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# Chiral Template Mediated Diastereoselective Intramolecular Diels–Alder Reaction Using Furan as a Diene. Toward the Synthesis of Enantiopure Trisubstituted Tetrahydroepoxyisoindolones

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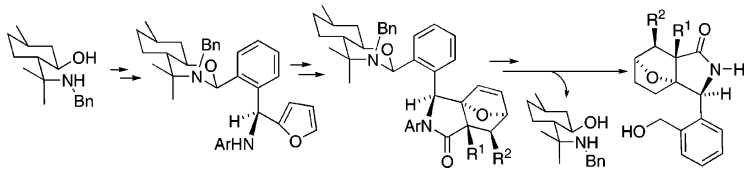


Chiral precursors to the intramolecular Diels–Alder reaction using furan as a diene (IMDAF) have been prepared by diastereoselective addition of furyllithium to imines attached to perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol. The acylation of the furylamines with α,β-unsaturated acyl chlorides and subsequent IMDAF reaction under thermal conditions provided the corresponding cycloadducts as single diastereoisomers. The hydrolytic elimination of the chiral template yielded enantiopure perhydroepoxyisoindolones with up to five stereocenters.

## Introduction

Intramolecular Diels–Alder reaction using furan as a diene (IMDAF) was described more than 20 years ago,[1] but it continues to attract a lot of attention because it allows for the regio- and stereocontrolled construction of polycyclic complex structures, which are building blocks for natural compounds.[2,3]

The effects of structural variations on both the furan system[4] and the dienophile[5] and the size of the tether between the two components[6] on the selectivity of the reaction are well documented, although the asymmetric version has been less studied.

The placement of a nitrogen atom in the tether connecting the diene and dienophile, followed by IMDAF reaction, allows for the construction of aza polyheterocycles present in the skeleton of interesting alkaloids.[7] In this respect, we have prepared enantiopure epoxytetrahydroisoindolines[8] and perhydroisoquinolines[9] by IMDAF reaction and benzoisoindoline derivatives[10] by intramolecular Diels–Alder reaction using styrene derivatives

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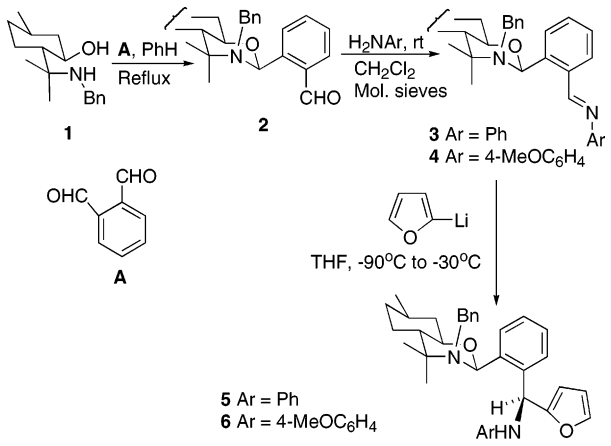
**SCHEME 1**




as dienes and perhydrobenzoxazines as chiral inductors and as sources of the nitrogen atom in the final heterocycle.

In this paper we summarize our results on the synthesis of enantiopure perhydroisoindolones[11] by diastereoselective IMDAF reaction using perhydro-1,3-benzoxazines as chiral templates. This approach differs from that used until now because the perhydrobenzoxazine is only used as a chiral inductor, and the (−)-8-aminomenthol is recovered in the final stage of the process.

The whole sequence of reactions requires the stereoselective preparation of furfurylamines and their transformation into the corresponding α,β-unsaturated amides to promote the IMDAF reaction. The template of the chiral perhydrobenzoxazine will serve as a chiral inductor in both the synthesis of amine derivatives and the cycloaddition reaction.

## Results and Discussion

The chiral furfurylamine derivatives **5** and **6** were synthesized in three steps and excellent yield (>90%) from (−)-8-*N*-benzylaminomenthol[12] (**1**) (Scheme 1). The condensation of **1** with *o*-phthalaldehyde in benzene for 16 h under Dean−Stark conditions provided the aldehyde **2** in 95% total yield, which was converted nearly quantitatively into **3** and **4** by reaction with aniline or *p*-methoxyaniline in dry dichloromethane in the presence of molecular sieves. Addition of a recently prepared 2.5 M solution of 2-furyllithium in THF to **3** or **4** at −30 °C, using THF as solvent, afforded the desired furylamines **5** and **6** in 96% and 98% yields, respectively, as single diastereomers. The chromatographic purification of furylamines on silica gel or alumina was unsuccessful also if the silica gel was previously deactivated with triethylamine. Compounds **5** and **6** decomposed under all chromatographic conditions tested. The *N*-benzylimine was also prepared by condensation of **2** with benzylamine, but their reaction with furyllithium yielded a very complex mixture of compounds.

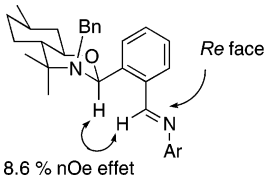



**FIGURE 1.** Preferred conformation in $CDCl_3$ solution for imine **3**.

The absolute configuration of the created stereocenter was assigned as *S* and later confirmed by X-ray diffraction analysis for the Diels−Alder cycloadducts. Interestingly, the sense of the excellent 1,4-stereoinduction is coincident with that previously described for 1,2-stereoinduction in related carbonyl derivatives[13,14] and explained on the basis of the structure of the imines. In fact, the preferred conformation of **3** in solution was determined on the basis of NOE experiments. A strong NOE effect (8.6%) was observed between the hydrogens at the *N*,*O*-ketal position and the imine group (Figure 1).

