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Stereochemistry and Mechanistic Insight in the [2^k+2^i+2^i] Annulations of Ketenes and Imines

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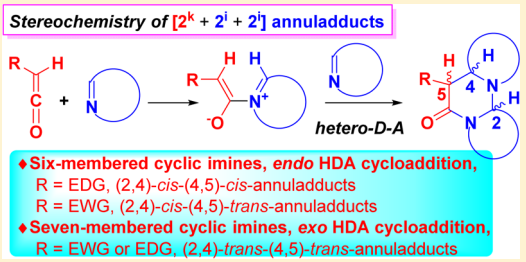
Supporting Information

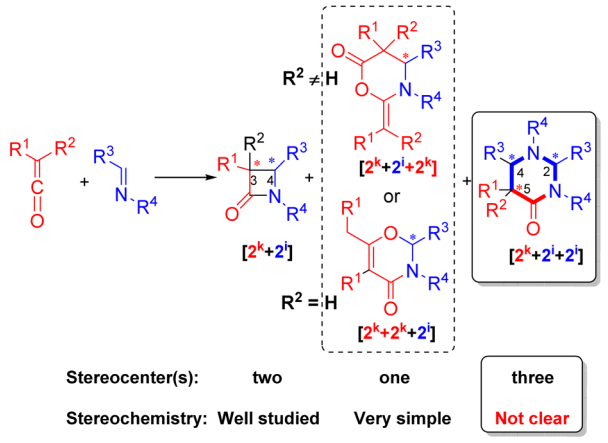
ABSTRACT: The stereochemistry and mechanistic insight in the annulations of one ketene molecule with two imine molecules ([2^k+2^i+2^i] annulation) are studied by using six-membered 3,4-dihydroisoquinoline as an imine probe. A concerted hetero-Diels–Alder cycloaddition mechanism is proposed to explain the stereochemical outcomes. In most cases, the zwitterionic 2-aza-1,3-butadiene-type intermediates, generated from ketenes and imines, undergo *endo* hetero-Diels–Alder cycloaddition with the second imine molecule. For ketenes with electron-donating substituents, (2,4)-*cis*-(4,5)-*cis*-[2^k+2^i+2^i] annuladducts formed stereospecifically, while, for ketenes with electron-accepting substituents, (2,4)-*cis*-(4,5)-*trans*-[2^k+2^i+2^i] annuladducts are generated stereospecifically. The [2^k+2^i+2^i] annulations of aryloxyketenes and 3,4-dihydroisoquinoline give stereodivergent products due to the occurrence of the stepwise nucleophilic annulation. However, in the [2^k+2^i+2^i] annulations of seven-membered cyclic imine dibenzo[*b*,*f*][1,4]oxazepine, the zwitterionic aza-butadiene-type intermediates exclusively undergo *exo* hetero-Diels–Alder cycloadditions with another molecule of imine to yield (2,4)-*trans*-(4,5)-*trans*-[2^k+2^i+2^i] annuladducts stereospecifically, regardless of the ketene substituents. The mechanistic model not only discloses the nature of the [2^k+2^i+2^i] annulations, but also can be used to explain and predict the stereochemistry of the [2^k+2^i+2^i] annuladducts from different ketenes and imines.



INTRODUCTION

The Staudinger cycloadditions between ketenes and imines have proven to be a powerful tool for the construction of *β*-lactams backbones,[1] which serve as key structural features in a series of antibiotics.[2] However, experimental results from several groups have demonstrated that there exist four annuloselective reaction pathways in the Staudinger cycloadditions depending upon the substituent effect of ketenes and imines: (1) [2^k+2^i] annulations between one ketene molecule and one imine molecule;[1] (2) [2^k+2^i+2^k] annulations between two molecules of disubstituted ketenes ($R^2 \neq H$) and one imine molecule;[3] (3) [2^k+2^k+2^i] annulations between two molecules of monosubstituted ketenes ($R^2 = H$) and one imine molecule;[4] and (4) [2^k+2^i+2^i] annulations between one ketene molecule and two imine molecules (Scheme 1).[5] The [2^k+2^i] annulations generate two stereocenters at the C3 and C4 positions of the *β*-lactam rings, and the stereoselectivity has been studied systematically by others[6] and our group,[7] and a comprehensively stereoselective rule was proposed by us.[5g,7a] The [2^k+2^i+2^k] and [2^k+2^k+2^i] annulations yield 2-(alkan-2-ylidene)-1,3-oxazinan-6-ones and 2,3-dihydro-1,3-oxazin-4-ones, respectively, bearing only one stereocenter in each kind of products, and the stereochemistry is quite simple. However, the [2^k+2^i+2^i] annulations give rise to substituted tetrahydropyrimidin-4(1*H*)-ones with three stereocenters ($R^1 \neq R^2$) at the C2, C4, and C5 positions (Scheme 1). The stereochemistry in this case seems to be more complex, and to date very few studies on the stereochemistry have been reported.[5b,i]

Scheme 1. Annuloselectivities and Stereochemistry of Each Kind of Product in the Ketene–Imine Reactions



In view of the significant importance of tetrahydropyrimidin-4(1*H*)-one derivatives in synthetic and medicinal chemistry (Figure 1),[8] the stereochemistry in the products of the [2^k+2^i+2^i] annulations is one of the major issues in this field.

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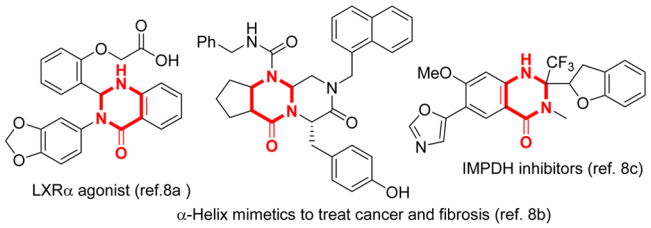

Figure 1. Representative tetrahydropyrimidin-4(1*H*)-ones in medicinal chemistry and therapic clinics.

The detailed stereostructures at C2, C4, and C5 stereocenters, as well as the mechanism for the generation of the stereochemistry, still remain a mystery. Herein, using 3,4-dihydroisoquinoline as an imine probe to react with various ketenes substituted by sterically and electronically different groups, we shed light on the stereochemistry in the $[2^k+2^i+2^i]$ annulations, and propose a plausible mechanism to explain and to further predict the stereochemical outcomes.

RESULTS AND DISCUSSION

Experimental Studies on the Stereochemistry. The stereochemistry studies commenced with pursuing a suitable imine probe to react with a series of ketenes to give predominantly or exclusively $[2^k+2^i+2^i]$ annulation products (annuladducts) in high yields. In our previous work,[5f−h] we reported that the Staudinger reactions of cyclic imines 3,4-dihydroisoquinoline (**1a**) and dibenzo[*b*,*f*][1,4]oxazepine (**1b**) with ketenes gave the corresponding $[2^k+2^i+2^i]$ annuladducts in satisfactory (76%) and low (7−12%) yields, respectively. These facts reveal that cyclic imine **1a** is more inclined to undergo the $[2^k+2^i+2^i]$ annulations than cyclic imine **1b**. Therefore, herein, we chose 3,4-dihydroisoquinoline (**1a**) as the imine probe, and reacted it with a variety of ketenes generated by photoinduced Wolff rearrangements of α-aminomethyl diazomethyl ketones **2a**,**b**, diazoacetates **2c**−**g**, diazoacetophenone (**2h**), 3-diazo-2-oxo-propanoate **2i**, and propanamides **2j**,**k** (Figure 2),[9] to

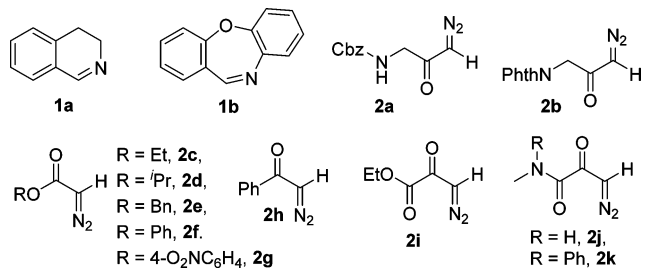

Figure 2. Selected ketene precursors and imine probes in the stereochemical investigations on $[2^k+2^i+2^i]$ annulations.

probe the $[2^k+2^i+2^i]$ annulations. The reactions were performed following our previous experimental procedures.[5f,g] The stereostructures of the $[2^k+2^i+2^i]$ annuladducts were assigned according to the coupling constants between the protons at C4 and C5 positions (J = 9−11 Hz for *trans*-isomers, J = 5−6 Hz for *cis*-isomers, generally) together with the observed NOE values between the protons at C2 and C4 positions (see Table 1). Assigning the stereostructures by this method is viable, as demonstrated by the XRD analysis of compound **4m** (vide post, Scheme 6).

