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Efficient Asymmetric Synthesis of Novel Gastrin Receptor Antagonist AG-041R via Highly Stereoselective Alkylation of Oxindole Enolates

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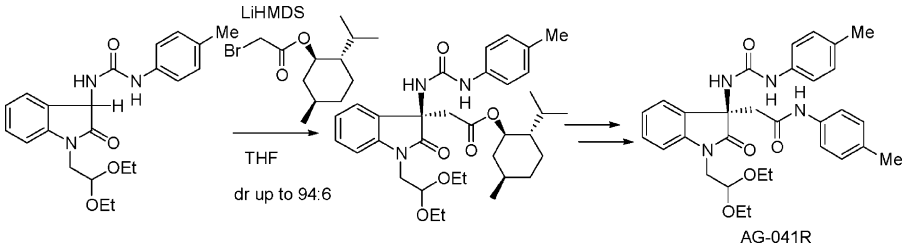


An efficient method for asymmetric synthesis of the potent Gastrin/CCK-B receptor antagonist AG-041R was developed. Core oxindole stereochemistry was established by asymmetric alkylation of oxindole enolates with bromoacetic acid esters, using *l*-menthol as a chiral auxiliary. The key alkylation reaction of the oxindole enolates generated tetrasubstituted chiral intermediates with high diastereoselectivity. The stereoselective alkylation reactions are described in detail.

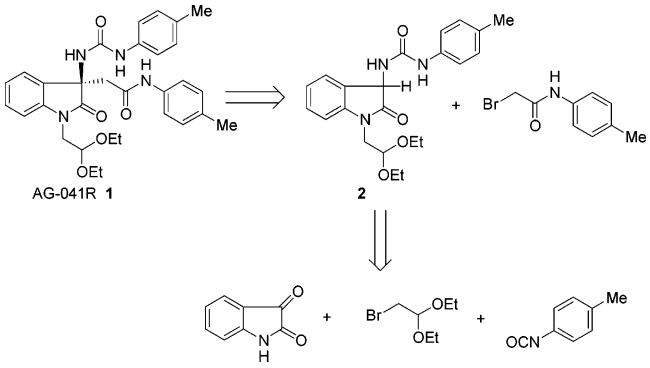
Introduction

AG-041R, 2-[(*R*)-1-(2,2-Diethoxyethyl)-2-oxo-3-(3-*p*-tolylureido)-2,3-dihydro-1*H*-indol-3-yl]-*N*-*p*-tolylacetamide (**1**), a novel oxindole derivative, was synthesized as a gastrin/CCK-B receptor antagonist.[1] This compound showed the most potent activity with an IC50 of 1.1 nmol, the highest bioavailability among the numerous oxindole derivatives synthesized, and demonstrated therapeutic efficacy with oral administration in animal models of gastric ulcer. AG-041R **1** was selected as a clinical candidate and, for the preclinical study, we investigated the scalable synthesis of the compound. Here we present synthesis of the compound based on the stereoselective alkylation of the oxindole enolates using *l*-menthyl bromoacetate as the chiral alkylation reagent. Efficient, chromatography-free synthesis suitable for the preparation of a large quantity of the compound was established.

Results and Discussion

Retrosynthetic analysis (Scheme 1) revealed that a strategy based on the alkylation of the oxindole derivatives would be the most straightforward to obtain the basic framework for our target compound. We soon realized that one of the challenges of synthesis would be the asymmetric alkylation of oxindole derivative **2**. Therefore, the focus was on identifying an efficient method for asymmetric alkylation reaction.

SCHEME 1. Retrosynthetic Analysis



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There are a number of synthetic methods employed to construct a quaternary stereocenter with high stereoselectivity.[2,3] Asymmetric alkylation with a phase transfer catalyst is one of the choices.[4,5] However, this method still requires a relatively large amount of chiral catalyst, which has a complicated structure and is difficult to obtain.