The attack from the *Re* face of the imine group can be rationalized by coordination of the hard lithium derivative to the harder oxygen atom[13] or by the presence of the benzyl group attached to the nitrogen atom, which makes the *Si* face more encumbered to the approach of the reagent.[14]

Amine **5** was subjected to acylation by treatment with acryloyl chloride at 0 °C in the presence of triethylamine using methylene chloride as solvent. The chromatographic purification of the resulting amide must be done on silica gel deactivated with triethylamine, but only a modest yield was obtained because the product was partially hydrolyzed. In addition, when the isolated amide or the N-acylation mixture was allowed to stand at room temperature, it partially evolved to the Diels−Alder cycloadduct. On the basis of these facts, and trying to improve the chemical yield of the intramolecular Diels−Alder process, we studied the cyclization without isolation of the intermediate amide. To this end, a mixture of the amine **5**, acryloyl chloride, and triethylamine in methylene chloride was stirred at rt until disappearance of the starting material (TLC), then the mixture was heated in a sealed tube by immersion in a bath at 50−60 °C, and the progress of the reaction was monitored by TLC and $^1$H NMR. These experimental conditions were used for the reactions of **5** and **6** with acryloyl and methacryloyl chlorides, but in the reactions with crotonoyl and cinnamoyl chlorides triethylamine must be changed to pyridine, and elimination of the excess of the base prior to the heating of the acylation mixture was necessary. Interestingly, the rate of cycloaddition of the methacryloyl derivatives was very slow, and the yields of the final adducts for the *p*-methoxyphenyl derivatives are higher than for the phenyl ones (Scheme 2 and Table 1). The moderate chemical yield for this

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**SCHEME 2**

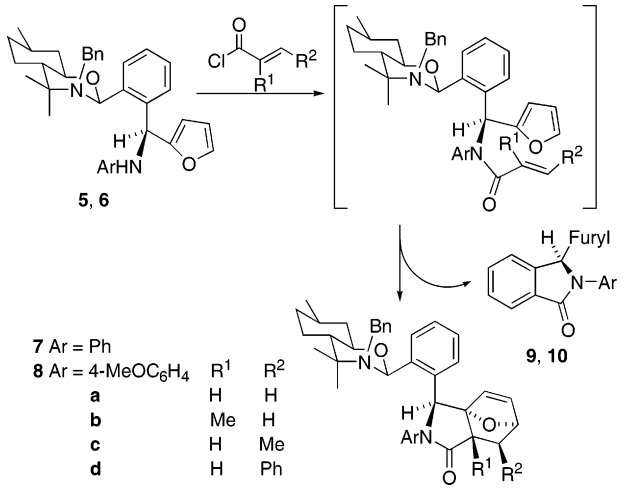


**TABLE 1. Synthesis of Intermediate Amides and IMDAF Reactions to 7 and 8 (Scheme 2)**

| entry | compd | acyl chloride | amide time (h) | IMDAF time (h) | product | yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **5** | acryloyl | 4 | 24 | **7a** | 55 |
| 2 | **5** | methacryloyl | 115 | 48 | **7b** | 33 |
| 3 | **5** | crotonoyl | 0.25 | 36 | **7c** | 37 |
| 4 | **5** | cinnamoyl | 0.25 | 24 | **7d** | 35 |
| 5 | **6** | acryloyl | 16 | 48 | **8a** | 73 |
| 6 | **6** | methacryloyl | 120 | 48 | **8b** | 49 |
| 7 | **6** | crotonoyl | 0.25 | 48 | **8c** | 51 |
| 8 | **6** | cinnamoyl | 24 | 24 | **8d** | 36 |

[a] Yields refer to isolated and purified compounds after column chromatography and are calculated from amines **5** and **6**.

reaction is a well-documented fact in both catalyzed[16] and uncatalyzed[17] processes and is a consequence of the reversible character of the reaction.

In all cases, except for the reaction of **5** with acryloyl chloride, isoindolone **9** (Ar = Ph) or **10** (Ar = PMP) was isolated in 10−15% yield. Formation of these compounds could be interpreted as a consequence of partial hydrolysis of **5** or **6**, rapid oxidation, and intramolecular lactamization. In addition, treatment of **5** in ethanol with dilute hydrochloric acid (2%) at room temperature for 45 min, in an open flask, provides the isoindolone **9** in excellent yield.

Interestingly, in the described reaction conditions the IMDAF reactions occurred with total facial selectivity, providing the *exo* adducts as single diastereomers, and traces of other cycloadducts were not detected in the $^1$H NMR spectra of the reaction mixtures. The facial selectivity is highly dependent on the solvent, and methylene chloride favors the formation of the *exo* adducts.[8,9] The compounds were isolated and purified by flash chromatography, and their stereochemistry was determined on the basis of $^1$H and $^{13}$C NMR spectroscopy and later confirmed by X-ray diffraction analysis (vide infra).

The transformation of the cycloadducts into the final enantiopure perhydroisoindolones was achieved, in two steps, with very good chemical yields (Scheme 3 and Table 2). To this end, compounds **7** and **8** were subjected to hydrogenation ($H_2$, 1 atm, rt) using 10% Pd on carbon as catalyst, and the reaction was monitored by TLC.