As summarized in Table 1, we give our observations. To more directly, simply, and clearly describe the stereochemistry, we used the *cis*- and *trans*-terminology rather than the *rel*(*R*,*S*) terminology, for example, used (2,4)-*cis*-(4,5)-*cis*-**4a** rather than *rel*(4b*R*,5*S*,13b*R*)-**4a**. The reaction between ketene **3a** and **1a** annulospecifically forms the $[2^k+2^i+2^i]$ annuladduct (2,4)-*cis*-(4,5)-*cis*-**4a** in 17% yield (Table 1, entry 1). Analogously, the annulospecific adduct **4b** exhibits the same stereochemistry as **4a** (Table 1, entry 2). For ketenes with strong electron-donating alkoxy groups such as ethoxy (**3c**), isopropoxy (**3d**), and benzyloxy (**3e**), the reactions proceed in the following two directions (Table 1, entries 3−5): (i) $[2^k+2^i+2^i]$ annulations affording stereospecific (2,4)-*cis*-(4,5)-*cis*--tetrahydropyrimidin-4(1*H*)-ones **4c**, **4d**, and **4e** in 7%, trace, and 36% yields, respectively; and (ii) $[2^k+2^i]$ annulations delivering stereospecific *trans*-β-lactams **5c**, **5d**, and **5e** in 26%, 14%, and 7% yields, respectively. However, the ketene **3f** substituted by a weakly electron-donating phenoxy group favorably underwent stereodivergent $[2^k+2^i+2^i]$ annulations (Table 1, entry 6), and two diastereomeric tetrahydropyrimidin-4(1*H*)-ones (2,4)-*cis*-(4,5)-*cis*-**4fa** and (2,4)-*cis*-(4,5)-*trans*-**4fb** were obtained in 30% and 55% yields, respectively, as well as the $[2^k+2^i]$ cycloadduct **5f** in 12% yield. The reaction of 4-nitrophenoxyketene (**3g**), however, gave rise to not only the expected (2,4)-*cis*-(4,5)-*trans*-**4gb** in 36% yield, but also a surprising (2,4)-*trans*-(4,5)-*trans*-**4gc** in 19% yield (Table 1, entry 7).[10] Subsequently, we investigated the stereochemistry of the $[2^k+2^i+2^i]$ annuladducts generated from a variety of electron-withdrawing group (EWG)-substituted ketenes **3h**−**k** and imine **1a** (Table 1, entries 8−11). The $[2^k+2^i+2^i]$ annulations of these ketenes occurred smoothly, and all gave rise to the corresponding (2,4)-*cis*-(4,5)-*trans*-tetrahydropyrimidin-4(1*H*)-ones **4h**−**k** in 31−67% total yields stereospecifically (Table 1, entries 8−11). The reaction of the sterically bulky ketene **3k** furnished three rotamers **4ka**, **4kb**, and **4kc** (Table 1, entry 11). Notably, $[2^k+2^i]$ cycloadduct β-lactam (**5h**, only a trace amount, Table 1, entry 8) was observed in the reaction of phenylketene (**3h**), but not in the other reactions of EWG-substituted ketenes **3g**,**i**−**k** (Table 1, entries 9−11).

Nature of the $[2^k+2^i+2^i]$ Annulations and Key Intermediates. The stereochemical analyses of the $[2^k+2^i+2^i]$ annulations in Table 1 disclose that the $[2^k+2^i+2^i]$ annulations of most ketenes with imines give stereospecific outcomes. To explain the observed stereospecificity, and to better understand the nature of the selective $[2^k+2^i+2^i]$ annulations, we need a full understanding of the involved key intermediates. As delineated in Scheme 2, under photoirradiation, the ketene precursor diazo compounds **2a**−**k** first undergo Wolff rearrangements to form the corresponding ketenes **3a**−**k**, which were *exo* attacked by the nucleophilic imine **1a** to generate zwitterionic aza-butadiene-type intermediates **6**. Probably because of the geometry and ring strain of the cyclic iminium moiety, the conrotatory ring closure of intermediates **6** is decreased. Only in the reactions of ketenes **3c**−**f** bearing strong electron-donating groups (EDGs) does the conrotatory ring closure occur, giving *trans*-β-lactams **5c**−**f** in considerable yields, because the electron-donating ketene substituents accelerate the ring closure,[7a] to some extent counteracting the adverse effect imposed by the cyclic iminium. In all cases in Table 1, as a result of the decreased direct conrotatory ring closure by the cyclic iminum moiety, the intermediates **6** have the opportunity to undergo [4+2] annulations with another molecule of imine **1a**, giving $[2^k+2^i+2^i]$ annuladducts tetrahydropyrimidin-4(1*H*)-ones **4**.[11] The [4+2] annulations proceed in either a concerted fashion or

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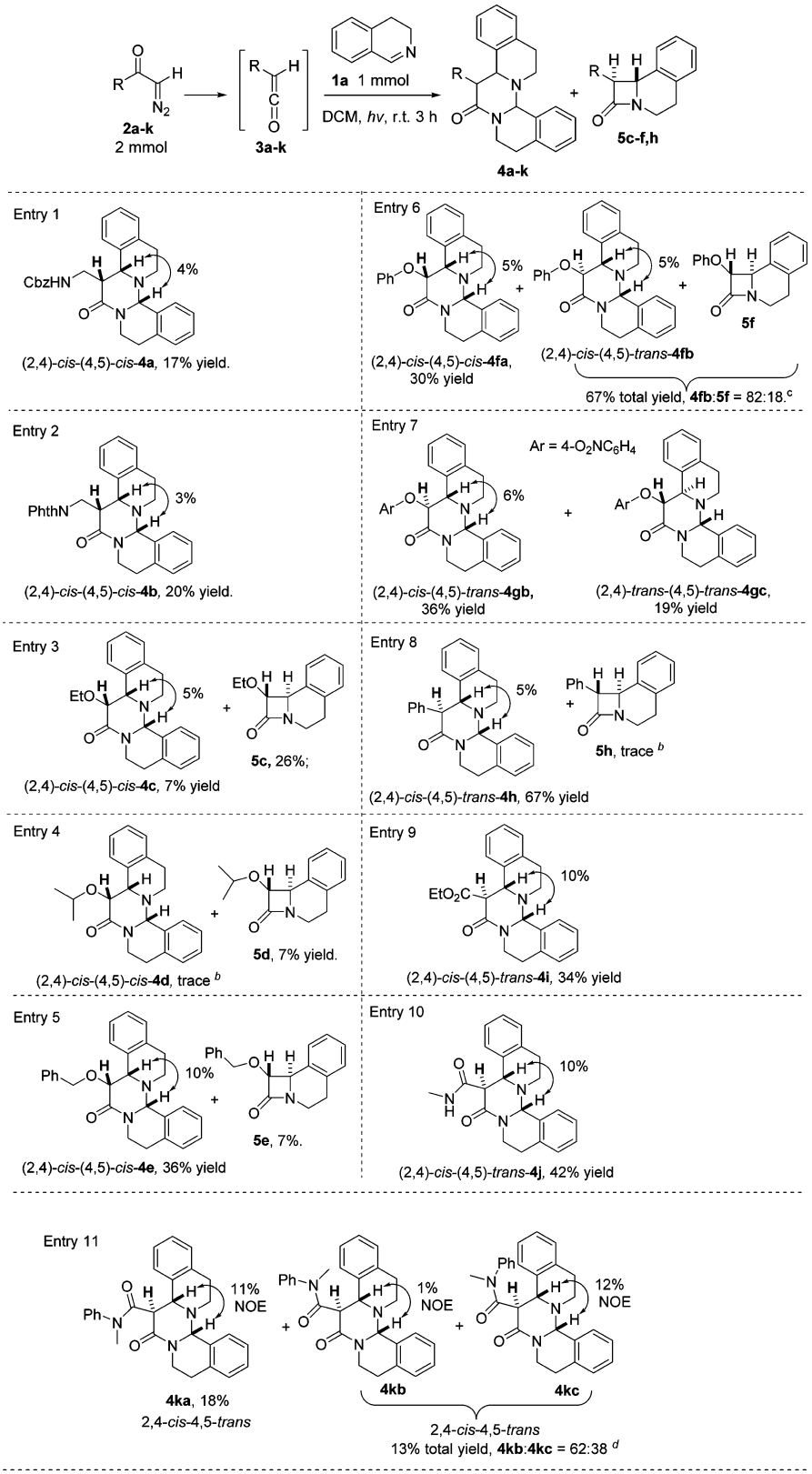
Table 1. [2^k+2^i+2^i] Annuladducts and Their Stereochemistry in the Annulations of Imine 1a with Different Ketenes 3[a]



[a]The stereostructures of the [2^k+2^i] cycloadducts β-lactams were assigned on the basis of the coupling constants between the protons at the C3 and C4 positions (J = 4−6 Hz for *cis*-isomers, J = 0−3 Hz for *trans*-isomers, generally). The percentages after the compound numbers are the isolated yields, while those beside the double-headed arrows are the NOE values between the two protons. [b]These compounds were isolated in a trace amount together with various impurities, as indicated by the ^{1}H NMR spectrum. Further purification of them failed. [c]Ratios were determined by the corresponding ^{1}H NMR spectra. [d]The less congested structure **4kb** was assigned as the major product.

