hetero-Michael addition to α,β-unsaturated aldehydes affords [3.2.0]heterobicycles in high diastereoselectivity. The rate and diastereoselectivity of the reaction depended on the (*E*)-4-heterocrotonate and size of the secondary amine. The enantiomers of the major diastereoisomer of oxa- and azabicyclo[3.2.0]heptane derivatives were separated by enzymatic kinetic resolution with immobilized *Candida antarctica* Lipase B (CALB), with *E* values up to 153. The absolute configuration of the nonacylated enantiomer of oxabicyclo[3.2.0]heptane was determined by single crystal X-ray analysis.

INTRODUCTION

Synthetic organic chemistry has reached a crucial point in which a new paradigm has been generated.[1] An increasing interest in multicomponent or cascade reactions reflects that tendency, making these reactions superior over a traditional single-step procedure, where only one or two new chemical bonds are formed.[2−12] In multicomponent cascade or domino reactions, three or more reagents in multiple transformations lead to the formation of complex structures with several new C−C or C−heteroatom bonds in a single operation. This new strategy has several advantages over the classical approach, such as lower cost, decreased time and energy consumption, therefore being environmentally benign.

In the course of our ongoing investigations in the field of aminocatalysis,[13−16] we recently discovered a new multicomponent cascade reaction (Scheme 1).[17] The reaction of α,β-unsaturated aldehyde **1**, *N*-benzyl-(*E*)-4-aminocrotonate **2**, and secondary amine **3** afforded the racemic bicyclic ester with general formula **4**, together with a certain amount of the byproduct, which contains a pyrrolidine ring. The formation of the byproduct was suppressed by using a 2-fold excess of the α,β-unsaturated aldehyde and secondary amine in respect to aminocrotonate in methylene chloride, in the presence of molecular sieves. The obtained ester **4** was reduced in situ, because of its instability, into the corresponding alcohol **5**. The reaction was highly diastereoselective, affording mainly one diastereoisomer of **4** (dr up to 65:1; isolated and characterized by a wide substrate scope as alcohol **5**). Both aromatic and aliphatic unsaturated aldehydes **1** can be used as Michael acceptors, and various cyclic or acyclic secondary amines **3** are tolerated.

The mechanism of the reaction can be rationalized by assuming that the reaction proceeds via a cascade that consists of an aza-Michael addition to an iminium ion derived from α,β-unsaturated aldehyde **1** and secondary amine **3**, followed by a second, intramolecular Michael addition. The last step of the cascade is the formation of a four-membered ring via an ester enolate attack on the newly formed iminium ion. (Scheme 1)[17]

The obtained bicyclic scaffold can be found in several pharmacophores with different biological activities. For example, the similar structures are known to be present in the modulating agents of the dopamine D_3 receptor[18,19] (the treatment of schizophrenia, depression, and Parkinson's disease (belaperidone),[20] in antibacterial agents (ecenofloxacin),[21] and in antitumor drugs (mitindomide)).[22] The strained bicyclo[3.2.0]heptane skeleton is an interesting object for further modifications for synthetic chemists engaged in the synthesis of natural products.[23] Therefore, the scope of the reaction needs to be broadened with other heteroatom substituted crotonates.

Domino reactions involving initiation by a hetero-Michael addition of amines,[24] thiols[25−27] and phenols[28−31] to α,β-unsaturated aldehydes are relatively well documented, but few

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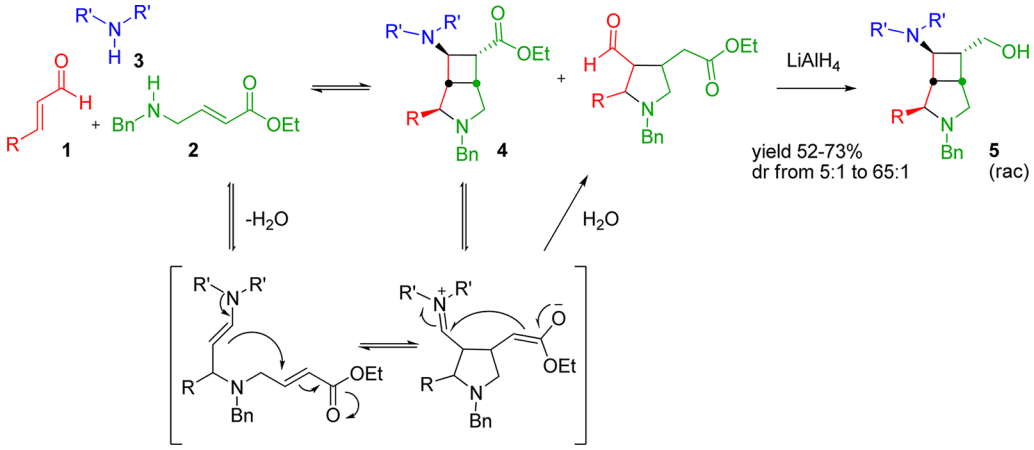
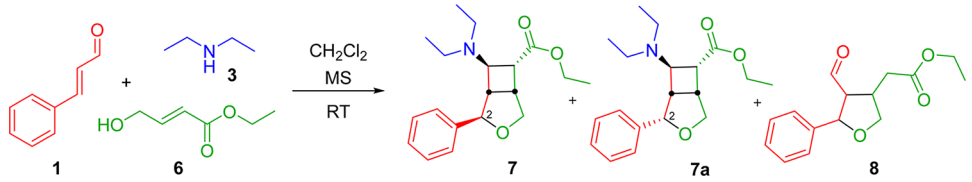
Scheme 1. Reaction between α,β-Unsaturated Aldehyde 1, *N*-Benzyl-(*E*)-4-aminocrotonate 2, and Secondary Amine 3



Scheme 2. Reaction Between α,β-Unsaturated Aldehyde 1, (*E*)-4-Hydroxycrotonate 6, and Secondary Amine 3



examples are available for the application of aliphatic alcohols in oxa-Michael reactions.[32,33] This is probably due to the low nucleophilicity of alcohols, the reversibility of the reaction and the competing acetal formation, making the oxa-Michael reaction, especially intermolecular, challenging.[34,35] At the same time 3-oxabicyclo[3.2.0]heptane derivatives are valuable synthetic intermediates, and they have been used in the synthesis of cyclobutane-fused nucleoside analogues.[36,37] This heterobicyclic skeleton has previously been synthesized via metal-catalyzed [2 + 2] cycloaddition.[38,39]

