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Entrapment and Kinetic Resolution of Stabilized Axial and Equatorial Conformers of Spiro-β-lactams

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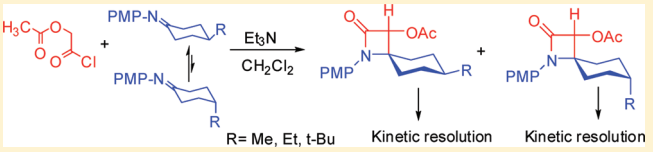
Supporting Information

ABSTRACT: The facile synthesis of the stabilized axial and equatorial conformers of spiro-β-lactams was achieved via entrapment of cyclohexanone imines (Schiff bases) with acetoxyacetyl chloride in a [2 + 2]-cycloaddition reaction followed by their kinetic resolution. The immobilization of the racemic substrates on an inert solid support significantly reduced the reaction time and improved the enantioselectivity of conformers during kinetic resolution. The mechanism of the formation of the spiro-β-lactams was explored using B3LYP/6-31+G* level quantum chemical calculations.



INTRODUCTION

The importance of β-lactam antibiotics for the treatment of bacterial infections is very well documented.[1] The development of new synthetic methodologies and ever-growing new applications of 2-azetidinones in the fields ranging from enzyme inhibition to gene activation have triggered a renewed interest in the building of novel β-lactam systems.[2] Spirocyclic β-lactams in particular behave as β-turn mimetics as well as cholesterol absorption inhibitors and are precursors of α-substituted β-amino acids.[3] Efficient methods have been developed to synthesize such unusual amino acids and one such method was published by Kambara et al.[4] Alonso et al.[3] combined the features of a spiro system and α,α-disubstituted β-lactams to propose the introduction of a [5.4]-spirolactam. More recently, various research groups have shown their interest in the synthesis of proline-derived stereoselective synthesis of spiro-β-lactams.[5]

The entrapment, separation, and stability of both the axial and the equatorial conformers in a cyclic system (e.g., cyclohexane) are interesting challenges for chemists. For example in monoalkyl-substituted cyclohexanes, significant potential energy differences between the axial and the equatorial conformers make it virtually impossible to detect and separate both at room temperature.[6] However, at low temperatures, even the less stable conformer may be easily frozen and detected by spectral (e.g., dynamic NMR) or other means.[7] The size of the alkyl group, the steric factors, and electrostatic interactions play important roles in the predominant formation and stability of a particular conformer, e.g., the bulkier substituents generally are more stabilized in equatorial conformations.[6]

In the present article, we report the first entrapment of both conformers of 4-alkyl-substituted cyclohexanones (imines) through spirane ring formation. The synthesized conformers of 4-substituted spiro[5.3]-2-azanonanone (spiro azetidinones) are stable at room temperature and could easily be separated in pure crystalline forms. The restricted conformers were also kinetically resolved using lipases. The use of inert solid support for the substrates substantially improved the efficacy of lipase-catalyzed hydrolysis of the corresponding acetates, affording the products with ∼99% enantiopurity. The confirmations of all the structures and relative conformational analysis was achieved by NMR and single crystal X-ray crystallography, besides determining the absolute configuration of one of the enantiomers. The reaction mechanism was explored using density functional (DFT) methods. As mentioned earlier similar kind of molecules have reportedly exhibited interesting biological activities;[8] in addition, the optically active spiro-β-lactams may be used as precursors of optically active unnatural β-(tertiary) amino acids (Figure 1). Relatively few efforts have been devoted toward the synthesis of cyclohexylidine-derived spiro-β-lactams;[9] besides, we have not come across the reports of their kinetic resolutions. It therefore became apparent that the synthesis and biocatalytic resolution of spiro-β-lactams may be an interesting as well as challenging task due to their conformational ambiguity and strained nature.

RESULTS AND DISCUSSION

Spiro-β-lactams were prepared using Staudinger chemistry with some modifications.[10] In our synthetic strategy we envisaged condensation of Schiff bases (**b**) derived from 4-alkyl-substituted cyclohexanones (**a**) and *p*-anisidine with acetoxyacetyl

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chloride (AAC, **c**) (Figure 1). The cycloalkanones were first condensed with *p*-anisidine in the presence of *p*-TSA in a Dean–Stark apparatus to obtain Schiff bases (**b**). The Schiff bases were subjected to [2 + 2] cycloaddition reactions with AAC to produce the desired racemic products in moderate to good yields. Using cyclohexanone as the model substrate, the reaction conditions were optimized and the cycloaddition reaction was performed at −78 °C in dichloromethane in the presence of triethylamine. The formation of racemic spiro-*β*-lactam **1** was smooth, and the product obtained as brown oil was purified by column chromatography. The structure of (±)-**1** was also confirmed from the spectral data.

The Schiff bases prepared from 4-methylcyclohexanone and 4-ethylcyclohexanone with *p*-anisidine in toluene were reacted under similar conditions. The product mixture was easily separated by column chromatography into its components, i.e., **2a** (98%), **2b** (2%), **3a** (98.5%), and **3b** (1.5%). The separation of the entrapped conformers was carried out on a silica gel column using ethyl acetate/hexane/heptane as eluent. In the NMR of **2a** and **2b** the equatorial and axial methyl signals were positioned at *δ* 0.92 (C 21.9) and *δ* 0.95 (C 17.8), respectively. The NMR data (Table 1 and Supporting Information) together with 2D correlation experiments led to the structure assignment of **2a** as (±)-3-acetoxy-1-(4-methoxyphenyl)-7(*e*)-methyl-2-oxo-1-azaspiro[3.5]-nonane and 3-acetoxy-1-(4-methoxyphenyl)-7(*a*)-methyl-2-oxo-1-azaspiro[3.5]nonane **2b**, respectively. The proposed structures **2a** and **2b** were finally confirmed by X-ray diffraction (XRD) (Supporting Information). Similarly, in the NMR of **3a** and **3b**, the C-7 methyl proton signal of the ethyl substituent was assigned at *δ* 0.86 (C, 37.9) and *δ* 0.88 (C, 34.1) respectively. The NMR data (Table 1) together with 2D correlation experiments (HSQC and HMBC) led to the structure assignment as (±)-3-acetoxy-1-(4-methoxyphenyl)-7(*e*)-ethyl-2-oxo-1-azaspiro[3.5]nonane **3a** and 3-acetoxy-1-(4-methoxyphenyl)-7(*a*)-ethyl-2-oxo-1-azaspiro[3.5]nonane **3b**, respectively. The proposed structures of spiro-*β*-lactams **3a** and **3b** were also confirmed by XRD.