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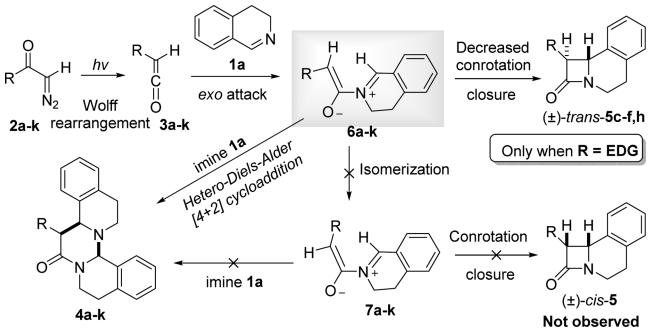
Scheme 2. Key Intermediates in the $[2^k+2^i+2^i]$ Annulations of Ketenes and Imines

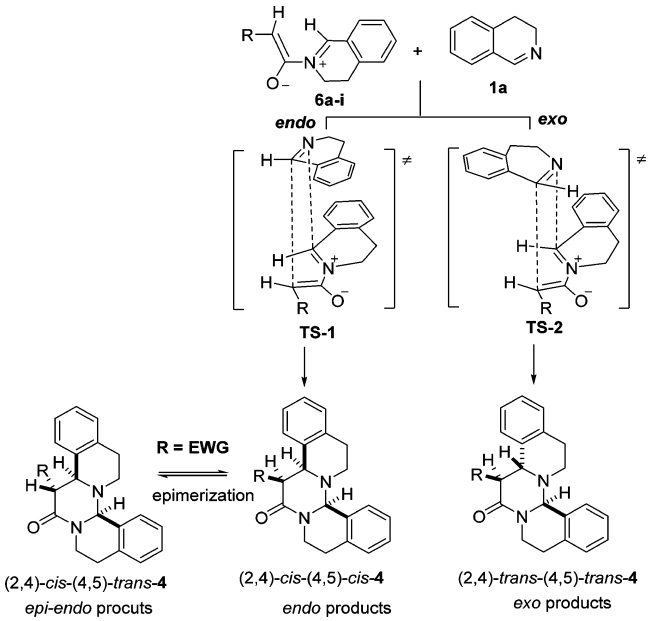


a stepwise nucleophilic addition. Within this context, the stereochemical outcomes of the $[2^k+2^i+2^i]$ annulations will be discussed in the following.

In our opinion, the stability of the zwitterionic intermediates **6**,[12] which act as 4π donors in the subsequent hetero-Diels–Alder cycloadditions, should be further clarified: whether they can isomerize over the C=C bond in the enolate moiety to form intermediates **7**. If the isomerization occurs, the *cis*-β-lactams **5** would be generated via the conrotatory ring closure of **7**. However, in all reactions listed in Table 1, *cis*-β-lactams **5** were not detected at all, ruling out the intermediacy of intermediates **7**. This conclusion is further supported by the accumulated evidence in our previous work on the reactions of ketenes and numerous cyclic imines.[5f−h,7] According to our previous DFT calculation and the current stereochemical outcomes,[5i] it can be put that the [4+2] annulations between intermediates **6** and cyclic imine **1a** probably take place through a concerted hetero-Diels–Alder cycloaddition.

Explanation on the Mechanism and Stereochemistry of the $[2^k+2^i+2^i]$ Annulations. From a Diels–Alder cycloaddition perspective, the models to explain the stereochemistry of the $[2^k+2^i+2^i]$ annulations listed in Table 1 are proposed and presented in Scheme 3. Because the [4+2] cycloadditions between intermediates **6** and imines **1** have been proposed to follow a concerted process, the two plausible transition states **TS-1** and **TS-2** are put forward. The *endo* cycloadditions through **TS-1** afford *endo* products (2,4)-*cis*-(4,5)-*cis*-**4**, while the *exo* cycloadditions through **TS-2** afford *exo* products (2,4)-*trans*-(4,5)-*trans*-**4**. We envision that (2,4)-*cis*-(4,5)-*cis*-**4** could epimerize into the *epi-endo* products (2,4)-*cis*-(4,5)-*trans*-**4** because the acidity of the protons adjacent to the carbonyl group is strong, especially when R is a strong EWG. This has been verified by a preliminary DFT calculation at the M06-2X and B3LYP levels of theory by taking *endo* product (2,4)-*cis*-(4,5)-*cis*-**4h** and *epi-endo* product (2,4)-*cis*-(4,5)-*trans*-**4h** as the examples, with substituent R as a weakly electron-withdrawing phenyl group. The free energy (ΔG) of the former *endo* product is 3.19 kcal/mol higher than the latter *epi-endo* product, indicating that the epimerization should occur smoothly. So a plausible explanation to the stereochemistry is given as follows. The hetero-Diels–Alder cycloadditions of intermediates **6a−k** generated from ketenes **3a−k** and imine **1a** all undergo *endo* cycloadditions to afford (2,4)-*cis*-(4,5)-*cis*-**4**, following the *endo* rule; however, for (2,4)-*cis*-(4,5)-*cis*-**4a−e**, no epimerization occurs, mainly because of the electron-donating Cbz-aminomethyl, phthalimidomethyl, ethoxy, isopropoxy, and benzyloxy substituents, and thus these *endo* cycloadducts survive and stay as the stereospecific formal

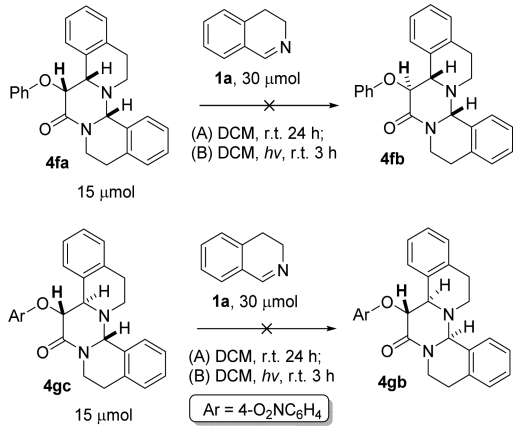
Scheme 3. Proposed Concerted Hetero-Diels–Alder Cycloaddition To Explain the Stereochemical Outcomes in the $[2^k+2^i+2^i]$ Annulations



$[2^k+2^i+2^i]$ cycloadducts (Table 1, entries 1−5). However, when strong EWGs appear at the α-positions of the *endo* cycloadducts, for example, (2,4)-*cis*-(4,5)-*cis*-**4h−k**, they were completely converted into the corresponding (2,4)-*cis*-(4,5)-*trans*-**4h−k** via epimerization, showing another form of stereospecificity (Table 1, entries 8−11).

However, exceptions exist in the formal $[2^k+2^i+2^i]$ cycloaddition of ketenes **3f** and **3g** with EDGs rather than EWGs, with two $[2^k+2^i+2^i]$ annuladducts in each case formed stereodivergently (Table 1, entries 6 and 7). The above concerted hetero-Diels–Alder cycloaddition model cannot explain the presence of (2,4)-*cis*-(4,5)-*trans*-**4fb** and **4gb**. As depicted in Scheme 4, at room temperature, the purified (2,4)-*cis*-(4,5)-*cis*-**4fa** with 2 equiv of imine **1a** was stirred for 24 h, or photoirradiated for 3 h; however, no epimerized (2,4)-*cis*-(4,5)-*trans*-**4fb** was detected by the ^{1}H NMR spectral analysis of the reaction mixtures, implying that the product **4fb** is generated through another pathway rather than through hetero-Diels–

Scheme 4. Epimerization Experiments of (2,4,5)-*cis*-4fa to (2,4)-*cis*-(4,5)-*trans*-4fb



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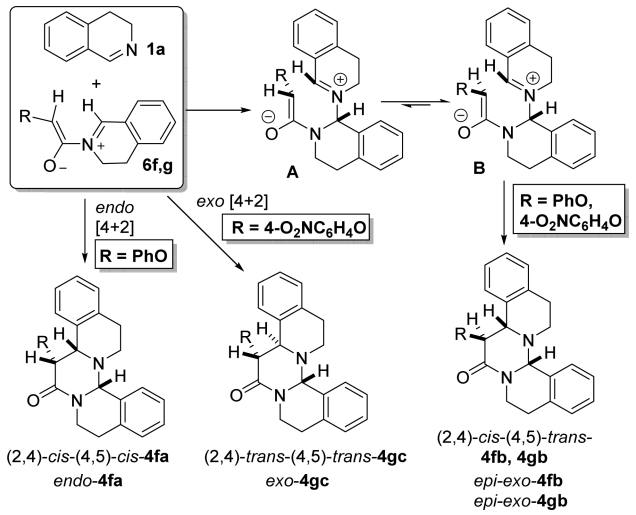
Alder cycloaddition and subsequent epimerization. A similar problem also exists in explaining the stereochemistry of (2,4)-*cis*-(4,5)-*trans*-**4gb**, which cannot undergo epimerization between (2,4)-*trans*-(4,5)-*trans*-**4gc**, under the conditions listed in Scheme 3. Therefore, we believe that (2,4)-*cis*-(4,5)-*trans*-**4fb** and **4gb** are generated by a stepwise [4+2] annulation between **6f,g** and **1a**.