RESULTS AND DISCUSSION

We envisioned that by using hydroxycrotonate instead of aminocrotonate it might also be possible to synthesize a 3-oxabicyclo[3.2.0]heptane skeleton via the multicomponent cascade reaction. When the reaction between cinnamic aldehyde **1a** (2 equiv), ethyl (*E*)-4-hydroxycrotonate **6** (1 equiv) and diethyl amine (2 equiv) was run under the same optimum conditions as in our previous work (CH_2Cl_2, rt, presence of molecular sieves), an oxabicyclic compound **7** and a tetrahydrofurane derivative **8** were obtained in a 96:4 ratio (Scheme 2, Figure 1). The reaction was moderately diastereoselective, affording only [3.2.0]-oxabicyclo heptane 2-*exo* and 2-*endo* diastereoisomers **7** and **7a** in a 5:1 ratio, respectively. The relative configuration of the product was determined by NMR.[17] The diastereoselectivity and the rate of the reaction could not be increased by changing the solvent or adding basic or acidic additives (see the Supporting Information).

To obtain a mechanistic insight, a ^{1}H NMR study of the multicomponent reaction was conducted and the kinetics of the process was monitored. The determination of the reaction products and limiting starting material (ethyl (*E*)-4-hydroxycrotonate **6**) was straightforward on the basis of their characteristic resonances in one-dimensional ^{1}H spectrum (Figure 2). Neither of the crucial intermediates, an iminium

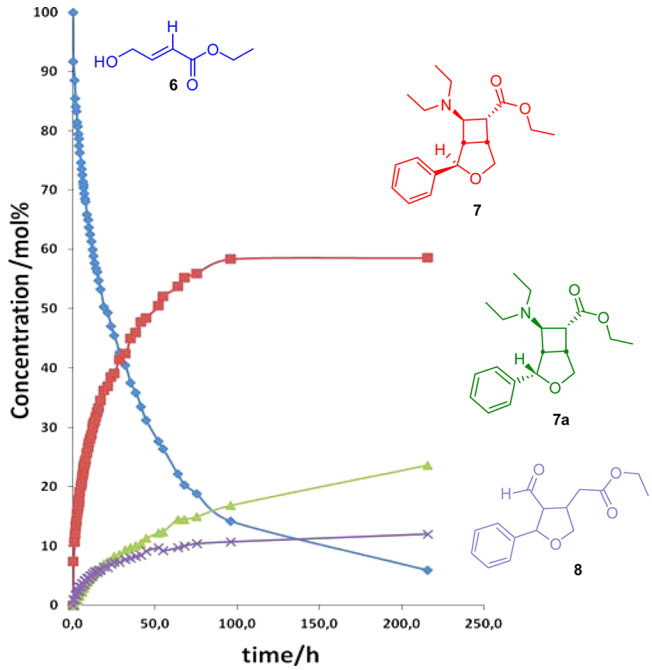


Figure 1. Reaction progress profile for the reaction in Scheme 2, obtained using ^{1}H NMR spectroscopy. Molecular sieves were added, and $CDCl_3$ was used as a reaction medium.

ion or oxa-Michael addition product, were observed. The conversion pathway of the starting material **6** and the formation of 2-*exo*-[3.2.0]oxabicyclo heptane ester **7**, its diastereoisomer **7a**, and aldehyde **8** in the reaction is presented in Figure 1. The formation of a monocycle and bicycle are competing reactions. It was assumed that the reaction would follow a similar pathway as with an aza-nucleophile (Scheme 1). However, it was not clear if the monocyclic structure was in equilibrium with the bicyclic product **7**. Since the diastereoisomeric ratio of 2-*exo*

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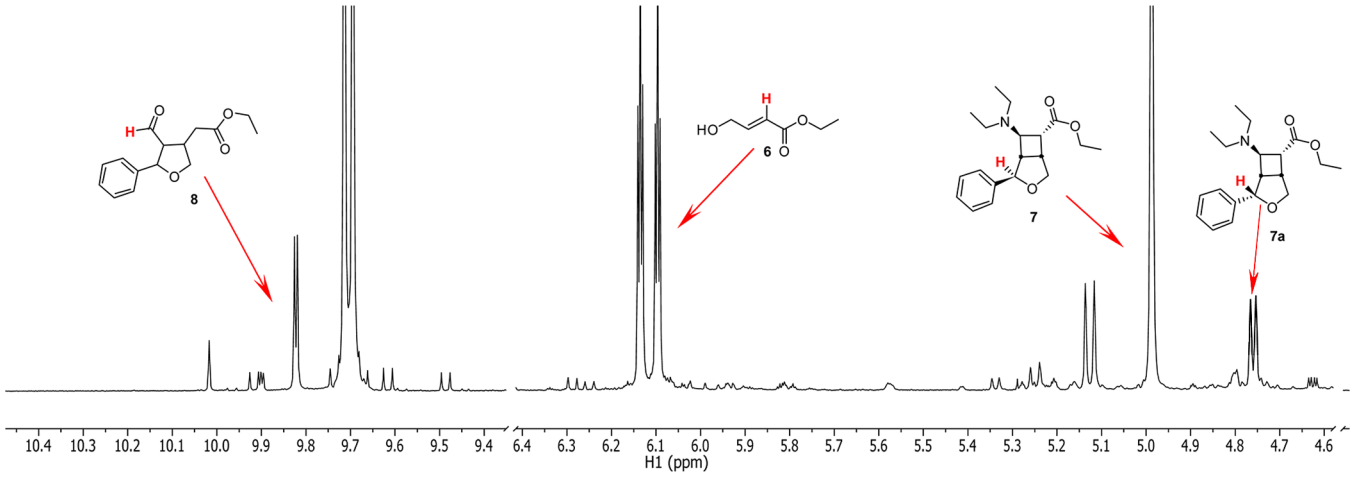
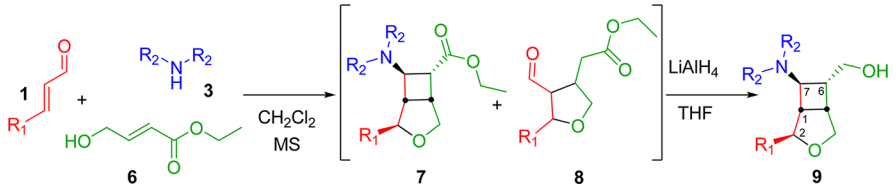


Figure 2. ^{1}H NMR spectrum of the reaction mixture after 25 h.