The cycloaddition reaction of 4-*tert*-butylcyclohexanone and *p*-anisidine Schiff base under similar experimental conditions resulted in the isolation of one product **4a** only. The NMR signals displayed a nine-proton singlet at *δ* 0.84 (C, 27.5). The NMR spectra (Table 1) together with 2D correlation experiments led to the structural assignment (±)-3-acetoxy-1-(4-methoxyphenyl)-7(*e*)-*tert*-butyl-2-oxo-1-azaspiro[3.5]nonane also confirmed by XRD.

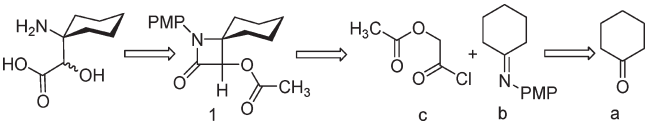

Figure 1. Retrosynthetic pathway for the synthesis of spiro-*β*-lactams.

The stability at ambient temperature of the both pairs of conformers, i.e., **2a**, **2b** and **3a**, **3b** can also be explained on the basis of their calculated relative energies (Table 1). The energy difference between **2a** and **2b** using the B3LYP/6-31+G* level is 2.14 kcal/mol; this is sufficiently different to distinguish the two species. However, the energy difference between the two isomers **3a** and **3b** is only on the order of 0.94 kcal/mol. It is apparent that very small energy differences between the isomers make both pairs highly stable at room temperature, though expectedly, the axial conformers with low population are at comparatively higher energy levels than their equatorial counterparts.

The next objective was to explore the most suitable lipase for catalyzing the enantioselective hydrolysis of spiro-*β*-lactams for their kinetic resolution. To achieve this objective, a panel of nine lipases and whole cell preparations obtained from commercial sources as well as an institutional repository were screened. The racemic spiro-*β*-lactam **2b** was not available in sufficient quantities and **4b** could not be detected; therefore, they could not be subjected to kinetic resolution studies. Thus, only spiro-*β*-lactams **1**, **2a**, **3a**, **3b**, and **4a** were subjected to biocatalytic kinetic resolutions.

From the preliminary screening experiments it is evident that AS lipase (Amano) hydrolyzed the racemates **3a** and **4a** only (Supporting Information). The lipases from Amano PS and PS-C showed satisfactory hydrolysis of racemic **3a** though slow reaction with **4a**. On the other hand, the whole cell preparation from native strain *Arthrobacter sp.* lipase (ABL, MTCC 5125) hydrolyzed all the substrates satisfactorily. Chiral HPLC analysis confirmed that Amano AS, PS, and PS-C were able to hydrolyze the given substrates with moderate to low enantioselectivity, while ABL was the most selective.

The racemic 3-acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro-[3.5]nonane **1** was incubated with ABL in aqueous in 0.1 M phosphate buffer, pH 7 at 25 °C. The reaction was sluggish; therefore, the use of cosolvents was attempted but without any success. The addition of emulsifier (TWEEN 80) showed a sign of some improvement (∼49% hydrolysis in 18–20 h), though not sufficient. It was therefore envisaged that the adsorption of the substrate over an inert solid support could be a useful alternative to improve the efficacy of the resolution. Hence, the racemic **1** was adsorbed on Celite support (200 mg on 2 g, 10 g/L) and subjected to enzymatic hydrolysis as above. Gratifyingly, the rate of hydrolysis was considerably improved and the hydrolysis time reduced from 20 h to just 4 h (conversion 49%), resulting in the formation of hydrolyzed alcohol (−)-**5** in 99% ee and the unhydrolyzed ester (+)-**1** in >97% ee (Scheme 1).

Similarly, the racemic 3-acetoxy-1-(4-methoxyphenyl)-7(*e*)-methyl-2-oxo-1-azaspiro[3.5]nonane **2a** and 3-acetoxy-7(*e*/*a*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane **3a**/**b** were also successfully resolved using ABL employing the immobilization

Table 1. NMR Data and the Calculated Energy Differences between the Isomers

	NMR data		
entry	^{1}H (*δ*)	^{13}C (*δ*)	ΔE^a
2a	0.92 (3H, d, *J* = 6.42 Hz eq methyl), 1.40 (C7-H, m)	21.9 (eq methyl), 31.1 (C7)	0.00
2b	0.95 (3H, d, *J* = 6.73 Hz ax. methyl), 1.79 (C7-*H*, m)	17.8 (ax. methyl), 25.0 (C7)	2.14
3a	0.86 (3H, t, *J* = 7.40 Hz, C7-CH_2CH_3), 1.21 (1H, m, C7-*H*)	11.4 (C-7 CH_2CH_3), 33.5 (C-7 CH_2CH_3), 37.9 (C-7).	0.0
3b	0.88 (3H, t, *J* = 7.19, C7-CH_2CH_3), 1.32 (2H, q, *J* = 6.82, CH_2), 1.81 (1H, m, C7-*H*)	12.1 (C-7 CH_2CH_3), 24.7 (C-7 CH_2CH_3), 34.1 (C-7).	0.97
4a	0.84 (9H, s, *tert*-butyl), 1.03 (1H, m, C7-*H*)	27.5 $(CH_3)_3$-, 32.3 $(-C(CH_3)_3)$, 46.5 (C-7).	–

[a] Relative energies are estimated using the density functional B3LYP/6-31+G* values; the corresponding absolute energy values are given in Supporting Information.