From nucleophilic stepwise [4+2] annulations, the stereochemistry of the $[2^k+2^i+2^i]$ annuladducts **4fb** and **4gb** is reasonably rationalized in Scheme 5. The [4+2] annulations

Scheme 5. Proposed Explanation on the Stereochemical Outcomes in the $[2^k+2^i+2^i]$ Annulations



were initiated by the Mannich-type addition of imine **1a** to intermediates **6f,g** to afford zwitterionic 2,4-diaza-1,5-hexadiene-type intermediates **A**. Different from the 4π intermediates **6**, **A** may isomerize to the sterically less congested and thermodynamically more stable enolate intermediates **B** under photo conditions because they are not conjugated systems, unlike conjugated 4π intermediates **6**. Subsequently, **B** undergoes an intramolecular nucleophilic addition, leading to (2,4)-*cis*-(4,5)-*trans*-**4fb**,**4gb** as the $[2^k+2^i+2^i]$ annuladducts. However, the concerted hetero-Diels–Alder cycloaddition is in competition with the stepwise nucleophilic addition. The reaction of **6f** (R = PhO) with **1a** alternatively undergoes an *endo* concerted [4+2] cycloaddition to afford (2,4)-*cis*-(4,5)-*cis*-**4fa**, while the reaction of **6g** (R = 4-$O_2NC_6H_4O$) with **1a** alternatively undergoes an *exo* concerted [4+2] cycloaddition to afford (2,4)-*trans*-(4,5)-*trans*-**4gc**. Surprisingly, in the studies in Table 1, only the reaction of 4-nitrophenoxyketene (**3g**) gave the *exo* cycloadduct **4gc**. The nitro group plays an important role in effecting the *exo* selectivity in the hetero-Diels–Alder cycloaddition. The energy profiles for the [4+2] cycloadditions of intermediates **6f,g** with imine **1a** at the M06-2X and B3LYP levels of theory were calculated, and the results are summarized in Figure 3. For the cycloaddition between **6f** (R = PhO) and **1a**, the possible *endo* and *exo* transition states *endo*-**TS1-f** and *exo*-**TS2-f** are formed with 13.34 and 20.97 kcal/mol activation free energy, respectively, indicating that the *endo* cycloaddition is favored. However, the presence of the nitro group in **6g** (R = 4-$O_2NC_6H_4O$) renders 19.85 and 17.36 kcal/mol activation free energy for *endo*-**TS1-g** and *exo*-**TS2-g**, respectively, indicating that *exo* cycloaddition is favored. The calculations also revealed that both *endo* and *exo* cycloadditions occur in a

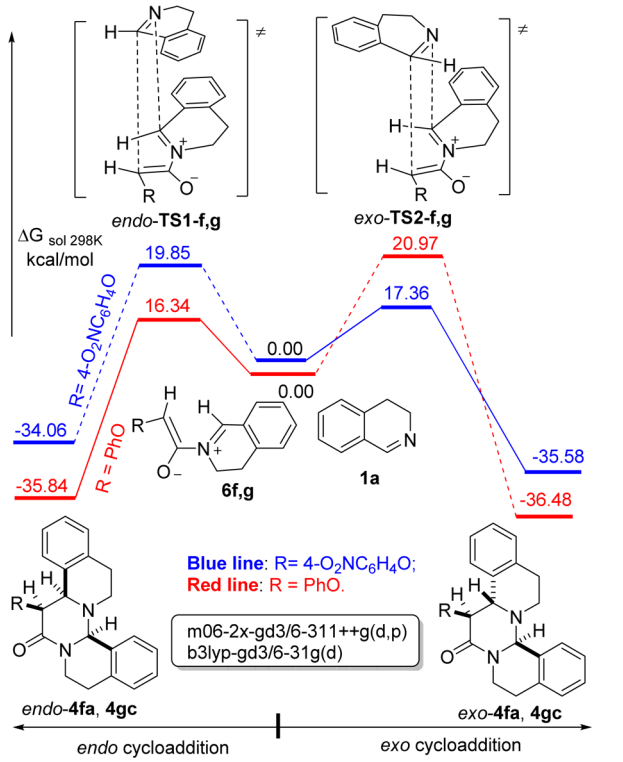


Figure 3. Calculated energy profiles for the [4+2] cycloadditions of intermediates **6f,g** with imine **1a** at the M06-2X and B3LYP levels of theory.

concerted but asynchronous fashion (for details, see the Supporting Information). However, the attempts in calculating the stepwise pathways failed, and we did not succeed in getting the TSs in this pathway possibly because of a favorable concerted pathway.

The zwitterionic intermediates **6** are synthetically analogous to the neutral and isolable 3-trialkylsilyloxy-2-aza-1,3-dienes.[13] On one hand, both of them can undergo conrotatory ring closure to form four-membered β-lactams. On the other hand, **6** can undergo [4+2] annulations with another imine molecule, in most cases following a concerted hetero-Diels–Alder cycloaddition pathway, even though sometimes a stepwise mechanism involving intermolecular Mannich-type addition and intramolecular nucleophilic addition is more likely. Similarly, the 3-trialkylsilyloxy-2-aza-1,3-dienes can also undergo [4+2] annulations with ketenes, following either a concerted hetero-Diels–Alder cycloaddition process or a two-step Mukaiyama-type process.

Role of Photoirradiation in the $[2^k+2^i+2^i]$ Annulations. The precedented $[2^k+2^i+2^i]$ annulations occurred mainly under photoirradiation conditions.[5] Thus, one may think the photoirradition possibly plays an important role in the reactions, for example, exciting the ground state of the 4π intermediates or imines, or something else. However, the above mechanistic studies reveal that photoirradiation does play a role in the ketene generation step, but not in the subsequent evolution of ketenes. To demonstrate this assumption, we performed the reactions under thermal conditions at room temperature by employing the corresponding acyl chlorides **2l** and **2m** as ketene precursors. The $[2^k+2^i+2^i]$ annulations of ketenes **3i** and **3m** took place smoothly, stereospecifically

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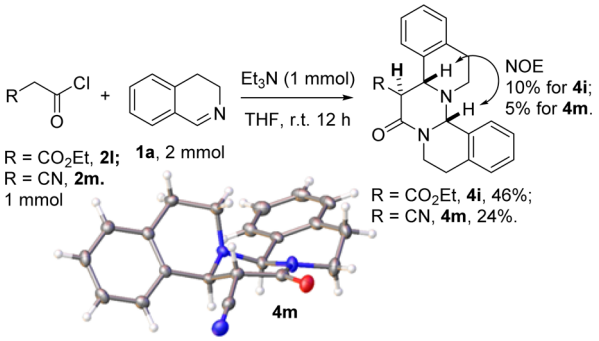
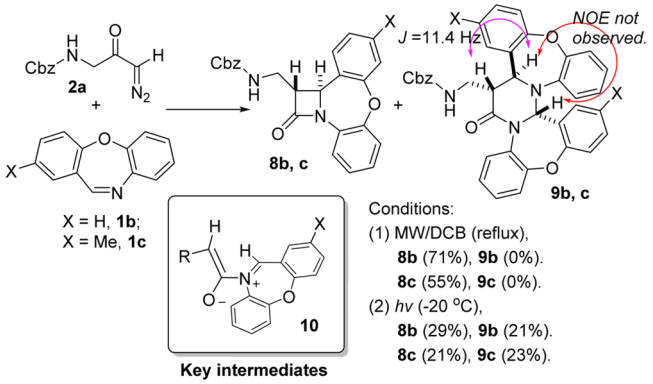
producing the annuladducts (2,4)-*cis*-(4,5)-*trans*-**4l** and **4m** in 46% and 24% yields, respectively (Scheme 6).

Scheme 6. [2^k+2^i+2^i] Annulations with Acyl Chlorides as Ketene Precursors



Actually, the [2^k+2^i+2^i] annulations in our previous work were affected by temperature, but not photoirradiation.[5f] Studies from our groups have disclosed that the conrotation of the zwitterionic intermediates in the Staudinger ketene−imine cycloadditions is closely associated with temperature: the higher is the temperature, the faster is the conrotation.[7] As shown in Scheme 7, at high temperature (180 °C) without

Scheme 7. Annuloselectivities in the Thermal and Photo Staudinger Ketene−Imine Cycloadditions



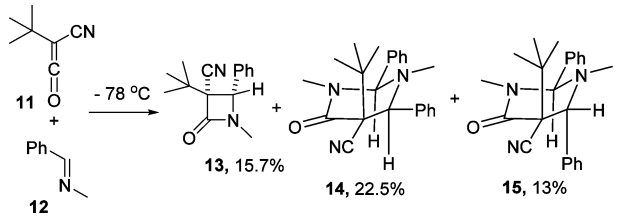
MW = microwave, *hv* = photoirradiation, DCB = 1,2-dichlorobenzene.