Table 1. Scope of the Multicomponent Reaction[a]



entry	compound	R_1	amine **3**	time (h)	ratio of **6**/**7**/**8**[b]	dr[c]	isolated yield **9**[d]
1	**9a**	Ph	Et_2NH	48	0/96/4	5:1	76
2	**9b**	Ph	pyrrolidine	72	0/64/36	4:1	43
3	**9c**	Ph	piperidine	48	8/44/48	1:1:4[e]	20 (43)[f]
4	**9d**	Ph	Me_2NH	72	21/79/0	6:1[g]	51
5	**9e**	*p*-MeO-Ph	Et_2NH	48	16/74/10	5:1	37
6	**9f**	*p*-Br-Ph	Et_2NH	48	8/84/8	5:1	55
7	**9g**	*p*-NO_2-Ph	Et_2NH	48	12/82/6	8:1	n.d.
8	**9h**	Me	Et_2NH	96	n.d.[h]	–[i]	51
9	**9i**	diMe	Et_2NH	96	n.d.[h]	–[i]	52

[a] α,β-Unsaturated aldehyde (2 equiv), amine (2 equiv), and hydroxycrotonate (1 equiv) were stirred in CH_2Cl_2 at rt for the appropriate time in the presence of MS. [b] Ratios were determined by ^{1}H NMR from the crude reaction mixture before reduction with $LiAlH_4$. [c] Ratio of (2-*exo*:2-*endo*) diastereoisomers was determined by ^{1}H NMR. [d] Isolated yield of the major diastereoisomer. [e] Ratio of 2-*exo*-6-*endo*-7-*exo*:2-*endo*-6-*endo*-7-*exo*:2-*exo*-6-*exo*-7-*endo* diastereoisomers. [f] Yield stated accordingly for 2-*exo*-6-*endo*-7-*exo* and 2-*exo*-6-*exo*-7-*endo* diastereoisomers. [g] Major diastereoisomer in 2-*exo*-6-*exo*-7-*exo*-configuration. 1 M Me_2NH in THF was used for the reaction. [h] Ratio was not determined because of overlapping of signals in ^{1}H NMR. [i] Only one diastereoisomer was detected.

and 2-*endo* isomers changed over time (from 5:1 at 48 h to 2.5:1 at 215 h to 1.3:1 in 22 days), the cascade was reversible. The reduction of the ester group excluded that equilibrium, so in the following reactions a one-pot procedure was employed.

Next, the scope of the multicomponent reaction was assessed under standard conditions. The summarized results in Table 1 show that the reaction has broad applicability, as various secondary amines **3** and α,β-unsaturated aldehydes **1** can be used. The diastereoisomeric ratio of the obtained bicycles was generally high, and it was determined from the crude mixture before the reduction of the ester by ^{1}H NMR. The predominant diastereoisomer of compound **7** was formed in a 2-*exo*-6-*endo*-7-*exo* configuration as depicted in the heading of Table 1. Exceptions to this general tendency were the compounds **9c** in 2-*exo*-6-*exo*-7-*endo* and **9d** in 2-*exo*-6-*exo*-7-*exo* configuration (Table 1, entries 3 and 4). The sterical hindrance of the secondary amine **3** had a strong influence on the chemoselectivity of the reaction, as pyrrolidine and piperidine (entries 2 and 3) gave a close to 1:1 mixture of the bicyclic product **7** and the tetrahydrofurane derivative **8**. On the other hand, sterically less demanding dimethyl amine gave no monocyclic product and resulted in the formation of a different diastereoisomer of bicycle **7** (entry 4). The reaction proceeded efficiently with different α,β-unsaturated aldehydes, not only with electron-rich aromatic substituents such as *p*-methoxyphenyl, but also with those that are electron-deficient, such as *p*-bromophenyl and *p*-nitrophenyl (entries 5–7). The reactions with aliphatic aldehydes did not proceed to completion, giving quite a lot of monocyclic product, and only one diastereomer of bicyclic product **7** was detected and isolated (entries 8, 9).

In general, the multicomponent cascade reaction of aromatic unsaturated aldehydes with (*E*)-4-hydroxycrotonate was less diastereo- and chemoselective than the corresponding reaction with *N*-benzyl-(*E*)-4-aminocrotonate.[17]

Our attempts to apply asymmetric organocatalytic approaches, such as iminium catalysis with chiral secondary amines (such as diaryl prolinol derivatives) or hydrogen

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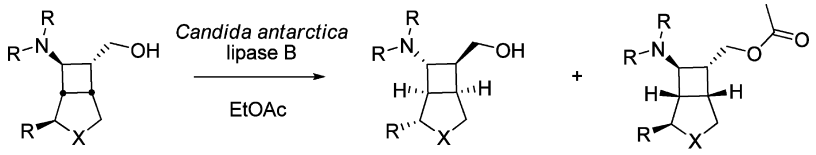
Table 2. Enzymatic Kinetic Resolution of Aza- and Oxa[3.2.0]bicyclic Compounds[a]



rac-9 (X = O, NBn)
rac-10b (X = NTs)

9A
(-)-10b

11
(+)-10b

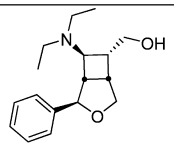
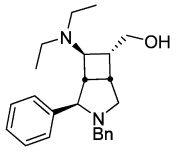
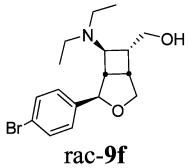
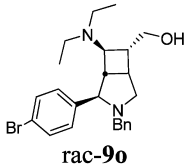
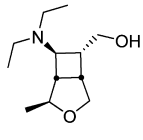
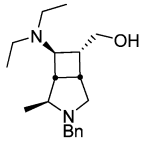
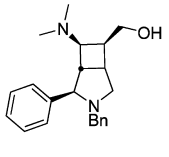
Entry	Compound	time (h)	Alcohol *ee* %	Hydrolyzed ester *ee* %	Conversion %	*E*
1	 rac-**9a**	2.5	86.4	89.8	49.0	52.7
2	 rac-**9j**	5	99.0	90.8	52.2	106
3	 rac-**9f**	2.5	89.7	90.6	49.8	60.5
4	 rac-**9o**	5	95.5	92.5	50.8	97.9
5	 rac-**9h**	2.5	81.6	94.7	46.3	92.1
6	 rac-**9r**	5	83.6	93.8	47.1	83.7
7	 rac-**9m**	23	68.9	66.8	50.8	10.1