**SCHEME 3**

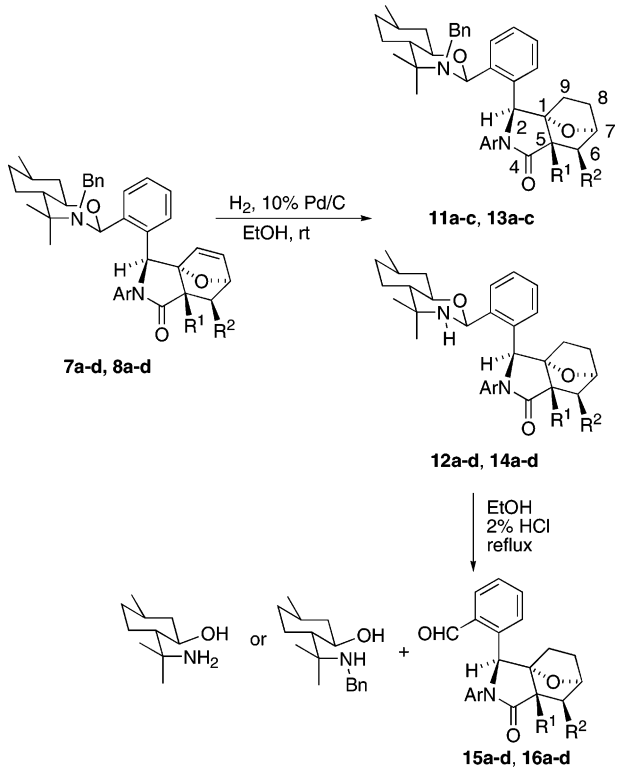


**TABLE 2. Hydrogenation of Compounds 7 and 8 and Hydrolysis to Lactams 15 and 16 (Scheme 3)**

| entry | compd | time (days) | hydrogenation products (yield, %)[a] | lactam (yield, %)[a] |
|---|---|---|---|---|
| 1 | **7a** | 2 | **11a** (87) | **15a** (93) |
| 2 | **7a** | 2.5 | **11a** (32), **12a** (56) | **15a** (95) |
| 3 | **7b** | 16 | **12b** (90) | **15b** (92) |
| 4 | **7c** | 5 | **11c** (10), **12c** (85) | **15c** (94) |
| 5 | **7d** | 20 | **12d** (54)[b,c] | **15d** (95) |
| 6 | **8a** | 2 | **13a** (85) | **16a** (92) |
| 7 | **8a** | 5 | **14a** (86) | **16a** (94) |
| 8 | **8b** | 5 | **13b** (44), **14b** (33)[c] | **16b** (92) |
| 9 | **8c** | 12 | **13c** (76), **14c** (15)[c] | **16c** (93) |
| 10 | **8d** | 19 | **14d** (90) | **16d** (94) |

[a] Yields refer to isolated and purified compounds after column chromatography. [b] The $^1$H NMR of the reaction mixture showed 40% lactam **15d** in the mixture. [c] Compounds **12d**, **14b**, and **14c** could not be obtained in pure form from the reaction mixture.

In these conditions, the hydrogenation of the double bonds occurred very slowly, except for unsubstituted derivatives **7a** and **8a**, and long periods of reaction were necessary to obtain the saturated derivatives. The hydrogenation products depend on the reaction time. Unsubstituted cycloadduct **7a** yielded the oxanorbornane **11a** after 2 days of reaction but a mixture of **11a** and debenzylated derivative **12a** (ca. 2:3) after 60 h of reaction (entries 1 and 2 in Table 2). In the same way, **8a** yielded the hydrogenation product **13a** or the hydrogenation−debenzylation compound **14a** after reaction for 2 or 5 days, respectively (entries 6 and 7). The control of the hydrogenation−hydrogenolysis reaction is not easy, but

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compounds **11**−**14** or mixtures of benzylated and debenzylated products can be used in the next step of the reaction without a problem because all of them gave the final lactams by hydrolysis.

Surprisingly, hydrogenation of cycloadduct **7d** gave the debenzylated oxanorbornane **12d** in moderate yield but accompanied by a 40% yield of aldehyde **15d** as a consequence of partial hydrolysis of the perhydrobenzoxazine moiety during the long period of reaction (entry 5).

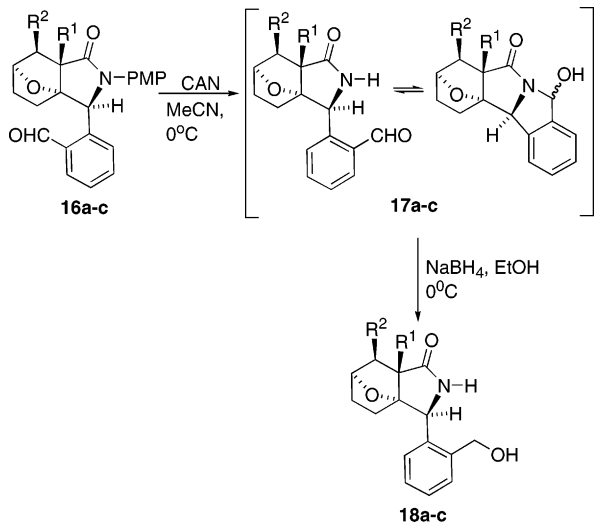
The relative stereochemistry of hydrogenation products was assigned by comparison of the coupling constants of the protons at the oxanorbornane system with those previously described for norbornane derivatives.[18] Thus, the value of the coupling constant ($^3J$ = 4.9−5.5 Hz) indicates a *trans* relationship between protons at C-5 and C-6 and also for protons at C-6 and C-7 ($^3J$ = 4.5−4.8 Hz) in compounds **11c** and **12d**. In addition, the absolute stereochemistry was determined by X-ray diffraction studies for compound **11a** to be 1*R*,2*S*,5*S*,7*S*,[19] which confirms the total diastereoselectivity in both the addition to the imine system and the *exo* IMDAF reaction.