photoirradiation, the zwitterionic intermediates **10**, which were generated from ketenes and imines **1b,c**, underwent a rapid intramolecular conrotation to form *β*-lactams **8b,c**, outcompeting the intermolecularly stepwise nucleophilic [4+2] annulations between **10** and **1b,c**, and no [2^k+2^i+2^i] annulations occurred. However, under photoirradiation at low temperature (−20 °C), the conrotation was significantly decreased, leading to the occurrence of the competent intermolecular [4+2] annulations, and consequently both [2^k+2^i] and [2^k+2^i+2^i] annuladducts (**8b,c** and **9b,c**) were isolated. On the basis of our previously reported coupling constants of the protons in C4 and C5 positions in the ^{1}H NMR spectra (J = 11.4 Hz)[5f,g] and X-ray crystallography,[5i] and the current NOE analysis of the protons at C2 and C4 positions, the stereochemistry of the [2^k+2^i+2^i] annuladducts was assigned as (2,4)-*trans*-(4,5)-*trans*. Similarly, the reactions of ketenes **3j** and **3k** with seven-membered cyclic imines **1b** or **1c** also gave the [2^k+2^i+2^i] annuladducts with the same (2,4)-*trans*-(4,5)-*trans* stereochemistry.[5g,i]

APPLICATION OF OUR MODEL

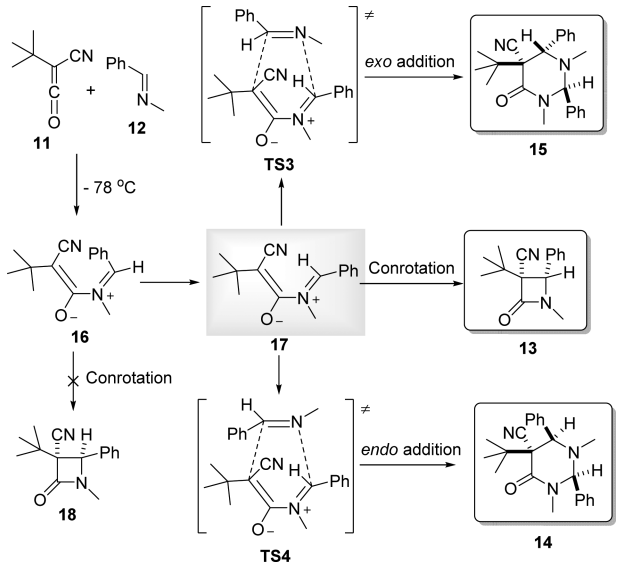
In 1977, Joullie's group reported three different annuladducts in the reaction between *tert*-butylcyanoketene (**11**) and linear imine *N*-benzylidene methylamine (**12**) (Scheme 8).[5b] At −78

Scheme 8. Jullie and Coworkers' Experimental Studies on the [2^k+2^i+2^i] Annuladducts from *tert*-Butylcyanoketene and Linear Imines



°C, the reaction gave *cis*-*β*-lactam **13** in 15.7% yield and two [2^k+2^i+2^i] annuladducts **14** in 22.5% yield and **15** in 13% yield. The stereochemical structures of **13**, **14**, and **15** were well assigned by the NOE studies. However, Joullie and co-workers did not propose a mechanism to explain and to further predict the stereochemical outcomes. Now our mechanistic model can successfully be applied to explain their results (Scheme 9). The

Scheme 9. Explanation on the Stereochemistry of [2^k+2^i+2^i] Annuladducts with Our Mechanistic Model



absence of *trans*-*β*-lactam **18** and the presence of *cis*-*β*-lactam **13** indicate that the key and long-lived intermediate is not **16**, but **17**, which is formed by isomerization of the iminium moiety of **16**. On one hand, conrotation of **17** gives *cis*-*β*-lactam **13**. On the other hand, **17** undergoes *exo* and *endo* hetero-Diels−Alder cycloadditions through transition states **TS3** and **TS4**, producing [2^k+2^i+2^i] annuladducts **15** and **14** in their own configurations, respectively. The configuration of the [2^k+2^i+2^i] annuladducts predicted by our model matches very well with those experimentally observed by Joullie and co-workers.

CONCLUSIONS

The stereochemistry in the [2^k+2^i+2^i] annulations involving one ketene molecule and two imine molecules was studied

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experimentally and analyzed mechanistically. The zwitterionic aza-butadiene-type intermediates, generated from ketenes and imines, in most cases underwent hetero-Diels–Alder cycloaddition with a second imine molecule, forming $[2^k+2^i+2^i]$ annuladducts tetrahydropyrimidin-4(1*H*)-one derivatives. Dependent on the ring-size of the cyclic imines and the substituents of ketenes, the stereochemistry and mechanism follow the empirical rules as following.

For the $[2^k+2^i+2^i]$ annulations of six-membered cyclic imines as exemplified by 3,4-dihydroisoquinoline, the generated zwitterionic aza-butadiene-type intermediates **6** mainly undergo *endo* hetero-Diels–Alder cycloadditions with another molecule of imines. For the ketenes with electron-donating substituents, (2,4)-*cis*-(4,5)-*cis*-$[2^k+2^i+2^i]$ annuladducts are formed stereospecifically. For the ketenes with electron-accepting substituents, (2,4)-*cis*-(4,5)-*trans*-$[2^k+2^i+2^i]$ annuladducts are finally generated stereospecifically by the complete epimerization of the (2,4)-*cis*-(4,5)-*cis*-products. For ketenes with aryloxy substituents, the $[2^k+2^i+2^i]$ annuladducts are generated stereodivergently, and the stereochemistry is difficult to predict. In this case, the [4+2] annulation of the corresponding zwitterionic aza-butadiene-type intermediates with the six-membered imines could follow *endo* or *exo* hetereo-Diels–Alder cycloaddition process and a two-step nucleophilic addition process.

For the $[2^k+2^i+2^i]$ annulations of seven-membered cyclic imines as exemplified by dibenzo[*b*,*f*][1,4]oxazepine, the zwitterionic aza-butadiene-type intermediates **10** exclusively undergo *exo* hetero-Diels–Alder cycloadditions with another molecule of imines. Consequently, regardless of the ketene substituents, (2,4)-*trans*-(4,5)-*trans*-$[2^k+2^i+2^i]$ annuladducts are formed stereospecifically.

The $[2^k+2^i+2^i]$ annulations of *N*-methyl linear imines with *tert*-butylcyanoketene deliver both (2,4)-*trans*-(4,5)-*trans*- and (2,4)-*cis*-(4,5)-*cis*-$[2^k+2^i+2^i]$ annuladducts, as the *exo* and *endo* Diels–Alder cycloadducts, respectively, of intermediates **17** with another molecule of *N*-methyl imines.

The current mechanistic model not only explains the nature of the $[2^k+2^i+2^i]$ annulations, but also provides a useful tool to predict the stereochemistry of the $[2^k+2^i+2^i]$ annuladducts from different ketenes and imines, even to design the efficient synthesis of the desired tetrahydropyrimidinone derivatives.

EXPERIMENTAL SECTION

General Information. Dichloromethane was refluxed over CaH_2 and freshly distilled prior to use, while tetrahydrofuran was refluxed over sodium with diphenyl ketone as an indicator and freshly distilled prior to use. Melting points were obtained on a melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer, while the NOE spectra were on a 600 MHz spectrometer, in $CDCl_3$ with TMS as an internal standard, and the chemical shifts (δ) are reported in parts per million (ppm). The IR spectra (KBr pellets, ν [cm^{-1}]) were taken on a FTIR spectrometer. HRMS measurements were carried out on an LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel GF254 plates, and the plates were visualized with UV light. All optimized geometries were calculated at the DFT B3LYP level[14] with the 6-311+G(d,p) basis set for all of the atoms with the Gaussian 09 suite of programs.[15]

The diazoacetates **2c–e** were prepared by the diazotization of the corresponding glycine ester hydrochlorides with $NaNO_2$ following McKenzie's procedures.[16] The other diazo compounds **2a**,**b**, **2f–k**, as well as the acyl chlorides **2l**,**m** were prepared according to our previous precedures.[5f–h]

Preparation of 3,4-Dihydroisoquiline (1a). 3,4-Dihydroisoquiline (**1a**) was prepared following Cava's procedure.[17] Tetrahydroisoquiline (5 g, 37.6 mmol) was treated with *N*-bromosuccinimide (7.3 g, 41.4 mmol) in 50 mL of CH_2Cl_2 at room temperature for 2 h. Next, 25 mL of 30% NaOH solution was added, and the mixture was stirred for another 3 h. The organic phase was washed with brine (20 mL × 3), dried over Na_2SO_4, and concentrated at reduced pressure (ca. 25 mmHg). The obtained residue oil was purified by distillation at vacuum to give the desired product (bp 98–100 °C/2 mmHg) as a colorless oil (2.30 g, 45%).

General Procedure for the Photoirradiation Reactions. Diazoacetate or diazomethyl ketone **2** (2 mmol) and imine **1a** (1 mmol, 131 mg) were placed into a quartz tube, and dissolved in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resultant yellow solution was then irradiated at room temperature (cooled by tap water) with a high-pressure mercury lamp for 3 h. Concentration of the resulting brown solution under reduced pressure (ca. 25 mmHg), and subsequent purification of the residues by column chromatography on silica gel with petroleum ether (60–90 °C) and ethyl acetate as eluent afforded the desired products **4** and **5**.