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Scheme 1. Lipase-Catalyzed Kinetic Resolution

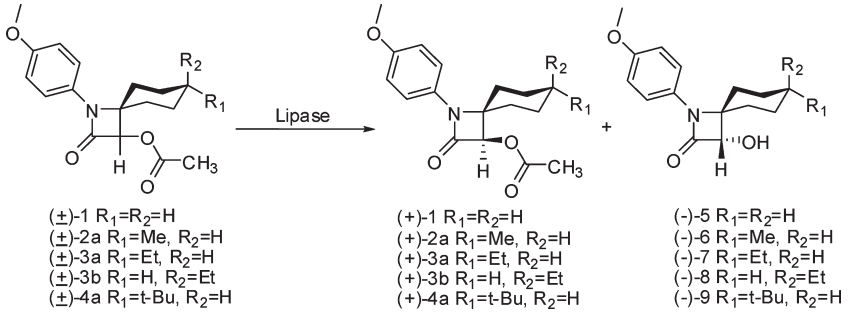

Table 2. Effect of Solid Support on Enzymatic Hydrolysis of 1, 2a, 3a, 3b, and 4a

compd	enzyme	support	time	convn, %	ee(OH), %	ee(OAc), %
1	ABL	nil	20 h	49	99	99
1	ABL	Celite	4 h	49	99	97
2a	ABL	nil	24 h	35.5	56	99
2a	ABL	Celite	4 h	41	65	99
3a	ABL	nil	36 h	48	99	99
3a	ABL	Celite	5 h	45	81	99
3b	ABL	silica	5.5 h	41	58	98
4a	AS	nil	8 days	44	39	50
4a	AS	silica	6 h	42	67	98.5

methodology (Scheme 1, Table 2). The conversion time in all the reactions significantly reduced with an improvement in the enantioselectivity (Supporting Information).

Kinetic resolution of racemic **4a** on the other hand was quite slow, and only the Amano AS and PS were able to hydrolyze it. Incubation for a period of 8 days with Amano AS showed conversion of 44% (50% ee), whereas with PS it was <5% for the product. The native lipase ABL also proved to be a complete failure for this substrate. Adsorption of **4a** over silica again proved to be very effective with Amano AS, furnishing the hydrolyzed product of 98.5% ee in 6 h (Supporting Information). These observations with lipase AS also support the results of earlier studies carried out to understand the steric requirements of lipases where it was indicated that lipases such as those belonging to genus *Pseudomonas*, *Candida*, *Mucor*, etc., are capable of accepting only small to medium size groups, while lipase from *Aspergillus niger* can accommodate comparatively larger groups.[11]

X-ray crystallographic data collected using a single crystal of the hydrolyzed enantiomer (−)-3-hydroxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-**5** (Supporting Information) obtained as a result of enzymatic resolution, established the absolute configuration as 3*S*. Therefore, the unreacted ester is assigned 3*R* as the absolute configuration.

If viewed critically, the cycloaddition reaction of substituted cycohexanone imine with ketene may result in the formation two groups of diastereomeric products, i.e., I and II (Figure 2).

In the case of unsubstituted cycloalkanes each of these diastereomers should give two pairs of enantiomers (four enantiomers). Similarly 4-substituted cyclohexanones with two stereogenic centers and additional molecular asymmetry originated from spiro structure should always result in the formation of four pairs of products (eight enantiomers, i.e., A−H, Figure 2). Thus, out of

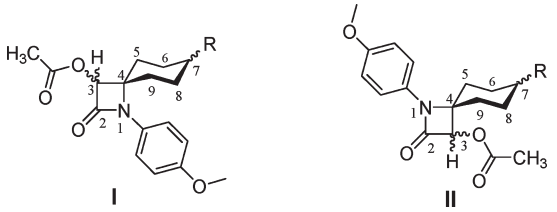

Figure 2. Possible formation of diastereomers.

the possible eight, four isomers should have nitrogen occupying the equatorial position (A−D) and the remaining four isomers with nitrogen occupying the axial position (E−H). However, it was found that only four isomers were formed with methyl and ethyl substitutions, whereas only two enantiomers were detected in the case of *tert*-butylcycloheaxane, all exhibiting N-equatorial orientation (Figure 3).

Interestingly, the outcome of the reaction may be rationalized on the basis of the following possible reaction mechanism. From the conformational analysis of cyclohexanones, it may be established that any substitution at C-4 in cyclohexanone may possibly occupy predominantly an equatorial position which is more stable than the axial one.[12] The synthesis of spiro-β-lactams was accomplished in two steps, and the intermediate Schiff bases generally existed in a dynamic equilibrium between equatorial and axial conformers through a flipping mechanism, the former being dominant. In 4-*tert*-butylcyclohexanone this equilibrium may shift entirely in favor of the equatorial conformer because of its more bulky nature.

In the Schiff bases obtained from 4-methyl- and 4-ethylcyclohexanones, a ketene can interact from two sides: (i) the equatorial side approach will result in the formation of an axial product, i.e., the N would occupy an axial position; (ii) the axial approach will lead to the equatorial product, i.e., the N would occupy an equatorial position.

The mechanism of the Staudinger reaction has been explained previously.[13] It involves a two-step mechanism which is initiated by the nucleophilic attack of the iminic nitrogen on the electron-deficient carbon of the ketene followed by a four-electron conrotatory electrocyclization that is subject to torquoelectonic effects.[13] The electrocyclic ring closure takes place to form the CC bond. The mechanism of this reaction was explored using quantum chemical methods, and the possible structures of the intermediates and the transition states on the reaction path have been discussed in literature.[13,14] In the present case, B3LYP/6-31+G* calculations indicate that the intermediate on this path leading to the formation of **2a** is found to be about 3.06 kcal/mol

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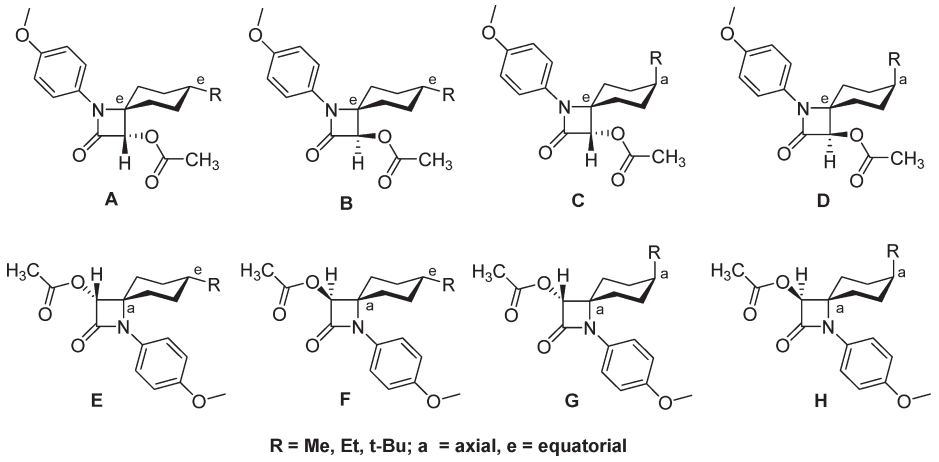

Figure 3. Formation of all the possible conformers of spiro-β-lactams.