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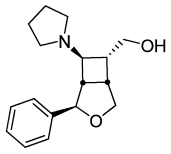
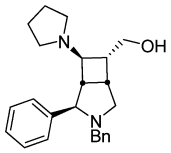
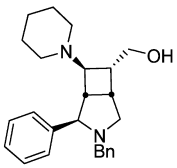
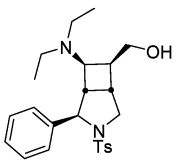
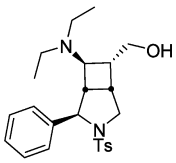
Table 2. continued

Entry	Compound	time (h)	Alcohol *ee* %	Hydrolyzed ester *ee* %	Conversion %	*E*
8	 rac-**9b**	2.5	95.3	80.4	54.2	34.4
9	 rac-**9k**	5	92.2	85.6	51.9	41.8
10	 rac-**9l**	5	95.4	85.6	52.7	48.5
11[b]	 rac-**10a**	72	43.5	62.6	41.0	6.6
12[b]	 rac-**10b**	72	68.5	97.5	41.3	153

[a]For the synthesis of *N*-benzyl azabicyclo[3.2.0]heptane derivatives, see ref 17. [b]K_2CO_3 was used as an additive to remove acid from the reaction media

bonding catalysts (quinidine, cinchonine, (*R*)-TRIP and chiral thiourea derivatives) to the oxa- or aza-Michael cascade reaction in order to generate enantiomeric aza- or oxabicyclo[3.2.0]heptane derivatives were unsuccessful, and racemic compounds were always obtained. As catalytic chemical methods failed to yield enantiopure bicyclic products, we looked into enzymatic kinetic resolution options. Lipases are widely used for the acylation of secondary and primary alcohols.[40,41] We chose immobilized lipase B of *Candida antarctica* (Novozym 435) as the catalyst and ethyl acetate as an acyl donor and reaction medium. A kinetic resolution of enantiomers of certain [3.2.0]heterobicycles **9** and **10** derivatives was run at room temperature (Table 2). The process was monitored by Chiral HPLC, which allows for the direct determination of the enzyme enantioselectivity *E*. The acylated enantiomer **11** and nonacylated enantiomer of **9** were separated by column chromatography, affording both enantiomers needed for biological assays. The enantiomeric purity of the acylated enantiomer was determined after hydrolysis of the ester.

The enzyme enantioselectivity *E* value greatly depended on the structure of the diastereoisomer of the bicyclic substrate (Table 2). It was found that the selectivity was slightly higher for *N*-benzyl bicycles (entries 2, 4, 9) than oxa-bicyclic compounds (entries 1, 3, 8). For the major diastereoisomer of *N*-benzylazabicyclo[3.2.0]heptanes, the kinetic resolution resulted in 90% *ee* for both enantiomers after the first resolution (entries 2, 4). To obtain substrates in high *ee* for biological activity testing, repeated resolutions were needed. The spatial arrangement around the chiral centers adjacent to the hydroxy

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group is the most important factor in stereoselectivity. The kinetic resolution of compounds in 6-*exo* configuration was slower and gave poorer selectivities (entries 7, 11). *N*-Tosylazabicyclo[3.2.0]heptanes **10**[42] did not provide a good fit with the enzyme, and the resolution slowed down drastically from 5 h to 3 days (entries 11, 12).

The absolute configuration of nonacylated enantiomer of **9f** was determined to be in (1*R*,2*S*,5*R*,6*S*,7*R*)-configuration by single crystal X-ray diffraction (see the Supporting Information). It is assumed that all 2-*exo*-6-*endo*-7-*exo* configuration enantiomers of oxabicyclo[3.2.0]heptane derivatives that have been acylated by Novozym 435 possess the same configuration as shown in the heading of Table 2. The absolute configuration of the azabicyclo[3.2.0]heptane derivatives was determined by us previously,[42] and enantiopreference of the enzyme was the same.

CONCLUSIONS

In summary, we have shown that a one-step multicomponent hetero-Michael/Michael/Mannich-type reaction is a general reaction that can be used for the synthesis of tetrasubstituted 3-oxabicyclo[3.2.0]heptane derivatives as well as 3-azabicyclo[3.2.0]heptane derivatives. This chemistry provides quick access to important pharmacophores, and could be used for the synthesis of starting materials for other heterocycles with more complicated structures. A method to obtain both enantiomers of the major diastereomer via enzymatic kinetic resolution immobilized lipase B of *Candida antarctica* (Novozym 435) was developed. The absolute configuration of resolved bicyclic compounds was unambiguously assigned by single crystal X-ray diffraction.

EXPERIMENTAL SECTION

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra 400 MHz instrument. Chemical shifts are reported in ppm with internal reference to TMS, and *J* values are given in Hertz. Mass spectra were obtained in GC−MS mode (EI, 70 eV). High resolution mass spectra were recorded on Accurate-Mass Q-TOF LC−MS spectrometer recorded by using AJ-ESI ionization. All HPLC analysis were done using Chiralcel AS-H or Lux Amylose-2 columns. Precoated silica gel 60 F_{254} plates were used for TLC.

Reactions sensitive to oxygen or moisture were conducted under Ar atmosphere in flame-dried glassware. Dichloromethane was freshly distilled from P_2O_5 and stored on K_2CO_3 and anhydrous tetrahydrofuran from $LiAlH_4$. Commercial reagents were used as received. Petroleum ether used had bp 40−60 °C.