Adducts **11a**−**c** and **12a**−**d** or **13a**−**c** and **14a**−**d** were converted into enantiopure lactams **15a**−**d** and **16a**−**d**, respectively, by refluxing with dilute (2%) aqueous alcoholic hydrochloric acid for 4−8 h (Scheme 3) in excellent yields (Table 2). At this stage, the stereochemistry for compounds **15c** and **16b**[19] was determined by X-ray diffraction analysis, which is coincident with that described for **11a**. In these reactions the chiral adjuvant (−)-8-aminomenthol was also recovered in 85−92% yield after purification of the products.

The interest in the synthesis of these perhydroepoxyisoindolones lies in the possibility to obtain the enantiopure N-unsubstituted derivatives, and to this end, compounds **16a**−**c** were subjected to deprotection. The elimination of the *p*-methoxyphenyl substituent at the nitrogen atom of these compounds was carried out by treatment of a solution of **16a**−**c** in acetonitrile with an aqueous solution of ceric ammonium nitrate (CAN) at 0 °C (Scheme 4).[20] Under these conditions compounds **17a**−**c** were obtained in 98% yield, as a mixture (70:30) of aldehydes and *N*,*O*-ketals, which were further reduced with sodium borohydride to compounds **18a**−**c** in excellent yield (98%) (Scheme 4).

In summary, a novel totally diastereoselective synthesis of enantiopure perhydroepoxyisoindolone derivatives has been developed by IMDAF. This reaction provides a facile method for the creation of densely functionalized molecules with up to five stereocenters and predictable regio- and stereochemistry. The starting compounds can be easily prepared from (−)-*N*-benzyl-8-aminomenthol in three steps, and a variety of different substituents can be introduced into the heterocyclic nucleus depending on the substitution of the double bond of the dienophile and the nature of the group attached at the nitrogen atom of the starting amine.

**SCHEME 4**




## Experimental Section

**Synthesis of Cycloadducts 7a−d and 8a−d. General Method.** To a stirred solution of the amine **5** or **6** (0.96 mmol) in dichloromethane (1.9 mL) at 0 °C were added triethylamine or pyridine (1.5 mmol) and the corresponding acyl chloride (1.4 mmol). The mixture was stirred at rt until the disappearance of the starting material (TLC), and then the mixture was heated in a sealed tube by immersion in an oil bath at 50−60 °C for the time given in Table 1. When pyridine was used as the base, the reaction mixture was filtered over silica gel deactivated with 5% $Et_3N$ before heating. The Diels−Alder adduct was purified by flash chromatography on silica gel (5% $Et_3N$, $CH_2Cl_2$, or hexanes−$CH_2Cl_2$).

**(1*R*,2*S*,2′*S*,4a′*S*,5*S*,7*S*,7′*R*,8a′*R*)-2-[2-(*N*-Benzyl-4,′4,′,7′-trimethyloctahydrobenzo[*e*][1,3]oxazin-2′-yl)phenyl]-3-(4-methoxyphenyl)-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]dec-8-en-4-one (8a).** Yield: 73%. Yellow solid. Mp: 102−104 °C (from hexane). $[\alpha]^{23}_D$ = +125.2 (*c* = 0.9, $CHCl_3$). $^1$H NMR (δ): 0.92 (s, 3H); 0.96 (d, 3H, *J* = 6.5 Hz); 1.00−1.08 (m, 2H); 1.23 (q, 1H, *J* = 11.7 Hz); 1.37 (s, 3H); 1.40−1.73 (m, 4H); 1.62 (dd, 1H, $J_1$ = 11.8 Hz, $J_2$ = 8.7 Hz); 1.99 (m, 1H); 2.32 (td, 1H, $J_1$ = 11.8 Hz, $J_2$ = 4.3 Hz); 2.63 (dd, 1H, $J_1$ = 8.7 Hz, $J_2$ = 3.3 Hz); 3.56 (td, 1H, $J_1$ = 10.4 Hz, $J_2$ = 3.9 Hz); 3.70 (d, 1H, *J* = 16.9 Hz); 3.79 (s, 3H); 4.10 (d, 1H, *J* = 16.9 Hz); 5.15 (dd, 1H, $J_1$ = 4.3 Hz, $J_2$ = 1.5 Hz); 5.84 (d, 1H, $J_1$ = 5.8 Hz); 6.02 (s, 1H); 6.14 (s, 1H); 6.32 (dd, 1H, $J_1$ = 5.8 Hz, $J_2$ = 1.5 Hz); 6.68 (d, 2H, *J* = 7.3 Hz); 6.77 (t, 2H, *J* = 7.3 Hz); 6.81−6.93 (m, 1H); 6.84 (d, 2H, *J* = 8.9 Hz); 7.25 (t, 2H, *J* = 4.0 Hz); 7.37 (d, 2H, *J* = 8.9 Hz); 7.40−7.45 (m, 1H); 7.74−7.77 (m, 1H). $^{13}$C NMR (δ): 21.7; 22.3; 24.9; 28.2; 29.1; 31.4; 35.1; 41.5; 44.5; 45.5; 46.6; 55.4; 58.4; 63.7; 77.3; 79.3; 84.9; 93.0; 114.4 (2C); 124.4; 125.2; 126.2 (2C); 126.8 (2C); 127.5 (2C); 127.9; 128.2; 129.1; 131.4; 132.4; 133.7; 136.6; 137.8; 143.3; 157.7; 175.2. IR (KBr): 3060; 3020; 1703; 1510; 769; 754; 722; 704 cm$^{-1}$. Anal. Calcd for $C_{39}H_{44}N_2O_4$ (604.78): C, 77.45; H, 7.33; N, 4.63. Found: C, 77.41; H, 7.55; N, 4.53.