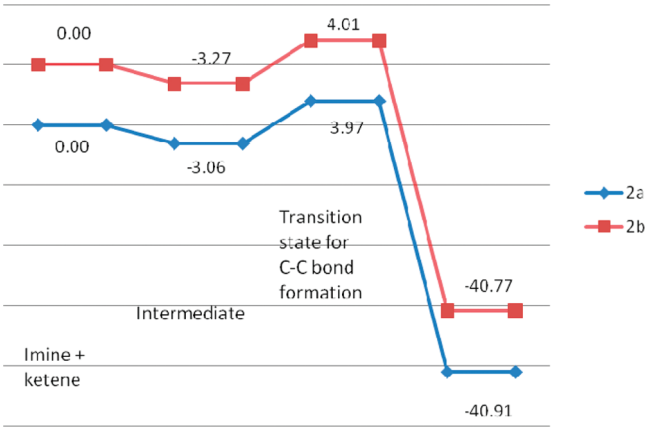

Figure 4. The potential energy surfaces for the formation of **2a** and **2b**. The relative energies are plotted in this graph. The graphs are exactly parallel, the *y*-axis representing energy (does not carry any scale). The relative values are estimated using B3LYP/6-31+G(d) level of quantum chemical calculations.

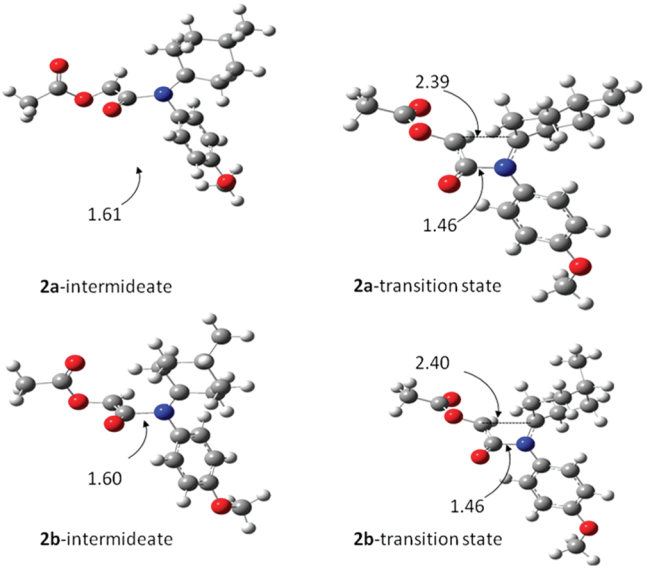

Figure 5. The 3D structures of the intermediates and the transition states on the paths of formation of **2a** and **2b**. Important bond distances are shown in angstroms.

more stable than the corresponding starting material. The barrier for the formation of **2a** from the intermediate is found to be approximately 7.03 kcal/mol. The formation of **2a** from the corresponding starting material is found to be highly exothermic (40.91 kcal/mol). The energy profile for the formation of the **2a** and **2b** are given in Figure 4. The 3D structures of the intermediates on the reaction path leading to the formation of **2a** and **2b** are given in Figure 5. The energy profiles are quite parallel, indicating that the reaction mechanism does not dictate the final thermodynamic preferences of the products.

The origin of preferential formation of **2a** over **2b** can be traced to the thermodynamic preferences of the starting material and that of the products. The energy differences between the equatorial and axial alternatives of the starting imine are found to provide some clues (Table 3). For example, the energy difference between imines leading to **2** is 2.0 kcal/mol, favoring the equatorial configuration. Similarly equatorial configuration of the imine leading to the formation of **3** is 0.85 kcal/mol. On the other hand, the energy difference between the two configurations of the imine leading to the formation of **4** is 5.27 kcal/mol. Because of the large energy difference between the two forms of the imine, **4a** is

Table 3. The Relative Energies (B3LYP/6-31+G(d); kcal/mol) of Various Structures on the Path Leading to the Formation of Final Spiro-β-lactams

structures	ΔE (equatorial − axial)
imines (**2a** vs **2b**)	1.99
imines (**3a** vs **3b**)	0.85
imines (**4a** vs **4b**)	5.27
intermediates (**2a** vs **2b**)	1.89
transition states (**2a** vs **2b**)	2.04
2a vs **2b**	2.14
3a vs **3b**	0.97

the only product found. When the energy difference between the axial and equatorial forms of the imine is small, both axial and equatorial products are formed (as in the case of **2** and **3**). Also the thermodynamic stability of the equatorial product is more in

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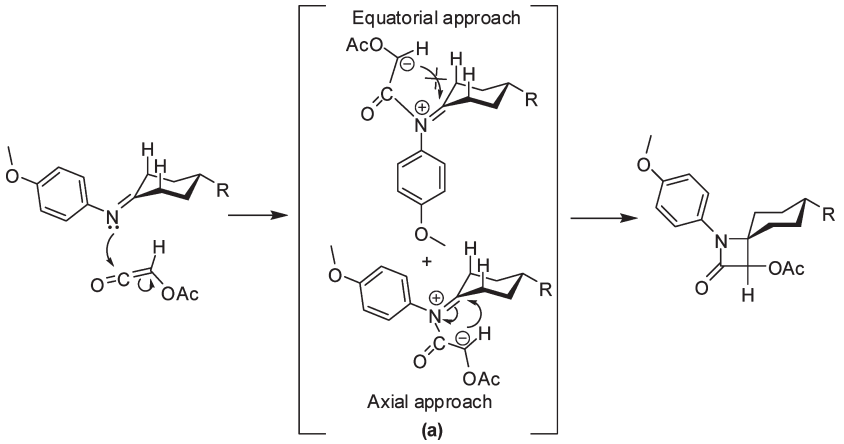

Figure 6. Possible mechanism of axial approach in β-lactam formation.

the product. Hence, it can be concluded that thermodynamic preferences in the starting imine as well as the thermodynamic stabilities of the final product both dictate the preferential formation of equatorial product in the reactions.