General Procedure for the Reactions of Acyl Chlorides 2l,m and Imine 1a. To an oven-dried bottle charged with a solution of imine **1a** (2 mmol, 262 mg) and triethylamine (101 mg, 1 mmol) in dry THF (4 mL) was dropwise added a solution of acyl chloride **2l** or **2m** (1 mmol) in dry THF (1 mL) during 1 min. Upon addition, the resultant mixture was stirred at room temperature for 12 h, followed by addition of ether (15 mL), washing with brine (15 mL), and drying over Na_2SO_4. Concentration under reduced pressure (ca. 25 mmHg) and purification of the residue by column chromatography on silica gel with petroleum ether (60–90 °C) and ethyl acetate as eluent afforded the desired product **4i** or **4m**.

Benzyl [[*rel*(4b*S*,5*S*,13b*R*)-4b,5,9,13b,15,16-Hexahydro-6-oxo-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′] diisoquinolin-5-yl]methyl]-carbamate (4a). Yellow oil. Yield 40 mg, 17%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.26 (m, 6H), 7.24–7.12 (m, 7H), 6.09 (d, *J* = 7.6 Hz, 1H), 5.38 (s, 1H), 5.07 (d, *J* = 2.5 Hz, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 3.53 (dd, *J* = 11.5, 5.9 Hz, 1H), 3.47–3.36 (m, 1H), 3.36–3.26 (m, 1H), 2.96–2.90 (m, 3H), 2.88–2.78 (m, 2H), 2.64–2.59 (m, 1H), 2.59–2.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 155.9, 136.7, 134.6, 133.5, 129.2, 128.4, 128.3, 128.0, 127.98, 127.95, 127.91, 127.84, 127.77, 127.2, 127.1, 126.6, 126.3, 125.2, 73.9, 66.2, 58.9, 47.0, 45.0, 40.1, 36.7, 28.6, 27.7. IR (film, KBr) ν (cm^{-1}): 1693, 1651, 1600, 1501, 1450, 1434, 1382, 1350, 1290, 1261, 1196, 1092, 1037. HRMS (ESI) calcd for $C_{29}H_{30}N_3O_3$ [M + H$^+$] *m*/*z*, 468.2287; found, 468.2280.

2-[[*rel*(4b*S*,5*S*,13b*R*)-4b,5,9,13b,15,16-Hexahydro-6-oxo-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-5-yl]methyl]-isoindoline-1,3-dione (4b). Yellow oil. Yield 46 mg, 20%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73–7.56 (m, 6H), 7.37–7.30 (m, 3H), 7.14–7.05 (m, 2H), 6.99 (m, 7.01–6.97, 1H), 5.17 (s, 1H), 4.53 (d, *J* = 3.2 Hz, 1H), 3.90–3.82 (m, 2H), 3.73–3.60 (m, 2H), 3.52–3.42 (m, 1H), 3.36–3.24 (m, 2H), 3.03–2.96 (m, 2H), 2.84–2.76 (m, 1H), 2.70–2.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 167.8, 136.8, 135.9, 134.9, 133.6, 133.4, 132.1, 129.0, 128.0, 127.7, 126.9, 126.6, 126.4, 125.7, 124.2, 122.9, 73.8, 58.2, 46.3, 43.2, 40.9, 37.0, 28.8, 27.3. IR (film, KBr) ν (cm^{-1}): 2930, 1774, 1754, 1653, 1498, 1459, 1430, 1384, 1356, 1320, 1289, 1268, 1244, 1166, 1105, 1090, 1075. HRMS (ESI) calcd for $C_{29}H_{26}N_3O_3$ [M + H$^+$] *m*/*z*, 464.1974; found, 464.1970.

***rel*(4b*R*,5*S*,13b*R*)-5-Ethoxy-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4c).** Colorless oil. Yield: 12 mg, 7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55–7.49 (m, 1H), 7.30–7.26 (m, 3H), 7.22–7.17 (m, 4H), 5.80 (s, 1H), 4.95–4.88 (m, 1H), 4.54 (d, *J* = 5.0 Hz, 1H), 3.96 (d, *J* = 5.0 Hz, 1H), 3.81 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.26 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 3.14 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.05–2.96 (m, 2H), 2.94–2.86 (m, 1H), 2.82–2.73 (m, 1H), 2.68 (dd, *J* = 16.4, 4.2 Hz, 1H), 2.48 (dd, *J* = 11.1, 7.2 Hz, 1H), 0.70 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 136.6, 136.1, 133.6, 132.7, 128.8, 128.6, 127.6, 127.5, 127.0, 126.7, 125.8, 125.2, 77.6, 75.1, 70.1, 61.6, 38.0, 37.1, 28.5, 28.4, 15.0. IR (film,

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KBr) ν (cm^{-1}): 2925, 1651, 1604, 1494, 1454, 1432, 1385, 1354, 1287, 1258, 1198, 1090, 1034, 747, 701. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_2$ [M + H^+] m/z, 349.1916; found, 349.1913.

***rel*(4b*R*,5*S*,13b*R*)-5-Benzyloxy-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4d).** Colorless crystals. Mp 163−164 °C. Yield: 74 mg, 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53−7.45 (m, 1H), 7.25−7.21 (m, 3H), 7.20−7.14 (m, 3H), 7.13−7.05 (m, 4H), 6.64 (d, J = 6.4 Hz, 2H), 5.81 (s, 1H), 4.93−4.89 (m, 1H), 4.87 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 5.0 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.08 (d, J = 5.0 Hz, 1H), 3.25 (td, J = 11.3, 4.4 Hz, 1H), 2.97 (d, J = 10.3 Hz, 2H), 2.94−2.85 (m, 1H), 2.81−2.71 (m, 1H), 2.64 (dd, J = 16.4, 4.0 Hz, 1H), 2.46 (dd, J = 11.2, 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 138.1, 136.6, 136.2, 133.7, 132.7, 128.9, 128.6, 127.8, 127.63, 127.55, 127.4, 127.1, 127.0, 126.8, 125.9, 125.6, 76.8, 75.6, 75.1, 61.5, 37.9, 37.2, 28.5, 28.4. IR (film, KBr) ν (cm^{-1}): 2923, 1651, 1496, 1454, 1429, 1386, 1354, 1321, 1286, 1264, 1243, 1166, 1133, 1105, 1090, 1075, 1051, 1034, 906, 814, 774, 745, 698. HRMS (ESI) calcd for $C_{27}H_{27}N_2O_2$ [M + H^+] m/z, 411.2073; found, 411.2076.

***rel*(4b*R*,5*S*,13b*R*)-5-Phenoxy-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4fa).** Colorless crystals. Mp 172−174 °C. Yield: 60 mg, 30%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58−7.46 (m, 1H), 7.33−7.26 (m, 2H), 7.22−7.14 (m, 3H), 7.08−7.02 (m, 2H), 6.97 (t, J = 7.1 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 7.6 Hz, 2H), 5.87 (s, 1H), 4.99−4.91 (m, 1H), 4.80 (d, J = 5.2 Hz, 1H), 4.67 (d, J = 5.2 Hz, 1H), 3.36 (ddd, J = 11.4, 4.4, 4.4 Hz, 1H), 3.08−2.92 (m, 3H), 2.83−2.74 (m, 2H), 2.56 (dd, J = 11.3, 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 160.4, 136.6, 135.8, 132.8, 132.5, 128.84, 128.83, 128.6, 127.8, 127.5, 127.1, 127.0, 126.3, 125.5, 121.9, 117.5, 78.0, 75.0, 61.8, 38.3, 37.0, 28.6, 28.4. IR (film, KBr) ν (cm^{-1}): 3024, 2927, 1655, 1595, 1491, 1455, 1431, 1390, 1354, 1322, 1287, 1227, 1165, 1132, 1099, 1070, 1033, 978, 880, 745, 693. HRMS (ESI) calcd for $C_{26}H_{25}N_2O_2$ [M + H^+] m/z, 397.1916; found, 397.1915.

***rel*(4b*R*,5*R*,13b*R*)-5-Phenoxy-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4fb).** Yellow oil. Yield: 109 mg, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59−6.87 (m, 13H), 6.03 (s, 1H), 4.97 (d, J = 9.4 Hz, 1H), 4.76 (ddd, J = 12.7, 4.4, 2.8 Hz, 1H), 4.69 (d, J = 9.4 Hz, 1H), 3.11−2.90 (m, 3H), 2.84−2.77 (m, 2H), 2.70−2.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 159.5, 136.5, 135.4, 133.5, 132.3, 129.2, 129.1, 128.8, 128.2, 127.8, 127.4, 127.3, 127.2, 125.9, 121.6, 116.6, 76.2, 74.4, 61.3, 38.3, 37.3, 28.9, 28.6. IR (film, KBr) ν (cm^{-1}): 3026, 2925, 1664, 1596, 1493, 1455, 1427, 1384, 1353, 1320, 1287, 1233, 1163, 1133, 1096, 1038, 911, 751, 690. HRMS (ESI) calcd for $C_{26}H_{25}N_2O_2$ [M + H^+] m/z, 397.1916; found, 397.1913.