**(1*R*,2*S*,2′*S*,4a′*S*,5*S*,7*S*,7′*R*,8a′*R*)-2-[2-(*N*-Benzyl-4′,4′,7′-trimethyloctahydrobenzo[*e*][1,3]oxazin-2′-yl)phenyl]-5-methyl-3-(4-methoxyphenyl)-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]-dec-8-en-4-one (8b).** Yield: 49%. Colorless solid. Mp: 92−93 °C (from hexane). $[\alpha]^{23}_D$ = +97.9 (*c* = 1.2, $CHCl_3$). $^1$H NMR (δ): 0.80−1.06 (m, 1H); 0.95 (s, 3H); 0.97 (d, 3H, *J* = 6.5 Hz); 1.06 (s, 3H); 1.15 (d, 1H, *J* = 11.6 Hz); 1.23 (q, 1H, *J* = 11.6 Hz); 1.36 (s, 3H); 1.42−1.76 (m, 5H); 1.99 (m, 1H); 2.59 (dd, 1H, $J_1$ = 11.6 Hz, $J_2$ = 4.7 Hz); 3.56 (td, 1H, $J_1$ = 10.5 Hz, $J_2$ = 3.7 Hz); 3.65 (d, 1H, *J* = 16.9 Hz); 3.80 (s, 3H); 4.07 (d, 1H, *J* = 16.9 Hz); 5.05 (dd, 1H, $J_1$ = 4.7 Hz, $J_2$ = 1.5 Hz); 6.05 (s, 1H); 6.09 (s, 1H); 6.11 (d, 1H, *J* = 5.8 Hz); 6.40 (dd, 1H, $J_1$ = 5.8 Hz, $J_2$ = 1.5 Hz); 6.68−6.70 (m, 2H); 6.78 (t, 2H, *J* = 7.5

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(19) See the Supporting Information for the ORTEP representation of the structures.

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Hz); 6.83−6.92 (m, 1H); 6.85 (d, 2H, $J$ = 9.1 Hz); 7.14−7.23 (m, 2H); 7.45 (d, 2H, $J$ = 9.1 Hz); 7.43−7.48 (m, 1H); 7.74 (dd, 1H, $J_1$ = 6.9 Hz, $J_2$ = 2.2 Hz). $^{13}$C NMR ($\delta$): 21.6; 22.3; 22.6; 24.9; 28.2; 31.4; 35.1; 38.8; 41.5; 44.9; 46.4; 52.6; 55.4; 58.4; 63.9; 77.1; 78.6; 84.7; 90.7; 114.3 (2C); 125.2; 125.7 (3C); 126.7 (2C); 127.5 (2C); 127.6 (2C); 129.1; 131.5; 131.7; 133.4; 135.7; 138.0; 143.4; 157.4; 178.1. IR (KBr): 3060; 3020; 1702; 1512; 770; 758; 721 cm$^{-1}$. Anal. Calcd for $C_{40}H_{46}N_2O_4$ (618.80): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.25; H, 7.26; N, 4.62.

**(1*R*,2*S*,2′*S*,4a′*S*,5*S*,6*S*,7*S*,7′*R*,8a′*R*)-2-[2-(*N*-Benzyl-4′,4′,7′-trimethyloctahydrobenzo[*e*][1,3]oxazin-2′-yl)phenyl]-6-methyl-3-(4-methoxyphenyl)-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]-dec-8-en-4-one (8c).** Yield: 51%. Yellow solid. Mp: 100−102 °C (from hexane). $[\alpha]^{23}_D$ = +102.7 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($\delta$): 0.93−1.08 (m, 1H); 0.94 (d, 3H, $J$ = 5.9 Hz); 0.97 (s, 6H); 1.17−1.29 (m, 2H); 1.37 (s, 3H); 1.45−1.59 (m, 1H); 1.61−1.75 (m, 3H); 1.99 (m, 1H); 2.12 (d, 1H, $J$ = 3.5 Hz); 2.70−2.75 (m, 1H); 3.57 (td, 1H, $J_1$ = 10.4 Hz, $J_2$ = 3.8 Hz); 3.67 (d, 1H, $J$ = 16.9 Hz); 3.74 (s, 3H); 4.09 (d, 1H, $J$ = 16.9 Hz); 4.91 (d, 1H, $J$ = 4.4 Hz); 5.92 (dd, 1H, $J_1$ = 5.9 Hz, $J_2$ = 1.2 Hz); 6.00 (s, 1H); 6.05 (s, 1H); 6.27 (d, 1H, $J$ = 5.9 Hz); 6.68−6.71 (m, 2H); 6.75−6.81 (m, 4H); 6.85−6.90 (m, 1H); 7.18−7.23 (m, 2H); 7.33−7.39 (m, 3H); 7.75−7.78 (m, 1H). $^{13}$C NMR ($\delta$): 17.1; 21.7; 22.4; 24.9; 28.3; 31.4; 35.1; 37.7; 41.5; 44.5; 46.6; 53.2; 53.3; 58.5; 63.7; 77.4; 82.8; 84.9; 93.7; 114.4 (2C); 124.4; 125.3; 126.0 (2C); 126.9 (2C); 127.6 (2C); 127.9; 128.3; 129.1; 131.4; 133.5; 133.8; 134.8; 137.9; 143.3; 157.6. IR (KBr): 3063; 3020; 1703; 1510; 754; 741; 718 cm$^{-1}$. Anal. Calcd for $C_{40}H_{46}N_2O_4$ (618.35): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.71; H, 7.33; N, 4.67.