Further support for the formation of N-equatorial spiro-β-lactams also came from what is now known as the Cieplak effect,[15] which is the theoretical basis for the stereochemical outcome in the irreversible addition of nucleophiles to compounds such as cycohexanones, postulating that hyperconjugative σ assistance favors the axial approach because CH bonds are better electron donors. In the first place, it appears that the Cieplak effect may not be applicable in this case, as the imine itself is the nucleophile. However, in the a two-step concerted addition reaction between the imine and the ketene, initial attack of the imine on the ketene carbon results in the formation of the intermediate (a), which is then followed by intramolecular axial side attack of the vinyl carbon (which may act as a nucleophile) on the sp^2 carbon of the cyclohexane ring, resulting in the formation of exclusively N-equatorial product (Figure 6). Consequently, there is a 50% reduction in the total number of isomers formed. Thus, the intramolecular Cieplak effect also provides a possible rationalization for the stereochemical outcome of the final product.

CONCLUSIONS

In conclusion, the entrapment and kinetic resolution of stabilized conformers of 4-alkyl-substituted cyclohexanones (imines) was successfully achieved via spiro-β-lactam formation. In the case of 4-methyl and 4-ethyl substituents, both the equatorial and axial conformers were stable and easily separated. Three of these stable conformers were also kinetically resolved. Furthermore, only an equatorial conformer was isolated and resolved for the 4-*tert*-butyl-substituted spiro-β-lactam. The unsubstituted cyclohexanone-derived spiro-β-lactams were also kinetically resolved, and the absolute configuration of the hydrolyzed product was determined by XRD. The confirmation of structures of all the products was accomplished by single crystal X-ray studies. Quantum chemical analysis suggests that the thermodynamical preference of the starting imines and the theromodyanamic preference of the final products lead to the observed preferential formation of the equatorial product rather than the kinetic control of the reaction mechanism of the Staudinger reaction.

EXPERIMENTAL SECTION

General Method for Preparation of Imines. A solution of cyclic ketone (50.0 mmol) and *p*-anisidine (6.15 g, 50.0 mmol) were refluxed in 100 mL of toluene, and the water formed was removed azeotropically using Dean−Stark apparatus. An excess of solvent was removed, and the imine was used without further purification.

(±)- 3-Acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]-nonane 1. Triethylamine (6.06 g, 60.0 mmol) was added to a stirred mixture of imine (4.06 g, 20.0 mmol) in dry dichloromethane (150 mL) at −78 °C. To this stirred solution was added acetoxyacetyl chloride (3.3 g, 24.0 mmol) dissolved in 50 mL of dichloromethane over a period of 30 min, maintaining the temperature at −78 °C. The reaction temperature was slowly raised to room temperature, and stirring was continued for 8 h. After the reaction was complete (TLC), the mixture was successively washed with 5% aqueous sodium bicarbonate (50 mL), 5% HCl (50 mL) and water (3 × 50 mL). The organic layer was dried and evaporated under reduced pressure. The oily product was purified using column chromatography (230−400 mesh silica gel and dichloromethane and hexane) to obtain **1**. Yield: 5.2 g (86%), IR (Neat), 2938, 2861, 1748, 1513, 1447, 1384, 1296, 1221, 1185, 1097, 831. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08−1.25 (2H, m, CH_2), 1.30−1.87 (5H, m, CH_2), 1.96−2.14 (3H, m, CH_2), 2.2 (3H, s, $OCOCH_3$), 3.80 (3H, s, OCH_3), 5.68 (1H, s, C_3-*H*), 6.88 (2H, d, J = 9.1 Hz, Ar-*H*), 7.41 (2H, d, J = 9.1 Hz, Ar-*H*). ^{13}C NMR (50 MHz): δ 20.8, 23.4, 24.5, 29.9, 34.0, 55.4, 67.8, 79.6, 114.4, 122.0, 128.9, 157.2, 162.8, 169.6. MS (m/z): 303, 244, 200, 205, 215, 160, 149, 112. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.11; H, 6.92; N, 4.56.

(±)- 3-Hydroxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]-nonane 5. To a stirred mixture of 1 M KOH (50 mL) and THF (30 mL) at 0 °C was added 3-acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (0.9 g, 3.0 mmol) dissolved in 10 mL of THF dropwise over a period of 1 h. The reaction mixture was further stirred for another 1 h, and after completion of the reaction, it was diluted with 30 mL of THF and saturated solution of $NaHCO_3$. Extraction with ethyl acetate (3 × 50 mL), washing with water, drying, and evaporation under reduced pressure gave **5**. Yield: 712 mg (91%), mp 157−9 °C, IR (KBr), 3353, 2919, 1718, 1511, 1393, 1358, 1248, 1207, 1150, 1113. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−2.27 (10H, m, CH_2), 3.77 (3H, s, OCH_3), 4.58 (1H, s, C_3-*H*), 5.03 (1H, s, O*H*), 6.82 (2H, d, J = 9.0 Hz, Ar-*H*), 7.37 (2H, d, J = 9.0 Hz, Ar-*H*). ^{13}C NMR (50 MHz) δ 23.5, 24.1, 24.9, 29.7, 34.5, 55.4, 68.5, 81.8, 114.3, 121.8, 129.3, 156.9, 167.7. ESI-MS (m/z): 284 (M^+ + Na), 226, 172, 135.

(±)-3-Acetoxy-1-(4-methoxyphenyl)-7(*e*)-methyl-2-oxo-1-azaspiro[3.5]nonane 2a. Compound **2** was prepared from imine

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(4.34 g, 20.0 mmol), triethylamine (6.06 g, 60.0 mmol), and acetoxyacetyl chloride (3.3 g, 24.0 mmol) following the procedure described for **1**. Yield: 4.8 g (76%), mp 108−9 °C. IR (KBr): 2954, 2925, 2856, 1736, 1512, 1349, 1225, 1142, 1114, 1090, 1032, 936. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (1H, dq, CH_2), 0.92 (3H, d, J = 6.4 Hz, C7-CH_3), 1.31 (1H, m, C H_2), 1.40 (1H, m, C H), 1.75−1.86 (3H, m, C H_2), 2.05−2.15 (3H, m, C H_2), 2.22 (3H, s, OCOCH_3), 5.73 (1H, s, C-3H), 6.89 (2H, d, J = 9.0 Hz, Ar-H), 7.43 (2H, d, J = 9.0 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 20.8, 21.9, 29.6, 31.1, 31.7, 31.9, 33.8, 55.5, 79.7, 114.7, 121.9, 129.0, 157.2, 162.7, 169.6. MS (m/z): 317, 259, 229, 217, 214, 200, 186, 168, 160, 149, 126.