Due to availability and ease of control of the reaction process, we investigated the stoichiometric alkylation of oxindole enolates with haloacetic acid esters using a commercially available chiral alcohol such as *l*-menthol as an auxiliary. Reactions of this type have rarely been studied to date, even though a substantial amount of effort to use *l*-menthol as a chiral auxiliary has been demonstrated.[6,7] To the best of our knowledge, only a single report has been published in which poor stereoselectivity was shown in the alkylation of oxindole derivatives with *l*-menthyl chloroacetate as a chiral electrophile.[8]

Synthesis of Urea 2. To synthesize the intermediate urea **2**, two possible sequences were considered, as shown in Scheme 2. We first tried alkylation of isatin **3**, but the reaction was rather messy and the yield of the product only moderate, most likely a result of the instability of both the isatin and the product under the reaction conditions. The overall yield of urea **2** from isatin **3** was only 23%. We next tried the sequence; the oxime formation proceeded quantitatively and the following alkylation was reasonably performed in DMA. The use of *t*-BuOK or NaH gave identical results for the alkylation reaction so we selected *t*-BuOK because of its ease of handling. Without purification, the product was hydrogenated in acetonitrile affording the aminooxindole derivative **8**. Product **8** was unstable and readily oxidized, and was therefore reacted with *p*-tolylisocyanate without purification affording urea **2**. Compound **2** was purified by filtration and washing with CH_3CN to give a 99% pure product. The yield of the product was 52% in 3 steps.

Diastereoselective Alkylation. The alkylation reaction of urea **2** proceeded efficiently in aprotic polar solvents such as DMF and DMSO and the racemic AG-041 was synthesized from the alkylation of urea **2** with methyl *p*-bromoacetanilide, and so we first tried the alkylation reaction with *l*-menthyl bromoacetate in DMF. The resulting diastereoselectivity of the reaction was low (Table 1, entry 1). Even at lower temperatures in DMF, only a slight degree of improvement in the stereoselectivity was observed (Table 1, entries 2 and 3). By using solvent THF, the selectivity showed a slight increase with *t*-BuOK as the base (Table 1, entry 4). When the reaction was performed in a less polar solvent with a lithium cation base, the diastereoselectivity was greatly increased even at room temperature (Table 1, entry 5). Although dioxane showed the best results in terms of diastereoselectivity for the reaction (Table 1, entry 6), it is rated a Class 2 solvent according to the ICH guideline and requires special handling because of its possible carcinogenic activity. Therefore, we selected THF for further study. The diastereoselectivity increased when the reaction was performed at a lower temperature (Table 1, entry 8) and was improved by the use of a slight excess of base (Table 1, entries 9 and 10). We also confirmed that *n*-BuLi could be directly used as a base without a significant side reaction (Table 1, entry 12).

Under the same reaction conditions, *l*-menthyl chloroacetate did not afford the target product. The stereoselectivity observed was low (57:43 major/minor, 81% yield) when an isomenthol derivative was used for the reaction. The borneol ester of bromoacetic acid also showed unsatisfactory results (66:34 major/minor, 90% yield).

Finally, we selected the reaction conditions shown in Table 1 (entry 9) for further scale-up. We have successfully performed the reaction on a scale of 100 g with a 92:8 diastereomeric ratio. Recrystallization of the crude product from a methanol/water solution gave a diastereomerically pure product in 55% yield.

Confirmation of the Absolute Configuration of the Major Product. The absolute configuration of the major product of the reaction was confirmed by X-ray analysis of **12**, derived from the *l*-menthol ester **9** (Scheme 3). Absolute configuration of the 3-position was confirmed to be R when the *l*-menthol ester of bromoacetic acid was used for the asymmetric reaction. An ORTEP drawing for the X-ray crystal structure of **12** is presented in the Supporting Information.