**(1*R*,2*S*,2′*S*,4a′*S*,5*S*,6*S*,7*S*,7′*R*,8a′*R*)-2-[2-(*N*-Benzyl-4′,4′,7′-trimethyloctahydrobenzo[*e*][1,3]oxazin-2′-yl)phenyl]-6-phenyl-3-(4-methoxyphenyl)-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]-dec-8-en-4-one (8d).** Yield: 36%. Colorless solid. Mp: 98−99 °C (from hexane). $[\alpha]^{23}_D$ = +24.9 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($\delta$): 0.95 (s, 3H); 0.96 (d, 3H, $J$ = 6.9 Hz); 0.95−1.04 (m, 1H); 1.12−1.36 (m, 2H); 1.39 (s, 3H); 1.43−1.73 (m, 4H); 1.99 (m, 1H); 2.89 (d, 1H, $J$ = 4.2 Hz); 3.57 (td, 1H, $J_1$ = 10.4 Hz, $J_2$ = 3.8 Hz); 3.71 (d, 1H, $J$ = 16.9 Hz); 3.80 (s, 3H); 3.97 (t, 1H, $J$ = 4.2 Hz); 4.11 (d, 1H, $J$ = 16.9 Hz); 5.27 (dd, 1H, $J_1$ = 4.2 Hz, $J_2$ = 1.4 Hz); 6.01 (d, 1H, $J$ = 5.8 Hz); 6.04 (s, 1H); 6.17 (s, 1H); 6.22 (dd, 1H, $J_1$ = 5.8 Hz, $J_2$ = 1.4 Hz); 6.69−6.71 (m, 2H); 6.79 (t, 2H, $J$ = 7.5 Hz); 6.84 (d, 2H, $J$ = 9.0 Hz); 6.86−6.94 (m, 1H); 7.11−7.14 (m, 2H); 7.16−7.28 (m, 5H); 7.41 (d, 2H, $J$ = 9.0 Hz); 7.38−7.44 (m, 1H); 7.76−7.79 (m, 1H). $^{13}$C NMR ($\delta$): 21.7; 22.3; 24.9; 28.2; 31.4; 35.1; 41.5; 44.6; 46.7; 48.3; 53.6; 55.4; 58.5; 63.8; 77.4; 83.0; 84.9; 94.2; 114.4 (2C); 124.4; 125.3; 126.0 (2C); 126.7; 126.9 (2C); 127.6 (2C); 128.0 (3C); 128.3 (2C); 128.4 (2C); 129.2; 131.3; 133.5; 133.6; 135.4; 139.0; 143.3; 157.6; 174.6. IR (KBr): 3060; 3030; 1702; 1636; 1513; 763; 716; 699; 668 cm$^{-1}$. Anal. Calcd for $C_{45}H_{48}N_2O_4$ (680.87): C, 79.38; H, 7.11; N, 4.11. Found: C, 79.46; H, 6.93; N, 4.29.

**Hydrolysis of Compounds 11−14 to 15a−d and 16a−d. General Method.** A solution of the perhydrobenzoxazine (4 mmol) in ethanol (60 mL) and 2% aqueous hydrochloric acid (30 mL) was refluxed until the hydrolysis was complete (TLC, 4−8 h). The aqueous layer was extracted with ethyl acetate (3 × 60 mL), and the organic extracts were washed with brine and dried ($MgSO_4$). The aldehydes were purified by flash chromatography on silica gel (deactivated with 5% $Et_3N$) using hexanes−EtOAc (3:1) as eluent.

**(1*R*,2*S*,5*S*,7*S*)-2-[3-(4-Methoxyphenyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]dec-2-yl]benzaldehyde (16a).** Yield: 94%. Colorless solid. Mp: 65−66 °C (from hexane). $[\alpha]^{23}_D$ = +42.0 ($c$ = 0.6, $CHCl_3$). $^1$H NMR ($\delta$): 0.95−1.03 (m, 1H), 1.40−1.51 (m, 2H), 1.87−2.04 (m, 1H), 1.94 (dd, 1H, $J_1$ = 12.1 Hz, $J_2$ = 9.5 Hz), 2.19−2.26 (m, 1H), 2.96 (dd, 1H, $J_1$ = 9.5 Hz, $J_2$ = 4.3 Hz), 3.71 (s, 3H), 4.71 (t, 1H, $J$ = 5.1 Hz), 6.75 (s, 1H), 6.77 (d, 2H, $J$ = 9.1 Hz), 7.39 (d, 2H, $J$ = 9.1 Hz), 7.41−7.63 (m, 3H), 7.90 (dd, 1H, $J_1$ = 7.2 Hz, $J_2$ = 1.5 Hz), 10.22 (s, 1H). $^{13}$C NMR ($\delta$): 28.3; 29.6; 35.7; 49.6; 55.3; 61.1; 76.9; 89.5; 113.9 (2C); 123.5 (2C); 126.5; 128.6; 131.3; 133.7; 134.4; 136.0; 139.1; 156.8; 175.2; 193.5. IR (KBr): 3060; 2953; 2872; 2749; 1696; 1600; 1576; 772; 748 cm$^{-1}$. Anal. Calcd for $C_{22}H_{21}NO_4$ (363.41): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.80; H, 5.88; N, 4.02.