(±)-3-Acetoxy-1-(4-methoxyphenyl)-7(*a*)-methyl-2-oxo-1-azaspiro[3.5]nonane 2b. Compound **2b** was obtained as a minor product in the synthesis of **2a**. Yield: 95 mg (2%), mp 93 °C. IR (KBr): 2952, 1746, 1511, 1383, 1246, 1228. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (2H, d, J = 6.7 Hz, C7 CH_3), 1.43 (3H, m, CH_2), 1.73−1.82 (4H, m, CH_2), 2.17 (1H, m, CH_2), 2.19 (3H, s, OCOCH_3), 2.28 (1H, m, CH_2), 3.80 (3H, s, OCH_3), 5.59 (1H, s, C-3H), 6.89 (2H, d, J = 8.5 Hz, Ar-H), 7.36 (2H, d, J = 8.5 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 18.3, 20.7, 25.9, 26.9, 29.2, 29.3, 29.8, 55.5, 67.8, 80.1, 114.6, 123.7, 128.9, 157.8, 163.3, 169.8. MS (m/z): 317, 257, 229, 217, 214, 168, 160, 149, 126.

(±)-3-Acetoxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane 3a. Compound **3a** was prepared from imine (4.62 g, 20.0 mmol), triethylamine (6.06 g, 60.0 mmol), and acetoxyacetyl chloride (3.3 g, 24.0 mmol) following the procedure described for **1**. Yield: 5.0 g (75%), mp 65−66 °C. IR (KBr): 2935, 1755, 1513, 1463, 1443, 1484, 1248, 1222, 1032, 914, 858. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (1H, dq, J = 3.9, 7.8 Hz, CH_2), 0.84 (3H, t, J = 7.5 Hz, C7-CH$_2$CH_3), 1.15 (1H, m, C7- H), 1.20−1.26 (3H, m, C H_2), 1.82 (3H, m, CH_2), 2.05 (1H, dq, J = 4.5 Hz, CH_2), 2.19 (3H, s, OCOCH_3), 3.79 (3H, s, OCH_3), 5.67 (1H, s, C-3H), 6.87 (2H, d, J = 8.9 Hz, Ar-H), 7.41 (2H, d, J = 8.9 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 11.4, 20.8, 29.2, 29.3, 29.6, 29.8, 33.8, 37.9, 68.0, 114.5, 122.0, 129.1, 157.2, 162.7, 169.6. MS (m/z): 331, 272, 243, 219, 182, 160, 149, 140.

(±) 3-Acetoxy-7(*a*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane 3b. Compound **3b** was obtained as a minor product in the synthesis of **3a**. Yield: 135 mg (1.5%), mp 102−3 °C, IR (KBr): 2953, 1741, 1512, 1384, 1250, 1229, 1115, 1098, 1016, 940, 832. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.2 Hz, C7-CH$_2$CH_3), 1.32 (2H, quin, J = 6.8 Hz, CH_2), 1.41−1.52 (4H, m, C H_2), 1.70−1.82 (3H, m, CH_2), 2.07−2.15 (1H, m, CH_2), 2.20 (3H, s, OCOCH_3), 2.25 (1H, m, CH_2), 3.80 (3H, s, OCH$_3$), 5.59 (1H, s, C-3H), 6.89 (2H, d, J = 8.2 Hz, Ar-H), 7.35 (2H, d, J = 8.2 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 12.0, 20.7, 24.8, 26.1, 26.9, 27.0, 30.1, 34.1, 55.5, 67.9, 80.1, 114.6, 123.7, 128.9, 157.8, 163.3, 169.8. MS (m/z): (M^+ + 1) 332, 273, 183, 160, 149, 140.

(±)-3-Acetoxy-7(*e*)-(1,1-dimethylethyl)-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane 4a. Compound **4a** was prepared from imine (5.18 g, 20.0 mmol), triethylamine (6.06 g, 60.0 mmol), and acetoxyacetyl chloride (3.3 g, 24.0 mmol) following the procedure described for **1**. Yield: 6.1 g (85%), mp 127−9 °C. IR (KBr): 2968, 2937, 2866, 1745, 1513, 1388, 1297, 1244, 1221, 1118, 1035, 1015. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (9H, s, *tert*-butyl), 0.91 (1H, m, CH_2), 1.03 (1H, m, CH_2), 1.84−1.91 (3H, m, CH_2), 2.02−2.16 (3H, m, CH_2), 2.19 (3H, s, OCOCH_3), 3.79 (3H, s, OCH$_3$), 5.67 (1H, s, C-3H), 6.87 (2H, d, J = 8.5 Hz, Ar-H), 7.42 (2H, d, J = 8.5 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 20.7, 24.2, 24.3, 27.5, 29.9, 32.3, 34.2, 46.6, 55.5, 67.9, 79.7, 114.5, 121.8, 129.1, 157.1, 162.7, 169.4. MS (m/z): 359, 301, 284, 272, 260, 242, 216, 200, 168, 149, 94.

(±)-3-Hydroxy-1-(4-methoxyphenyl)-7(*e*)-methyl-2-oxo-1-azaspiro[3.5]nonane 6. Compound **6** was prepared by stirring a mixture of 1 M KOH (50 mL), THF (30 mL), and 3-acetoxy-1-(4-methoxyphenyl)-7(e)-methyl-2-oxo-1-azaspiro[3.5]nonane **2a** (951 mg, 3.0 mmol) following the procedure described for **5**. Yield: 775 mg (93%), mp 112−3 °C. IR (KBr): 3285, 2951, 2925, 2866, 1703, 1511, 1441, 1344, 1247, 1151, 1118, 1088, 1075, 1036, 833. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, d, J = 6.0 Hz, C7-CH_3), 1.26 (2H, m, CH_2), 1.43 (2H, m, C H_2), 1.68−1.75 (3H, m, CH_2), 1.98−2.21 (3H, m, CH_2), 3.77 (3H, s, OCH$_3$), 4.61 (1H, s, C-3H), 6.83 (2H, d, J = 9.0 Hz, Ar-H), 7.38 (2H, d, J = 9.0 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 21.9, 29.5, 31.5, 32.0, 32.4, 34.1, 55.4, 68.5, 81.4, 114.3, 121.8, 129.2, 157.0, 168.0. MS (m/z): 275, 257, 247, 229, 218, 202, 186, 160, 149, 126, 108, 93. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.53; H, 7.53; N, 5.13.