General Procedure for the Synthesis of Racemic Compound 9. To a solution of the corresponding aldehyde **1** (3.0 mmol) in anhydrous CH_2Cl_2 (10 mL) in the presence of molecular sieves (4 Å), secondary amine **3** (3.0 mmol) and (*E*)-4-hydroxycrotonate **6** (1.5 mmol) were added. The mixture was stirred at room temperature for 20−96 h. The mixture was concentrated in a vacuum, and the crude bicyclic ester **7** was reduced with $LiAlH_4$ (10.8 mmol) in anhydrous THF (20 mL). After 16 h, the reaction mixture was cooled to 0 °C, and the reaction was quenched by the addition of water and an aqueous solution of 4 M aq NaOH. The mixture was dried over K_2CO_3. The crude product was purified by chromatography on silica gel (CH_2Cl_2:MeOH/NH_3 eluent system) affording bicyclic alcohol **9**.

General Procedure for Enzymatic Kinetic Resolution of 9 and 10. Immobilized lipase B of *Candida antarctica* (Novozym 435) (50 mg) was added to a solution of the racemic compound **9** or **10** (50 mg) in EtOAc (1.0 mL). The resulting mixture was stirred occasionally at room temperature and monitored by TLC. Reaction was stopped when about 50% conversion was achieved, typically after 2.5−5 h. Immobilized lipase was filtered off, and the filtrate was concentrated under reduced pressure. This mixture was purified by chromatography on silica gel affording alcohol **9** (A-enantiomer) and ester **11**. As the enantiomeric excess of ester **11** could not be determined by chiral HPLC, it was hydrolyzed to **9** (B-enantiomer), with 4 M NaOH in MeOH by stirring 3 h at room temperature.

(7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9a. 40.4 mg, yield 76%. Light yellow oil: dr (2-*exo*:2-*endo*) 5:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 6H), 2.14 (s, 1H), 2.44−2.55 (m, 1H), 2.57−2.69 (m, 4H), 2.78−2.84 (m, 1H), 2.97−3.06 (m, 1H), 3.09 (dd, J = 8.1, 5.0 Hz, 1H), 3.67−3.83 (m, 3H), 4.09 (dd, J = 10.2, 1.4 Hz, 1H), 4.94 (s, 1H), 7.23−7.30 (m, 3H), 7.30−7.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.5 (2C), 35.3, 39.6, 41.8 (2C), 47.2, 61.9, 62.4, 66.2, 84.3, 125.9 (2C), 127.4, 128.5 (2C), 140.9; IR (KBr, neat), ν (cm^{-1}) 3085, 2960, 1454, 1062, 765; m/z (EI^+) 275 (M^+, 0.62%), 188 (43), 129 (100), 98 (47); HRMS (ESI^+) calculated for $(C_{17}H_{26}NO_2)^+$ 276.1958 [M + H^+], found 276.1960.

HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 96/4, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 8.6 min, $t_{(-)\text{-B}}$ = 13.1 min. $[\alpha]^{25}_{D}$ +57.6 (*c* 0.82 in $CHCl_3$, *ee* = 96%), $[\alpha]^{25}_{D}$ −63.6 (*c* 0.86 in $CHCl_3$, *ee* > 99%).

(7-*exo*-(Diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9a-2-*endo* diastereoisomer. 9.7 mg, yield 18%. Light yellow transparent oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (t, J = 7.1 Hz, 6H), 1.97−2.09 (m, 2H), 2.12−2.28 (m, 2H), 2.44 (tt, J = 9.2, 6.0 Hz, 1H), 2.58 (t, J = 5.5 Hz, 1H), 2.88−2.98 (m, 1H), 3.06−313 (m, 1H), 3.66−3.83 (m, 3H), 4.29 (d, J = 10.2 Hz, 1H), 4.77 (d, J = 5.0 Hz, 1H), 7.17−7.27 (m, 1H), 7.28−7.42 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.9, 35.7, 39.8, 41.0, 45.76, 55.5, 61.5, 68.2, 82.5, 126.3, 127.2, 128.0, 137.8; HRMS (ESI^+) calculated for $(C_{17}H_{26}NO_2)^+$ 276.1958 [M + H^+], found 276.1954.

7-*exo*-(Diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]-heptane-6-*endo*-carboxylate 7 (9a-2-*exo* diethyl ester). 25 mg, yield 41%. Yellow oil: Column chromatography petroleum ether:EtOAc 10−50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 6H), 1.21 (t, J = 7.1 Hz, 3H), 2.60 (q, J = 7.2 Hz, 4H), 3.02−3.19 (m, 3H), 3.46 (dd, J = 7.0, 5.7 Hz, 1H), 3.74 (dd, J = 10.3, 6.4 Hz, 1H), 3.84 (dd, J = 10.2, 2.0 Hz, 1H), 4.04−4.19 (m, 2H), 4.92 (s, 1H), 7.16−7.22 (m, 4H), 7.22−7.34 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.2, 14.4, 36.6, 41.5, 42.6, 47.4, 60.6, 60.9, 67.8, 84.3, 125.8, 127.5, 128.5, 140.6, 172.1; HRMS (ESI^+) calculated for $(C_{19}H_{28}NO_3)^+$ 318.2064 [M + H^+], found 318.2062.

(2-*exo*-Phenyl-7-*exo*-(pyrrolidin-1-yl)-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9b. 182.7 mg, yield 43%. Yellow oil, dr (2-*exo*:2-*endo*) 4:1. After 24 and 48 h, additional 3 equiv of cinnamaldehyde and pyrrolidine were added: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78−1.86 (m, 4H), 2.42−2.63 (m, 7H), 2.99−3.15 (m, 2H), 3.64−3.78 (m, 3H), 4.09 (d, J = 10.2 Hz, 1H), 4.94 (s, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.29−7.38 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.3 (2C), 36.0, 39.9, 47.1, 51.3 (2C), 61.4, 65.8, 66.3, 84.1, 125.8 (2C), 127.3, 128.5 (2C), 140.9; IR (KBr, neat), ν (cm^{-1}) 3385, 2957, 1012, 729; m/z (EI^+) 273 (M^+, 0.40%), 186 (35), 127 (100), 96 (36); HRMS (ESI^+) calculated for $(C_{17}H_{24}NO_2)^+$ 274.1802 [M + H^+], found 274.1802.

HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 80/20, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 6.8 min, $t_{(-)\text{-B}}$ = 10.8 min. $[\alpha]^{25}_{D}$ +60° (*c* 0.74 in $CHCl_3$, *ee* = 95.3%), $[\alpha]^{25}_{D}$ −55° (*c* 0.72 in $CHCl_3$, *ee* = 80.4%).