**(1*R*,2*S*,5*S*,7*S*)-2-[5-Methyl-3-(4-methoxyphenyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]dec-2-yl]benzaldehyde (16b).** Yield: 92%. Colorless solid. Mp: 159−160 °C (from hexane). $[\alpha]^{23}_D$ = +1.4 ($c$ = 0.8, $CHCl_3$). $^1$H NMR ($\delta$): 0.83−0.90 (m, 1H); 1.35 (s, 3H); 1.44−1.58 (m, 3H); 1.94−1.96 (m, 1H); 2.45−2.51 (m, 1H); 3.72 (s, 3H); 4.58 (t, 1H, $J$ = 5.3 Hz); 6.73 (s, 1H); 6.78 (d, 2H, $J$ = 9.1 Hz); 7.45 (d, 2H, $J$ = 9.1 Hz); 7.50−7.57 (m, 3H); 7.91 (dd, 1H, $J_1$ = 5.7 Hz, $J_2$ = 2.0 Hz); 10.3 (s, 1H). $^{13}$C NMR ($\delta$): 22.7; 24.8; 29.3; 46.2; 54.2; 55.3; 61.4; 76.2; 91.1; 114.0 (2C); 123.5 (2C); 127.5; 128.5; 131.7; 133.9; 134.0; 135.8; 139.1; 156.8; 178.7; 193.1. IR (KBr): 3060; 3016; 2925; 2853; 2767; 1691; 1602; 1573; 768; 752 cm$^{-1}$. Anal. Calcd for $C_{23}H_{23}NO_4$ (377.43): C, 73.19; H, 6.14; N, 3.71. Found: C, 72.98; H, 5.98; N, 3.68.

**(1*R*,2*S*,5*S*,6*S*,7*S*)-2-[6-Methyl-3-(4-methoxyphenyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]dec-2-yl]benzaldehyde (16c).** Yield: 93%. Colorless solid. Mp: 136−137 °C (from hexane). $[\alpha]^{23}_D$ = +26.6 ($c$ = 0.7, $CHCl_3$). $^1$H NMR ($\delta$): 0.89−0.99 (m, 1H); 1.17 (d, 3H, $J$ = 7.0 Hz); 1.37−1.48 (m, 1H); 1.68−1.82 (m, 2H); 2.34 (d, 1H, $J$ = 4.8 Hz); 2.60−2.68 (m, 1H); 3.70 (s, 3H); 4.48 (t, 1H, $J$ = 4.4 Hz); 6.68 (s, 1H); 6.75 (d, 2H, $J$ = 9.0 Hz); 7.38 (d, 2H, $J$ = 9.0 Hz); 7.45 (d, 1H, $J$ = 7.7 Hz); 7.50−7.61 (m, 2H); 7.88 (d, 1H, $J$ = 7.2 Hz); 10.2 (s, 1H). $^{13}$C NMR ($\delta$): 15.8; 23.3; 28.8; 41.5; 55.2; 57.0; 61.1; 80.9; 90.1; 113.9 (2C); 123.3 (2C); 126.4; 128.6; 131.3; 133.7; 134.4; 135.9; 139.2; 156.6; 175.1; 193.4. IR (KBr): 3078; 2988; 2963; 2926; 2876; 1698; 1672; 1601; 1576; 1513; 776 cm$^{-1}$. Anal. Calcd for $C_{23}H_{23}NO_4$ (377.43): C, 73.19; H, 6.14; N, 3.71. Found: C, 73.02; H, 6.20; N, 3.57.

**(1*R*,2*S*,5*S*,6*S*,7*S*)-2-[6-Phenyl-3-(4-methoxyphenyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]dec-2-yl]benzaldehyde (16d).** Yield: 94%. Colorless solid. Mp: 90−91 °C (from hexane). $[\alpha]^{23}_D$ = −51.8 ($c$ = 0.9, $CHCl_3$). $^1$H NMR ($\delta$): 0.93−1.01 (m, 1H); 1.49 (td, 1H, $J_1$=11.9 Hz, $J_2$ = 5.0 Hz); 1.59−1.76 (m, 2H); 3.10 (d, 1H, $J$ = 5.3 Hz); 3.71 (s, 3H); 3.91 (t, 1H, $J$ = 4.7 Hz); 4.89 (t, 1H, $J$ = 5.0 Hz); 6.77 (d, 2H, $J$ = 9.0 Hz); 6.81 (s, 1H); 7.19−7.41 (m, 5H); 7.43 (d, 2H, $J$ = 9.0 Hz); 7.46−7.64 (m, 3H); 7.89 (dd, 1H, $J_1$ = 5.9 Hz, $J_2$ = 1.6 Hz); 10.23 (s, 1H). $^{13}$C NMR ($\delta$): 24.4; 28.9; 52.7; 54.7; 55.3; 61.3; 80.5; 90.5; 114.0 (2C); 123.4 (2C); 126.5; 126.6; 128.1 (2C); 128.5 (2C); 128.7; 131.3; 133.8; 134.5; 136.1; 138.5; 139.1; 156.7; 174.7; 193.5. IR (Nujol): 3060; 1694; 1600; 1576; 753; 701 cm$^{-1}$. Anal. Calcd for $C_{28}H_{25}NO_4$ (439.50): C, 76.52; H, 5.73; N, 3.19. Found: C, 76.26; H, 5.86; N, 2.98.