(±)-7(*e*)-Ethyl-3-hydroxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane 7. Compound **7** was prepared by stirring a mixture of 1 M KOH (50 mL) in THF (30 mL), and 3-acetoxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5] nonane **3a** (1.0 g, 3.0 mmol) following the procedure described for **5**. Yield: 800 mg (92%), mp 100−1 °C. IR (KBr): 3353, 3023, 2961, 2940, 2846, 1730, 1414, 1393, 1296, 1253, 1128, 1096, 1032, 947, 923, 808. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.5 Hz, C7-CH$_2$CH_3), 1.12−1.41 (5H, m, CH_2), 1.69−1.81 (3H, m, CH_2), 1.94−2.19 (3H, m, CH_2), 3.75 (3H, s, OCH$_3$), 4.58 (1H, s, C-3H), 6.81 (2H, d, J = 9.0 Hz, Ar-H), 7.37 (2H, d, J = 9.0 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 12.1, 29.6, 29.8, 30.1, 30.4, 34.4, 38.6, 55.8, 69.2, 81.9, 114.7, 122.1, 129.7, 157.2, 168.4. MS (m/z): 289, 232, 160, 149, 140, 134, 122, 93. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.81; H, 7.99; N, 4.76.

(*S*)-(−)-3-Hydroxy-7(*a*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-8. Compound **8** was obtained by resolution of **3b**, mp 144−46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.5 Hz, C7-CH$_2$CH_3), 1.25−1.40 (5H, m, CH_2), 1.69−1.81 (3H, m, C H_2), 1.95−2.22 (3H, m, CH_2), 3.78 (3H, s, OCH$_3$), 4.55 (1H, s, C-3H), 6.83 (2H, d, J = 9.2 Hz, Ar-H), 7.34 (2H, d, J = 9.2 Hz, Ar-H). ^{13}C NMR (100 MHz): δ 12.6, 24.2, 25.2, 26.9, 27.4, 29.7, 33.7, 55.5, 68.4, 81.8, 114.4, 122.6, 129.2, 157.2, 167.4. MS (m/z): (M^+ + 1) 290, 161, 149, 140, 135, 94. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.69; H, 7.97; N, 4.79.

(±)-7(*e*)-(1,1-Dimethylethyl)-3-hydroxy-2-oxo-1-(4-methoxyphenyl)-1-azaspiro[3.5]nonane 9. Compound **9** was prepared by stirring a mixture of 1 M KOH (40 mL), THF (25 mL), and 3-acetoxy-7(*e*)-(1,1-dimethylethyl)-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane **4a** (718 mg, 2.0 mmol) following the procedure described for **5**. Yield: 650 mg (91%), mp 180 °C. IR (KBr): 3426, 2931, 1722, 1513, 1392, 1297, 1249, 1080. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (9H, s, *tert*-butyl), 1.02 (1H, t, CH_2), 1.24 (1H, q, CH_2), 1.49 (1H, m, CH_2), 1.76−1.88 (3H, m, CH_2), 1.95 (1H, dt, J = 3.8 Hz, CH_2), 2.08 (1H, dt, J = 3.31, CH_2), 2.25 (1H, dd, J = 2.03 Hz, 2.17, CH_2), 3.77 (3H, s, OCH$_3$), 4.59 (1H, s, C-3H), 6.83 (2H, d, J = 8.8 Hz, Ar-H), 7.39 (2H, d, J = 8.9 Hz, Ar-H). ^{13}C NMR (125 MHz): δ 24.6, 25.0, 27.6, 29.8, 32.6, 34.5, 47.0, 55.4, 68.5, 81.6, 114.3, 121.7, 129.3, 156.9, 168.0. MS (m/z): 317, 168, 160, 149, 134, 94. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.79; H, 8.49; N, 4.46.

Methods for Enzyme-Catalyzed Resolution of Spiro-β-lactams. *(R)-(+)-3-Acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro-[3.5]nonane (+)-**1**.* (±)-3-Acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (0.4 g) was added to aqueous phosphate buffer (40 mL, 0.1 M, pH 7.0) and Tween 80 (1.0 g). To the above solution was added a wet pallet of a whole cell preparation of ABL (0.4 g, 1100 units/mg) with continuous shaking at 200 rpm. During the course of the reaction, the temperature was maintained at 30 ± 1 °C. Thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC) were carried out to monitor the progress of the reaction. After completion of the reaction (18−20 h approx., 49% conversion), the reaction was terminated by adding ethyl acetate and was extracted with ethyl acetate (3 × 30 mL). The organic layer was combined and washed with water. The combined organic solvent layer was then dried and evaporated under reduced pressure to furnish a mixture comprising hydrolyzed alcohol and unhydrolyzed ester, which was separated by column

chromatography (230−400 mesh silica gel) using dichloromethane and hexane as eluent giving (*R*)-(+)-3-acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**1** (180 mg, 90%) ee 99%, $[\alpha]_D^{25}$ +35.0 (*c* 1.0, $CHCl_3$) and (*S*)-(−)-3-hydroxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-**5** (160 mg, 92%) ee 99% (chiral HPLC), $[\alpha]_D^{25}$ −46.0 (*c* 1.0, $CHCl_3$).

*(R)-(+)-3-Acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**1***. (±)-3-Acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane **1** (100 mg) adsorbed on Celite (400 mg) and phosphate buffer (10 mL, 0.1M. pH 7.0) was placed in a 25 mL culture tube. To the above suspension was added a wet pallet of a whole cell preparation of ABL (100 mg) and was kept in orbital shaker at 200 rpm. During the course of the reaction, temperature was maintained at 25 ± 1 °C. Thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC) were carried out to monitor the progress of the reaction after every hour. After completion of the reaction (4 h approx., 49% conversion), the reaction was terminated. The usual workup and separation by CC gave (3*R*)-(+)-3-acetoxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**1** (47 mg, 94%) ee 99%, $[\alpha]_D^{25}$ +35.0 (*c* 1.0, $CHCl_3$) and (3*S*)-(−)-3-hydroxy-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-**5** (39 mg, 91%) ee 97% (chiral HPLC), $[\alpha]_D^{25}$ −46.0 (*c* 1.0, $CHCl_3$).