***rel*(4b*R*,5*R*,13b*R*)-5-(4-Nitrophenoxy)-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4gb).** Colorless crystals. Mp 245−246 °C. Yield: 77 mg, 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.7 Hz, 2H), 7.55 (dd, J = 5.1, 4.0 Hz, 1H), 7.36−7.27 (m, 4H), 7.24−7.19 (m, 1H), 7.19−7.12 (m, 2H), 6.91−6.83 (m, 1H), 6.19 (s, 1H), 6.00 (d, J = 7.7 Hz, 1H), 4.86 (ddd, J = 12.8, 4.3, 3.0 Hz, 1H), 4.67 (d, J = 10.5 Hz, 1H), 4.03 (d, J = 10.5 Hz, 1H), 3.14 (ddd, J = 12.4, 3.2, 3.2 Hz, 1H), 3.02−2.85 (m, 3H), 2.81 (ddd, J = 15.9, 2.8, 2.8 Hz, 1H), 2.77−2.70 (m, 1H), 2.68−2.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 147.4, 147.0, 136.7, 135.2, 133.3, 132.3, 130.8, 129.5, 128.6, 127.9, 127.44, 127.41, 127.2, 127.0, 125.0, 123.9, 74.8, 64.2, 52.4, 38.5, 36.2, 28.7, 28.5. IR (film, KBr) ν (cm^{-1}): 2926, 1643, 1605, 1518, 1494, 1456, 1428, 1386, 1346, 1317, 1287, 1242, 1186, 1156, 1110, 1095, 1047, 850, 750, 729, 689, 651. HRMS (ESI) calcd for $C_{26}H_{24}N_3O_3$ [M + H^+] m/z, 426.1818; found, 426.1812.

***rel*(4b*R*,5*R*,13b*S*)-5-(4-Nitrophenoxy)-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4gc).** Colorless crystals. Mp 261−263 °C. Yield: 40 mg, 19%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.7 Hz, 1H), 7.37−7.20 (m, 5H), 7.16 (t, J = 7.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 6.73 (t, J = 7.4 Hz, 1H), 5.60 (d, J = 7.8 Hz, 1H), 5.57 (s, 1H), 5.00−4.90 (m, 1H), 4.25 (d, J = 10.8 Hz, 1H), 3.96 (d, J = 10.8 Hz, 1H), 3.82 (ddd, J = 11.6, 4.3, 4.3 Hz, 1H), 3.49−3.39 (m, 1H), 3.39−3.28 (m, 2H), 3.27−3.17 (m, 1H), 3.06 (dd, J = 16.4, 4.1 Hz, 1H), 2.86 (dd, J = 16.1, 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 146.8, 146.7, 136.1, 135.8, 134.0, 133.4, 129.5, 129.3, 128.4, 127.6, 127.41 (2C), 126.9, 125.1, 124.6, 123.5, 78.6, 58.1, 50.8, 45.9, 41.9, 29.3, 28.2. IR (film, KBr) ν (cm^{-1}): 2923, 1635, 1602, 1514, 1489, 1466, 1435, 1370, 1343, 1302, 1282, 1245, 1145, 1112, 846, 784, 761, 752, 725, 693. HRMS (ESI) calcd for $C_{26}H_{24}N_3O_3$ [M + H^+] m/z, 426.1818; found, 426.1818.

***rel*(4b*S*,5*R*,13b*R*)-5-Phenyl-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6-one (4h).** Colorless crystals. Mp 175−176 °C. Yield: 128 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60−7.53 (m, 1H), 7.32−7.27 (m, 4H), 7.22−7.09 (m, 6H), 6.90−6.84 (m, 1H), 6.17 (s, 1H), 6.12 (d, J = 7.7 Hz, 1H), 4.84 (ddd, J = 12.9, 4.2, 3.5 Hz, 1H), 4.70 (d, J = 10.4 Hz, 1H), 3.86 (d, J = 10.3 Hz, 1H), 3.20−3.11 (m, 1H), 3.00−2.86 (m, 3H), 2.82−2.75 (m, 1H), 2.75−2.68 (m, 1H), 2.63−2.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 139.8, 137.0, 136.3, 133.2, 132.8, 129.7, 129.1, 128.8, 128.5, 127.8, 127.6, 127.4, 127.15, 127.07, 127.00, 124.9, 74.7, 64.5, 52.5, 38.6, 36.3, 28.9, 28.7. IR (film, KBr) ν (cm^{-1}): 3027, 2924, 1644, 1494, 1454, 1426, 1384, 1354, 1287, 1242, 1188, 1154, 1094, 1039, 922, 750, 727, 699. HRMS (ESI) calcd for $C_{26}H_{25}N_2O$ [M + H^+] m/z, 381.1967; found, 381.1961.

Ethyl *rel*(4b*R*,5*S*,13b*S*)-4b,5,9,13b,15,16-Hexahydro-6-oxo-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinoline-5-carboxylate (4i). Colorless crystals. Mp 141−142 °C. Yield: 64 mg, 34% from **2g**, 87 mg, 46% from **2j**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55−7.47 (m, 1H), 7.31−7.23 (m, 3H), 7.23−7.16 (m, 2H), 7.17−7.10 (m, 2H), 6.96 (d, J = 7.4 Hz, 1H), 6.00 (s, 1H), 4.93 (d, J = 10.4 Hz, 1H), 4.79 (ddd, J = 12.9, 4.4, 3.1 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.77 (d, J = 10.4 Hz, 1H), 3.08 (ddd, J = 12.4, 3.3, 3.3 Hz, 1H), 2.99−2.85 (m, 2H), 2.77 (dt, J = 15.9, 2.9 Hz, 1H), 2.69−2.53 (m, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 164.4, 136.5, 136.0, 133.2, 132.2, 129.3, 128.5, 127.7, 127.40, 127.36, 127.0, 126.2, 125.8, 74.4, 61.6, 59.6, 52.8, 38.2, 36.3, 28.6, 28.5, 14.1. IR (film, KBr) ν (cm^{-1}): 2929, 1729, 1652, 1494, 1455, 1428, 1390, 1355, 1333, 1304, 1286, 1241, 1177, 1146, 1094, 1034, 940, 747, 727, 669. HRMS (ESI) calcd for $C_{23}H_{25}N_2O_3$ [M + H^+] m/z, 377.1865; found, 377.1867.

***rel*(4b*R*,5*R*,13b*S*)-*N*-Methyl-4b,5,9,13b,15,16-hexahydro-6-oxo-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinoline-5-carboxamide (4j).** Colorless crystals. Mp 170−172 °C. Yield: 76 mg, 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56−7.51 (m, 1H), 7.31−7.26 (m, 2H), 7.22−7.13 (m, 4H), 7.10−7.08 (m, 1H), 6.51 (d, J = 3.7 Hz, 1H), 5.92 (s, 1H), 5.39 (d, J = 9.1 Hz, 1H), 4.49 (ddd, J = 12.9, 4.4, 4.4 Hz, 1H), 3.45 (d, J = 9.1 Hz, 1H), 3.32−3.23 (m, 1H), 2.91 (d, J = 4.8 Hz, 3H), 2.97−2.83 (m, 2H), 2.78 (dt, J = 15.8, 3.9 Hz, 1H), 2.66−2.58 (m, 1H), 2.56−2.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 166.0, 137.7, 136.6, 133.1, 132.4, 129.0, 128.2, 127.79, 127.75, 127.2, 127.0, 126.7, 126.2, 73.8, 57.7, 53.8, 38.9, 37.0, 28.8, 28.6, 26.9. IR (film, KBr) ν (cm^{-1}): 2922, 1655, 1638, 1578, 1561, 1544, 1493, 1458, 1431, 1354, 1286, 1242, 1157, 1094, 1037, 921, 751. HRMS (ESI) calcd for $C_{22}H_{24}N_3O_2$ [M + H^+] m/z, 362.1869; found, 362.1868.

***rel*(4b*R*,5*R*,13b*S*)-*N*-Methyl-*N*-phenyl-4b,5,9,13b,15,16-hexahydro-6-oxo-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinoline-5-carboxamide (4ka).** Colorless crystals. Mp 198−199 °C. Yield: 39 mg, 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52−7.32 (m, 7H), 7.23−7.14 (m, 4H), 7.13−7.07 (m, 1H), 6.79−6.74 (m, 1H), 5.69 (s, 1H), 4.77 (ddd, J = 12.6, 3.9, 3.9 Hz, 1H), 4.65 (d, J = 9.3 Hz, 1H), 4.29 (d, J = 9.3 Hz, 1H), 3.69 (ddd, J = 10.8, 5.1, 5.1 Hz, 1H), 3.11 (ddd, J = 12.3, 2.8, 2.8 Hz, 1H), 2.97 (ddd, J = 10.8, 4.2, 4.2 Hz, 1H), 2.87 (s, 3H), 2.81−2.71 (m, 3H), 2.40 (dd, J = 11.0, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 167.0, 144.7, 136.9, 135.5, 134.0, 132.6, 129.5, 129.4, 129.1, 128.2, 127.8, 127.7, 127.2, 127.00, 126.96, 126.1, 124.3, 74.1, 58.9, 48.5, 38.4, 37.5, 35.6, 28.6, 28.2. IR (film, KBr) ν (cm^{-1}): 2926, 1660, 1638, 1595, 1496, 1455, 1420, 1380, 1358, 1324, 1287, 1269, 1233, 1155, 1116, 774, 752, 702, 666. HRMS (ESI) calcd for $C_{28}H_{28}N_3O_2$ [M + H^+] m/z, 438.2182; found, 438.2185.