**Elimination of the *p*-Methoxyphenyl Substituent with CAN. Synthesis of Lactams 18a−c. General Method.** To a solution of the corresponding lactam **16** (1 mmol) in acetonitrile (10.4 mL) at 0 °C was added dropwise a solution of CAN (1.67 g, 3 mmol) in water (13.9 mL). The mixture was stirred at rt until the reaction was complete (TLC, 30 min to 1 h). Then the aqueous layer was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum, giving a 98% yield of colorless oils as 70:30 mixtures of aldehydes and *N*,*O*-ketals **17a−c**. The residue was dissolved in ethanol (15 mL), and $NaBH_4$ (1.5 mmol) was added slowly at 0 °C. The solution was stirred at rt until the reduction was finished (TLC) and quenched by addition of dilute (5%) hydrochloric acid. Ethanol was eliminated under vacuum, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel using hexanes−$CH_2Cl_2$ (4:1, v/v) as eluent.

**(1*R*,2*S*,5*S*,7*S*)-2-(2-Hydroxymethylphenyl)-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]decan-4-one (18a).** Yield: 98%. Colorless solid. Mp: 194−195 °C (from ethanol). $[\alpha]^{23}_D$ = +13.4 ($c$ = 0.4, EtOH/$H_2O$ (9:1)). $^1$H NMR ($\delta$): 1.17−1.28 (m, 1H); 1.44−

1.54 (m, 2H); 1.88−1.95 (m, 1H); 1.93 (dd, 1H, $J_1$ = 12.0 Hz, $J_2$ = 9.5 Hz); 2.12−2.13 (m, 1H); 2.46 (br s, 1H); 2.84 (dd, 1H, $J_1$ = 9.5 Hz, $J_2$ = 4.6 Hz); 4.68 (t, 1H, $J$ = 4.9 Hz); 4.72 (dd, 1H, $J_1$ = 12.3 Hz, $J_2$ = 2.7 Hz); 4.88 (dd, 1H, $J_1$ = 12.3 Hz, $J_2$ = 2.7 Hz); 5.36 (s, 1H); 6.09 (br s, 1H); 7.28−7.44 (m, 4H). $^{13}$C NMR ($CDCl_3$/acetone-$d_6$, $\delta$): 28.8; 29.4; 34.9; 47.7; 55.4; 62.3; 76.7; 92.9; 125.7; 127.9; 128.0; 128.9; 136.8; 138.2; 178.0. IR (KBr): 3260 (br); 2990; 2940; 1680; 1610; 770; 720 cm$^{-1}$. Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.33; H, 6.44; N, 5.34.

**(1*R*,2*S*,5*S*,7*S*)-2-(2-Hydroxymethylphenyl)-5-methyl-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]decan-4-one (18b).** Yield: 98%. Colorless solid. Mp: 88−89 °C (from ethanol). $[\alpha]^{23}_D$ = +22.0 ($c$ = 0.2, $CHCl_3$). $^1$H NMR ($\delta$): 1.31 (s, 3H); 1.37−1.52 (m, 4H); 1.84−1.93 (m, 1H); 2.26−2.31 (m, 1H); 3.00 (br s, 1H); 4.50 (t, 1H, $J$ = 5.3 Hz); 4.65 (d, 1H, $J$ = 12.4 Hz); 4.90 (d, 1H, $J$ = 12.4 Hz); 5.34 (d, 1H, $J$ = 0.8 Hz); 6.33 (br s, 1H); 7.30−7.34 (m, 2H); 7.43−7.47 (m, 2H). $^{13}$C NMR ($\delta$): 22.6; 25.3; 29.0; 45.0; 52.0; 56.1; 62.2; 76.3; 94.3; 125.8; 128.0; 128.2; 129.6; 136.1; 138.4; 181.5. IR (KBr): 3397 (br); 2972; 1686; 772 cm$^{-1}$. Anal. Calcd for $C_{16}H_{19}NO_3$ (273.33): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.22; H, 6.95; N, 5.02.

**(1*R*,2*S*,5*S*,6*S*,7*S*)-2-(2-Hydroxymethylphenyl)-6-methyl-10-oxa-3-azatricyclo[5.2.1.0$^{1,5}$]decan-4-one (18c).** Yield: 98%. Colorless solid. Mp: 162−163°C (from ethanol). $[\alpha]^{23}_D$ = +10.8 ($c$ = 0.4, $CHCl_3$). $^1$H NMR ($\delta$): 1.06−1.28 (m, 1H); 1.14 (d, 3H, $J$ = 7.0 Hz); 1.44 (td, 1H, $J_1$ = 11.7 Hz, $J_2$ = 5.6 Hz); 1.64−1.80 (m, 2H); 2.19 (d, 1H, $J$ = 5.1 Hz); 2.46−2.52 (m, 1H); 2.77−2.86 (br s, 1H); 4.42 (t, 1H, $J$ = 4.8 Hz); 4.67 (d, 1H, $J$ = 12.3 Hz); 4.83 (d, 1H, $J$ = 12.3 Hz); 5.24 (d, 1H, $J$ = 1.5 Hz); 6.20 (br s, 1H); 7.20−7.41 (m, 4H). $^{13}$C NMR ($\delta$): 15.7; 23.2; 29.5; 41.1; 55.3; 55.8; 62.9; 80.9; 93.9; 125.9; 128.2; 128.6; 129.4; 137.1; 137.8; 178.1. IR (KBr): 3432 (br); 2971; 1677; 1560; 766 cm$^{-1}$. Anal. Calcd for $C_{16}H_{19}NO_3$ (273.33): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.48; H, 7.19; N, 4.98.

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**Supporting Information Available:** General experimental methods and physical and spectral characteristics for compounds **2**−**7a**−**d** and **9**−**15a**−**d** and copies of $^1$H NMR and $^{13}$C NMR spectra for compounds **2**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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