(2-*exo*-Phenyl-7-*endo*-(piperidin-1-yl)-3-oxabicyclo[3.2.0]-heptan-6-*exo*-yl)methanol 9c 2-*exo*-7-*endo*-6-*exo* diastereomer (major). 190 mg, yield 43%. Yellow amorphous solid, mp 52−58 °C. After 24 h, additional 3 equiv of cinnamaldehyde and pyrrolidine were added: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39−1.52 (m, 2H), 1.55−1.66 (m, 4H), 2.19 (d, J = 7.6 Hz, 1H), 2.23−2.68 (m, 4H), 2.86−2.94 (m, 1H), 2.98 (t, J = 7.0 Hz, 1H), 3.15−3.28 (m, 1H), 3.69 (dd, J = 11.9, 1.5 Hz, 1H), 3.91 (dd, J = 9.5, 2.4 Hz, 1H), 4.00 (dd, J = 9.4, 7.3 Hz, 1H), 4.15 (dd, J = 11.9, 3.0 Hz, 1H), 4.88 (s, 1H), 5.29 (s, 1H), 7.22−7.28 (m, 3H), 7.29−7.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.7, 25.1 (2C)37.8, 40.7, 48.7, 51.6 ((2C, bs), 63.6, 64.4, 71.8, 84.6, 125.3 (2C), 126.7, 127.8 (2C), 140.3; IR (KBr, neat), ν (cm^{-1}) 3373, 2935, 1452, 1036, 732; m/z (EI^+) 287 (M^+, 0.48%),

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200 (37), 141 (100), 110 (53); HRMS (ESI^+) calculated for $(C_{18}H_{26}NO_2)^+$ 288.1958 [M + H^+], found 288.1862.

(2-*exo*-Phenyl-7-*exo*-(piperidin-1-yl)-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9c 2-*exo*-7-*exo*-6-*endo* diastreoisomer. 89 mg, yield 20%. Yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.42−1.53 (m, 2H), 1.57−1.66 (m, 4H), 2.26−2.31 (m, 1H), 2.32−2.41 (m, 4H), 2.46−2.55 (m, 2H), 3.00−3.07 (m, 1H), 3.10 (dd, J = 7.9, 4.9 Hz, 1H), 3.66−3.71 (m, 1H), 3.71−3.75 (m, 2H), 4.09 (dd, J = 10.2, 0.9 Hz, 1H) 4.90 (s, 1H), 7.23−7.26 (m, 2H), 7.30−7.36 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.3, 25.5 (2C), 35.4, 39.0, 46.6, 51.3 (2C), 61.8, 66.2, 67.0, 84.4. 125.9 (2C), 127.3, 128.5 (2C), 140.8; HRMS (ESI^+) calculated for $(C_{18}H_{26}NO_2)^+$ 288.1958 [M + H^+], found 288.1857.

(7-*exo*-(Dimethylamino)-2-*exo*-phenyl-3-oxabicyclo[3.2.0]-heptan-6-*exo*-yl)methanol 9d. 96.5 mg, yield 51%. Light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.15−2.20 (m, 1H), 2.24 (s, 6H), 2.85−2.94 (m, 2H), 3.12−3.23 (m, 1H), 3.70 (dd, J = 11.9, 1.8 Hz, 1H), 3.91 (dd, J = 9.5, 2.4 Hz, 1H), 3.99 (dd, J = 9.4, 7.2 Hz, 1H), 4.17 (dd, J = 11.9, 3.1 Hz, 1H), 4.91 (s, 1H), 5.14 (s, 1H), 7.22−7.26 (m, 1H), 7.26−7.29 (m, 2H), 7.29−7.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.9, 41.5, 43.2 (2C), 49.9, 64.1, 66.7, 72.4, 85.2, 125.9 (2C), 127.4, 128.4 (2C), 140.9; IR (KBr, neat), ν (cm^{-1}) 3181, 2905, 1497, 1057, 729; m/z (EI^+) 273 (M^++H, 0.11%), 160 (57), 101 (100); HRMS (ESI^+) calculated for $(C_{15}H_{22}NO_2)^+$ 248.1645 [M^+], found 248.1646.

(7-*exo*-(Diethylamino)-2-*exo*-(4-methoxyphenyl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol 9e. 174 mg, yield 37%. Light yellow solid: mp 62−65 °C; dr (2-*exo*:2-*endo*) 5:1; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 6H), 2.04 (s, 1H), 2.44−2.55 (m, 1H), 2.56−2.68 (m, 4H), 2.79 (dd, J = 6.8, 4.5 Hz, 1H), 2.97−3.10 (m, 2H), 3.66 (dd, J = 10.2, 6.1 Hz, 1H), 3.80 (s, 3H) 3.71−3.79 (m, 2H), 4.05 (d, J = 10.0 Hz, 1H), 4.89 (s, 1H), 6.83−6.91 (m, 2H), 7.14−7.23 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.4 (2C), 35.3, 39.6, 41.8 (2C), 46.8, 55.3, 61.9, 62.3, 65.8, 83.9, 113.8 (2C), 127.4, 132.9 (2C), 158.9; IR (KBr, neat), ν (cm^{-1}) 2975, 2859, 1611, 1513, 1251, 1184, 1031, 825; m/z (EI^+) 273 (M^++H, 1%), 218 (52), 129 (100), 98 (39); HRMS (ESI^+) calculated for $(C_{18}H_{28}NO_3)^+$ 306. 2064 [M + H^+], found 306.2066.

(2-*exo*-(4-Bromophenyl)-7-*exo*-(diethylamino)-3-oxabicyclo-[3.2.0]heptan-6-*endo*-yl)methanol 9f. 117.3 mg, yield 55%. Colorless sticky oil (rac). (+)-A-enantiomer was crystallized from EtOAc, resulting in white crystals: mp 94 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 6H), 2.02 (bs, 1H), 2.44−2.54 (m, 1H), 2.55−2.69 (m, 4H), 2.80 (dd, J = 6.9, 4.5 Hz, 1H), 2.94−3.06 (m, 2H), 3.67 (dd, J = 10.2, 6.2 Hz, 1H), 3.70−3.82 (m, 2H), 4.05−4.12 (m, 1H), 4.88 (s, 1H), 7.12−7.17 (m, 2H), 7.40−7.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.5 (2C), 35.2, 39.4, 41.9 (2C), 47.2, 61.9, 62.3, 66.4, 83.6, 121.2, 127.6 (2C), 131.6 (2C), 139.9; IR (KBr, neat), ν (cm^{-1}) 3145, 2975, 1458, 1062, 1010; m/z (EI^+) 355 (M^+, 0.05%), 268 (19), 266 (19), 129 (100), 98 (53); HRMS (ESI^+) calculated for $(C_{17}H_{25}BrNO_2)^+$ 354.1063 [M + H^+], found 354.1062.

HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 90/10, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 9.4 min, $t_{(-)\text{-B}}$ = 13.9 min. $[\alpha]^{25}_D$ +66° (c 0.57 in $CHCl_3$, ee = 89.7%), $[\alpha]^{25}_D$ −59° (c 0.84 in $CHCl_3$, ee = 90.6%).

(7-*exo*-(Diethylamino)-2-*exo*-methyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9h. 166 mg, yield 51%. Light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 6H), 1.05 (d, J = 6.6 Hz, 3H), 2.31 (bs, 1H) 2.41 (ddd, J = 12.4, 7.9, 5.1 Hz, 1H), 2.47 (dd, J = 8.0, 5.1 Hz, 1H), 2.50−2.58 (m, 4H), 2.58−2.65 (m, 1H), 2.92−3.03 (m, 1H), 3.61−3.76 (m, 3H), 4.00 (dd, J = 10.2, 1.0 Hz, 1H), 4.02−4.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.4 (2C), 18.6, 34.4, 39.1, 41.8 (2C), 47.7, 61.8, 62.0, 65.1, 79.4; m/z (EI^+) 213 (M^+, 0.72%), 129 (100), 112 (55), 98 (59); IR (KBr, neat), ν (cm^{-1}) 3143, 2967, 1454, 1112, 1051; HRMS (ESI^+) calculated for $(C_{12}H_{24}NO_2)^+$ 214.1802 [M + H^+], found 214.1801.

HPLC: (Chiracel Lux Amylose-2 column, hexanes/2-propanol/ethanol = 94/5/1, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 10.5 min, $t_{(-)\text{-B}}$ = 11.6 min. $[\alpha]^{25}_D$ +19° (c 0.71 in $CHCl_3$, ee = 81.6%), $[\alpha]^{25}_D$ −19° (c 0.19 in $CHCl_3$, ee = 94.7%).

(7-*exo*-(Diethylamino)-2,2-dimethyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9i. 181 mg, yield 52%. Yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.1 Hz, 6H), 1.09 (s, 3H), 1.30 (s, 3H), 2.34−2.45 (m, 2H), 2.47−2.62 (m, 5H), 2.78 (t, J = 5.9 Hz, 1H), 2.94−3.05 (m, 1H), 3.60−3.78 (m, 3H), 3.97 (d, J = 10.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.6 (2C), 22.2, 24.8, 35.4, 38.7, 41.6 (2C), 50.0, 57.6, 61.8, 64.8, 81.0; m/z (EI^+) 227 (M^+, 0.31%) 140 (67), 129 (100), 112 (24), 98 (54); IR (KBr, neat), ν (cm^{-1}) 3245, 2969, 1378, 1183, 1014; HRMS (ESI^+) calculated for $(C_{13}H_{26}NO_2)^+$ 228.1958 [M + H^+], found 228.1959.

(3-Benzyl-7-*exo*-diethylamino-2-*exo*-phenyl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl)methanol 9j. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 98/2, 0.05% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 11.3 min, $t_{(-)\text{-B}}$ = 16.6 min. $[\alpha]^{25}_D$ +10 (c 0.82 in CH_2Cl_2, ee = 99%), $[\alpha]^{25}_D$ −10 (c 0.47 in CH_2Cl_2, ee = 95%).

(3-Benzyl-2-*exo*-phenyl-7-*exo*-pyrrolidin-1-yl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl) methanol 9k. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 98/2, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 18.3 min, $t_{(-)\text{-B}}$ = 24.8 min. $[\alpha]^{25}_D$ +10 (c 1.22 in CH_2Cl_2, ee = 96%), $[\alpha]^{25}_D$ −11 (c 1.46 in CH_2Cl_2, ee = 99%).

(3-Benzyl-2-*exo*-phenyl-7-*exo*-piperidin-1-yl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl) methanol 9l. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 97/3, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 10.2 min, $t_{(-)\text{-B}}$ = 14.8 min. $[\alpha]^{25}_D$ +19 (c 0.37 in CH_2Cl_2, ee = 95%), $[\alpha]^{25}_D$ −20 (c 0.37 in CH_2Cl_2, ee = 99%).

(3-Benzyl-7-*exo*-dimethylamino-2-*exo*-phenyl-3-azabicyclo-[3.2.0]hept-6-*exo*-yl)methanol 9m. HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 98/2, 0.05% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(A)}$ = 17.8 min, $t_{(B)}$ = 13.5 min.

(3-Benzyl-7-*exo*-diethylamino-2-*exo*-*p*-bromophenyl-3-azabicyclo[3.2.0]hept-6-*endo*-yl) methanol 9o. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 98/2, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(-)\text{-A}}$ = 14.5 min, $t_{(+)\text{-B}}$ = 18.9 min. $[\alpha]^{25}_D$ −2.4 (c 0.90 in CH_2Cl_2, ee = 96%), $[\alpha]^{25}_D$ +4.8 (c 2.94 in CH_2Cl_2, ee = 99%).

(3-Benzyl-7-*exo*-diethylamino-2-*exo*-methyl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl)methanol 9r. HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 98/2, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 22.2 min, $t_{(-)\text{-B}}$ = 20.9 min. $[\alpha]^{25}_D$ +31 (c 0.16 in CH_2Cl_2, ee = 99%), $[\alpha]^{25}_D$ −28 (c 0.61 in CH_2Cl_2, ee = 94%).