*(R)-(+)-3-Acetoxy-7(e)-methyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**2a***. (±)-3-Acetoxy-7(*e*)-methyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (100 mg) adsorbed on Celite (500 mg) was suspended in an aqueous phosphate buffer (5 mL, 0.1 M, pH 7.0). To the above solution was added 100 mg of a whole cell preparation of ABL. The reaction mixture was continuously shaken in an orbital shaker at 200 rpm and 25 ± 1 °C. The progress of the reaction was monitored by TLC and chiral HPLC every hour. The reaction was terminated after a certain degree of conversion (4 h approx., 41% conversion), and the usual workup gave (*R*)-(+)-3-acetoxy-7(*e*)-methyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**2a** (50 mg, 92%) ee 65%, $[\alpha]_D^{25}$ +21.5 (c 0.4, $CHCl_3$) and (*S*)-(−)-3-hydroxy-7(*e*)-methyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-6 (39 mg, 92%) ee 99%, $[\alpha]_D^{25}$ -66.2 (c 1.0, $CHCl_3$).

*(R)-(+)-3-Acetoxy-7(e)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**3a***. (±)-3-Acetoxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (50 mg) was suspended in aqueous phosphate buffer (5 mL, 0.1 M, pH 7.0). To the above solution were added 100 mg of a wet pallet of a whole cell preparation of ABL and 0.5 mL of DMF. The reaction mixture was stirred at 22 °C. The progress of the reaction was monitored by TLC and chiral HPLC. The reaction was terminated after a certain degree of conversion (36 h approx., 48% conversion), and the usual workup gave (*R*)-(+)-3-acetoxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**2a** (22 mg, 85%) ee 99%, $[\alpha]_D^{25}$ +30.4 (*c* 0.44, $CHCl_3$) and (*S*)-(−)-3-hydroxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-7 (19 mg, 92%) ee 99% (chiral HPLC), $[\alpha]_D^{25}$ −60.8 (*c* 0.38, $CHCl_3$).

*(R)-(+)-3-Acetoxy-7(e)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**3a***. (±)-3-Acetoxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (60 mg) adsorbed on Celite (250 mg) was suspended in an aqueous phosphate buffer (5 mL, 0.1 M, pH 7.0). To the above solution were added 200 mg of a whole cell preparation of ABL and 0.5 mL of acetonitrile. The reaction mixture was continuously shaken in an orbital shaker at 300 rpm and 22 ± 1 °C. Thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC) were carried out to monitor the progress of the reaction after every hour. After a certain degree of conversion (5 h approx., 43% conversion), the reaction was terminated by adding ethyl acetate. The usual workup and CC gave (*R*)-(+)-3-acetoxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**3a** (23 mg), ee 82%, $[\alpha]_D^{25}$ + 36.3 (*c* 0.5, $CHCl_3$) and (*S*)-(−)-3-hydroxy-7(*e*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-7 (19 mg, 92%), ee 99% (chiral HPLC), $[\alpha]_D^{25}$ −61 (*c* 0.5, $CHCl_3$).

*(R)-(+)-3-Acetoxy-7(a)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**3b***. Compound (+)-**3b** was resolved using the procedure mentioned for (+)-**3a** from (±)-3-acetoxy-7(*a*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (50 mg) adsorbed on silica/Celite (125 mg), aqueous phosphate buffer (2 mL, 0.1 M, pH 7.0), and lipase AS/ABL (50 mg) at 300 rpm and 24 ± 1 °C. After a certain degree of conversion (5.5 h approx., 33% conversion), the reaction was terminated by adding ethyl acetate. The usual workup gave (*R*)-(+)-3-acetoxy-7(*a*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**3b** (29 mg, 78%) ee 33%, $[\alpha]_D^{25}$ +7.0 (*c* 1, $CHCl_3$) and (*S*)-(−)-3-hydroxy-7(*a*)-ethyl-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]-nonane (−)-**8** (11.5 mg, 92%) ee 98% (chiral HPLC), $[\alpha]_D^{25}$ −35.5 (*c* 0.5, $CHCl_3$).

*(R)-(+)-3-Acetoxy-7(e)-(1,1-dimethylethyl)-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (+)-**4a***. Compound (+)-**4a** was resolved using the procedure mentioned for (+)-**1** from (±)-3-acetoxy-7(*e*)-(1,1-dimethylethyl)-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (100 mg) adsorbed on silica (500 mg), aqueous phosphate buffer (5 mL, 0.1M. pH 7.0), and lipase Amano AS (200 mg). The reaction mixture was shaken at 300 rpm and 23 ± 1 °C. After a certain degree of conversion (5 h approx., 42% conversion), the reaction was terminated by adding ethyl acetate. The usual workup gave (*R*)-(+)-3-acetoxy-7(*e*)-(1,1-dimethylethyl)-1-(4-methoxyphenyl)-2-oxo-1-azaspiro-[3.5]-nonane (+)-**4a** (53 mg, 91%) ee 67%, $[\alpha]_D^{25}$ +14.6 (*c* 1, $CHCl_3$) and (*S*)-(−)-3-hydroxy-7(*e*)-(1,1-dimethylethyl)-1-(4-methoxyphenyl)-2-oxo-1-azaspiro[3.5]nonane (−)-**9** (32 mg, 86%) ee 98.5% (chiral HPLC), $[\alpha]_D^{25}$ −60.0 (*c* 0.5, $CHCl_3$).

X-ray Crystallography. Compounds **2a**, **2b**, **3a**, **3b**, **4a**, and (−)-**5** were crystallized in CH_2Cl_2 at room temperature. The data were collected at 298 K on a Siemens P4 single crystal X-ray diffractometer using the XSCANS package. The data were collected by the $\theta-2\theta$ scan mode with a variable scan speed up to a maximum of $2\theta = 60°$ using graphite monochromatized Mo K_α radiations (λ = 0.71073 Å). To monitor the stability of the crystal, 3 standard reflections were measured after every 97 reflections. The data were corrected for Lorentz and polarization effects.

The structures were solved by direct methods using SIR97[16] and refined by full-matrix least-squares refinement techniques on F^2 using SHELXL-97[17] in the WINGX package[18] of programs. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were attached, geometrically riding on their respective carrier atoms with U_{iso} being 1.5, 1.2, and 1.2 times the U_{iso} of their carrier methyl, methylene, and aromatic carbon atoms, respectively. The crystal data and refinement details are given in Supporting Information.

Computational Methods. Ab initio density functional calculations (DFT)[19] have been performed to obtain absolute energies of the important species referred to in this article. Complete optimizations have been performed on all the structures using the B3LYP method[20] and 6-31+G(d) basis set using the Gaussian03 software.[21]

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data, X-ray structures, computational data, and cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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