***rel*(4b*R*,5*R*,13b*S*)-*N*-Methyl-6-oxo-*N*-phenyl-4b,5,9,13b,15,16-hexahydro-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]-diisoquinoline-5-carboxamide (Two Inseparable Rotamers).** Colorless oil. Total yield: 29 mg, 13%.

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Minor Rotamer (4kb). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59−7.03 (m, 13H), 6.05 (s, 1H), 5.05 (d, J = 10.8 Hz, 1H), 4.86 (ddd, J = 12.0, 4.4, 2.6 Hz, 1H), 3.77 (d, J = 10.8 Hz, 1H), 3.34 (s, 3H), 3.30−3.23 (m, 2H), 2.99−2.92 (m, 2H), 2.87−2.76 (m, 2H), 2.27 (ddd, J = 12.0, 4.4, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 165.5, 143.5, 136.5, 135.9, 133.2, 132.5, 129.39, 129.30, 128.6, 127.58, 127.51, 127.40, 127.37, 127.2, 126.9, 126.2, 125.5, 74.7, 59.8, 48.2, 38.0, 37.6, 36.3, 29.7, 28.6. IR (film, KBr) ν (cm^{-1}): 2925, 1655, 1642, 1594, 1495, 1462, 1427, 1388, 1354, 1300, 1283, 1241, 1143, 1115, 771, 742, 700, 678. HRMS (ESI) calcd for $C_{28}H_{28}N_3O_2$ [M + H^+] m/z, 438.2182; found, 438.2179.

Major Rotamer (4kc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59−7.03 (m, 13H), 5.27 (s, 1H), 4.85−4.78 (m, 1H), 4.56 (d, J = 10.7 Hz, 1H), 3.66 (d, J = 10.7 Hz, 1H), 3.29−3.14 (m, 2H), 3.20 (s, 3H), 3.10−3.01 (m, 2H), 2.69 (dd, J = 15.5, 3.2 Hz, 2H), 2.42 (dd, J = 12.5, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 164.9, 143.6, 136.0, 135.9, 135.0, 133.3, 129.26, 129.23, 129.0, 128.1, 127.5, 127.41, 127.37, 127.29, 126.5, 125.4, 125.0, 78.5, 54.2, 47.1, 45.8, 41.3, 37.0, 28.9, 28.0. IR (film, KBr) ν (cm^{-1}): 2925, 1655, 1642, 1594, 1495, 1462, 1427, 1388, 1354, 1300, 1283, 1241, 1143, 1115, 771, 742, 700, 678. HRMS (ESI) calcd for $C_{28}H_{28}N_3O_2$ [M + H^+] m/z, 438.2182; found, 438.2179.

***rel*(4b*R*,5*R*,13b*S*)-4b,5,9,13b,15,16-Hexahydro-6-oxo-6*H*,8*H*-pyrimido[2,1-*a*:4,3-*a*′]diisoquinoline-5-carbonitrile (4m).** Colorless crystals. Mp 196−197 °C. Yield: 40 mg, 24%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58−7.51 (m, 1H), 7.51−7.45 (m, 1H), 7.32−7.26 (m, 4H), 7.22−7.18 (m, 1H), 7.17−7.13 (m, 1H), 5.94 (s, 1H), 4.84 (ddd, J = 13.2, 4.5, 2.8 Hz, 1H), 4.81 (d, J = 10.6 Hz, 1H), 3.85 (d, J = 10.6 Hz, 1H), 3.10 (ddd, J = 12.5, 3.3, 3.3 Hz, 1H), 3.01−2.87 (m, 2H), 2.84−2.76 (m, 1H), 2.67 (d, J = 16.0 Hz, 1H), 2.64−2.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 136.3, 134.1, 133.1, 131.4, 129.5, 128.8, 128.3, 128.2, 127.34, 127.31, 127.28, 126.5, 117.6, 74.7, 59.7, 38.9, 38.4, 36.0, 28.40, 28.36. IR (film, KBr) ν (cm^{-1}): 2927, 1660, 1537, 1455, 1430, 1389, 1354, 1308, 1285, 1261, 1241, 1157, 1131, 1094, 1048, 881, 795, 737, 657. HRMS (ESI) calcd for $C_{21}H_{20}N_3O$ [M + H^+] m/z, 330.1606; found, 330.1606.

***trans*-1-Ethoxy-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]-isoquinolin-2-one (5c).** Yellowish oil. Yield: 56 mg, 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31−7.09 (m, 4H), 4.58 (s, 1H), 4.45 (d, J = 1.4 Hz, 1H), 3.98 (ddd, J = 12.8, 6.6, 3.6 Hz, 1H), 3.81 (q, J = 7.0 Hz, 2H), 3.17 (ddd, J = 13.0, 9.5, 5.2 Hz, 1H), 3.00 (ddd, J = 16.0, 9.5, 6.6 Hz, 1H), 2.76 (ddd, J = 16.0, 4.2, 4.2 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 134.0, 133.5, 129.6, 127.6, 127.0, 125.8, 89.1, 66.0, 57.3, 37.2, 28.2, 15.2. IR (film, KBr) ν (cm^{-1}): 2975, 1755, 1455, 1370, 1333, 1298, 1205, 1133, 1102, 1053, 745. HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ [M + H^+] m/z, 218.1181; found, 218.1180.

***trans*-1-Isopropoxy-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]-isoquinolin-2-one (5d).** Yellowish oil. Yield: 32 mg, 14%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.14 (m, 4H), 4.54 (s, 1H), 4.47 (d, J = 1.4 Hz, 1H), 3.98 (ddd, J = 13.0, 6.6, 3.6 Hz, 1H), 3.94 (hept, J = 6.0 Hz, 1H), 3.16 (ddd, J = 13.0, 9.7, 5.1 Hz, 1H), 3.00 (ddd, J = 16.0, 9.5, 6.6 Hz, 1H), 2.76 (ddd, J = 16.0, 4.2, 4.2 Hz, 1H), 1.31 (t, J = 6.0 Hz, 3H), 1.30 (t, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 134.1, 133.7, 129.6, 127.5, 127.0, 125.8, 87.4, 72.9, 58.3, 37.2, 28.3, 22.6, 22.4. IR (film, KBr) ν (cm^{-1}): 2969, 1753, 1456, 1384, 1318, 1263, 1199, 1180, 1142, 1102, 1036, 838, 744. HRMS (ESI) calcd for $C_{14}H_{18}NO_2$ [M + H^+] m/z, 232.1338; found, 232.1337.

***trans*-1-Benzyloxy-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]-isoquinolin-2-one (5e).** Yellowish solid. Mp 61−62 °C. Yield: 20 mg, 7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46−7.29 (m, 5H), 7.23−7.17 (m, 2H), 7.15−7.08 (m, 1H), 6.99−6.97 (m, 1H), 4.89 (d, J = 11.7 Hz, 1H), 4.76 (d, J = 11.7 Hz, 1H), 4.60 (s, 1H), 4.52 (d, J = 1.5 Hz, 1H), 3.97 (ddd, J = 13.0, 6.7, 3.7 Hz, 1H), 3.16 (ddd, J = 13.0, 9.5, 5.2 Hz, 1H), 2.98 (ddd, J = 16.0, 9.5, 6.7 Hz, 1H), 2.73 (ddd, J = 16.0, 4.4, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 137.0, 134.0, 133.3, 129.5, 128.6, 128.1, 128.0, 127.6, 127.0, 125.8, 88.6, 72.5, 57.5, 37.2, 28.2. IR (film, KBr) ν (cm^{-1}): 2924, 1755, 1494, 1454, 1383, 1349, 1298, 1206, 1129, 1101, 1049, 1028, 854, 742, 699. HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ [M + H^+] m/z, 280.1332; found, 280.1335.

***trans*-1-Phenoxy-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]-isoquinolin-2-one (5f).** Yellowish oil. Yield: 32 mg, 12%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58−6.93 (m, 10H), 5.11 (d, J = 1.6 Hz, 1H), 4.81 (s, 1H), 4.09 (ddd, J = 12.8, 6.4, 3.4 Hz, 1H), 3.23 (ddd, J = 12.8, 10.0, 4.8 Hz, 1H), 3.05−2.95 (m, 1H), 2.87−2.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.0, 157.3, 134.1, 129.8, 129.79, 129.67, 127.9, 126.2, 122.5, 121.0, 116.1, 86.7, 57.7, 37.5, 28.4. IR (film, KBr) ν (cm^{-1}): 2925, 1761, 1493, 1455, 1384, 1353, 1287, 1133, 1096, 1038, 752, 691. HRMS (ESI) calcd for $C_{17}H_{16}NO_2$ [M + H^+] m/z, 266.1181; found, 266.1179.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00279.

Copies of ^{1}H, ^{13}C, and NOE NMR spectra of products **4** and **5**, and computed energies of all stationary points and coordinates of all stationary points for the formation of **4fa**, **4gc**, and **4h** (PDF)

X-ray data for compound **4m** (CIF)

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Notes

The authors declare no competing financial interest.

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