(7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo-[3.2.0]heptan-6-*exo*-yl)methanol 10a.[42] 34 mg, yield 20.5%. Light yellow sticky oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 6H), 2.12 (d, J = 6.1 Hz, 1H), 2.34 (s, 3H), 2.40−2.59 (m, 4H), 2.87−2.95 (m, 1H), 2.96−3.03 (m, 1H), 3.08 (t, J = 7.0 Hz, 1H), 3.61−3.72 (m, 3H), 4.03 (dd, J = 12.0, 3.1 Hz, 1H), 4.85 (s, 1H), 6.99−7.06 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.16−7.22 (m, 3H), 7.38−7.43 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.0, 21.4, 37.2, 42.5, 43.0, 51.4, 53.7, 61.3, 64.0, 69.6, 126.4 (2C), 127.0 (2C), 127.5, 128.5 (2C), 129.2 (2C), 136.4, 140.6, 142.9; HRMS (ESI^+) calculated for $(C_{24}H_{33}N_2O_3S)^+$ 249.2206 [M + H^+], found 249.2203.

HPLC: (Chiralcel AS-H column, hexanes/ethanol = 92/8, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(-)\text{-A}}$ = 20.6 min, $t_{(+)\text{-B}}$ = 14.4 min. $[\alpha]^{25}_D$ −52 (c 0.66 in CH_2Cl_2, ee = 88%), $[\alpha]^{25}_D$ +59 (c 0.51 in CH_2Cl_2, ee = 93%).

(7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo-[3.2.0]heptan-6-*endo*-yl)methanol 10b. 37 mg, yield 22%. White solid: mp 115−121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.1 Hz, 6H), 2.32 (s, 3H), 2.48−2.58 (m, 5H), 2.63−2.68 (m, 1H), 2.68−2.73 (m, 1H), 3.06−3.16 (m, 1H), 3.36 (dd, J = 11.3, 8.3 Hz, 1H), 3.62−3.75 (m, 2H), 3.87 (dd, J = 11.3, 1.9 Hz, 1H), 4.83 (s, 1H), 6.98−7.08 (m, 4H), 7.14−7.23 (m, 3H), 7.32−7.36 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.2 (2C), 21.4, 34.5, 40.0, 41.7 (2C), 47.2, 49.3, 61.6, 62.5, 69.0, 126.7 (2C), 127.0 (2C), 127.5, 128.5 (2C), 129.1 (2C), 136.1, 140.4, 142.8; IR (KBr, neat), ν (cm^{-1}) 2968, 2972, 1550, 1346, 1161; HRMS (ESI^+) calculated for $(C_{24}H_{33}N_2O_3S)^+$ 249.2206 [M + H^+], found 249.2206.

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HPLC: (Chiralcel AS-H column, hexanes/ethanol = 92/8, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(-)\text{-A}}$ = 19.5 min, $t_{(+)\text{-B}}$ = 10.5 min. $[\alpha]^{25}_{D}$ −27 (*c* 0.29 in CH_2Cl_2, *ee* = 96%), $[\alpha]^{25}_{D}$ +26 (*c* 0.24 in CH_2Cl_2, *ee* = 98%).

■ ASSOCIATED CONTENT

Supporting Information

Chiral-phase HPLC chromatograms and crystallographic data (CIF files), NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Marek, I. *Chem.—Eur. J.* **2008**, *14*, 7460−7468.
(2) Ruijter, E.; Scheffelaar, R.; Orru, R. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234−6246.
(3) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300−1308.
(4) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463−472.
(5) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367−378.
(6) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634.
(7) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89.
(8) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237−294.
(9) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167−178.
(10) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857−7870.
(11) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581.
(12) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341−5378.
(13) Laars, M.; Ausmees, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. *J. Org. Chem.* **2009**, *74*, 3772−3775.
(14) Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, *19*, 641−645.
(15) Kanger, T.; Kriis, K.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *J. Org. Chem.* **2007**, *72*, 5168−5173.
(16) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559−2562.
(17) Kriis, K.; Ausmees, K.; Pehk, T.; Lopp, M.; Kanger, T. *Org. Lett.* **2010**, *12*, 2230−2233.
(18) Drescher, K.; Haupt, A.; Unger, L.; Turner, S. C.; Braje, W.; Grandel, R. *Chem. Abstr.* **2006**, *144*, 390732.
(19) Drescher, K.; Haupt, A.; Unger, L.; Turner, S. C.; Braje, W.; Grandel, R. PCT Int. Appl. WO 2006040176.
(20) Sosunov, E. A.; Gainullin, R. Z.; Danilo, P., Jr.; Anyukhovsky, E. P.; Kirchengast, M.; Rosen, M. R. *J. Pharm. Exp. Ther.* **1999**, *290*, 146−152.
(21) Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 370−373.
(22) Hasinoff, B. B.; Creighton, A. M.; Kozlowska, H.; Thampatty, P.; Allan, W. P.; Yalowich, J. C. *Mol. Pharmacol.* **1997**, *52*, 839−845.
(23) Miesch, M. *Curr. Org. Synth.* **2006**, *3*, 327−340.
(24) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058−11076.
(25) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Org. Biomol. Chem.* **2012**, *10*, 3969−3973.
(26) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. *Org. Lett.* **2012**, *14*, 1090−1093.
(27) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, 959−980.
(28) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574−581.
(29) Lingen, H. L.; van; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953−1958.
(30) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481−1484.
(31) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627−1630.
(32) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988−999.
(33) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218−1228.
(34) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 3039−3041.
(35) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658−8664.
(36) Figueras, A.; Miralles-Llumá, R.; Flores, R.; Rustullet, A.; Busqué, F.; Figueredo, M.; Font, J.; Alibés, R.; Maréchal, J.-D. *ChemMedChem* **2012**, *7*, 1044−1056.
(37) Alibes, R.; Alvarez-Larena, A.; de March, P.; Figueredo, M.; Font, J.; Parella, T.; Rustullet, A. *Org. Lett.* **2006**, *8*, 491−494.
(38) Sarkar, N.; Nayek, A.; Ghosh, S. *Org. Lett.* **2004**, *6*, 1903−1905.
(39) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6716−6717.
(40) Faber, K. *Biotransformations in Organic Chemistry*; Springer: Heidelberg, 2004.
(41) Oger, C.; Marton, Z.; Brinkmann, Y.; Bultel-Ponce, V.; Durand, T.; Graber, M.; Galano, J. M. *J. Org. Chem.* **2010**, *75*, 1892−1897.
(42) Reinart-Okugbeni, R.; Ausmees, K.; Kriis, K.; Werner, F.; Rinken, A.; Kanger, T. *Eur. J. Med. Chem.* **2012**, *55*, 255−261.