SCHEME 2. Synthesis of Intermediate Urea 2

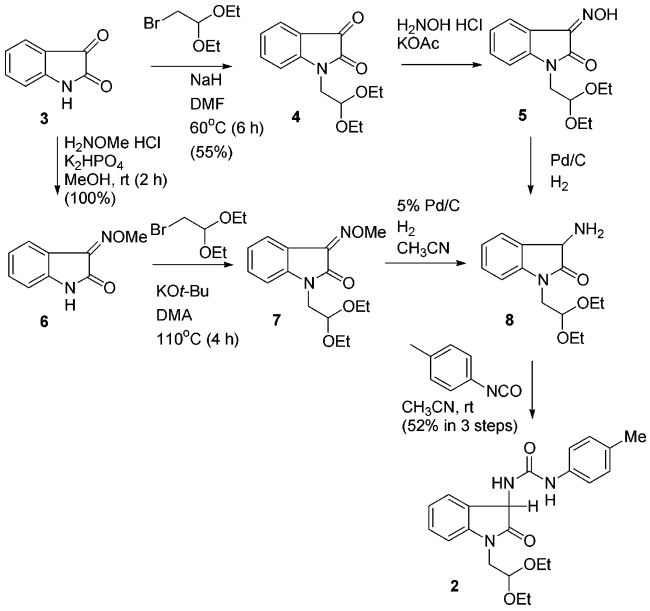

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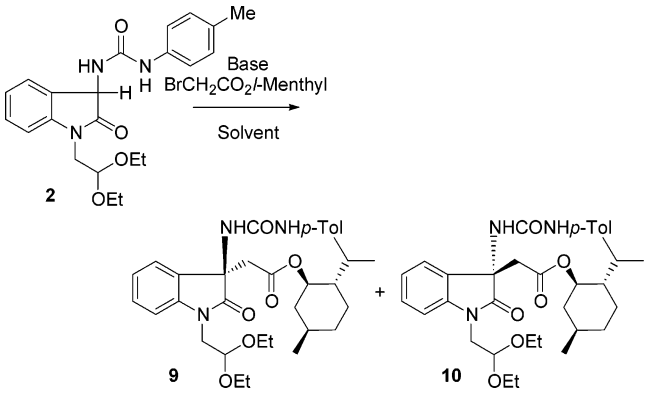
TABLE 1. Diastereoselective Alkylation of the Urea 2 with *l*-Menthyl Bromoacetate



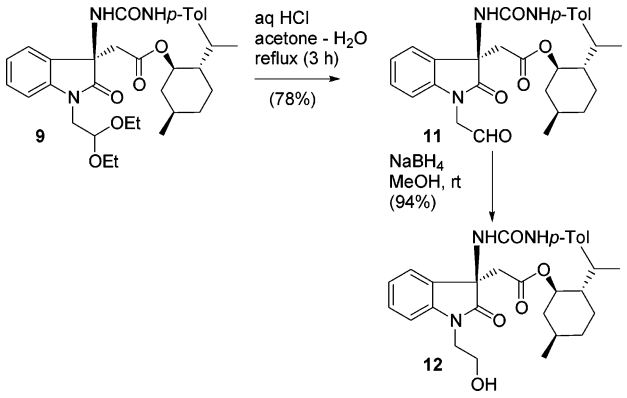
entry[a]	solvent	base	equiv of base	temp (°C)	**9**:**10** ratio[e]
1	DMF	*t*-BuOK	1.1	−10	60:40[f]
2	DMF	*t*-BuOK	1.1	−60	75:25[f]
3	DMF−toluene	*t*-BuOK	1.1	−78	80:20[f]
4	THF	*t*-BuOK	1.1	−10	75:25[f]
5[b]	THF	LiHMDS	1.0	20	90:10[f]
6[b,c]	dioxane	LiHMDS	1.0	20	92:8[f]
7[b,c]	*t*-BuOMe	LiHMDS	1.0	20	*g*
8	THF	LiHMDS	1.0	0	92:8[h]
9	THF	LiHMDS	1.1	0	93:7[h]
10[d]	THF	LiHMDS	1.2	0	94:6[h]
11	THF	LiHMDS	1.1	−15	94:6[h]
12	THF	*n*-BuLi	1.1	0	93:7[h]

[a] Unless otherwise noted, the reaction was carried out with 1.2 equiv of *l*-menthyl bromoacetate. [b] 1.1 equiv of *l*-menthyl bromoacetate was used. [c] LiHMDS in hexane was used. [d] 1.3 equiv of *l*-menthyl bromoacetate was used. [e] The conversion appeared excellent as determined by HPLC analysis, the products were not isolated, thus only product ratios not yields were determined. [f] Determined by ^{1}H NMR analysis of the crude reaction mixture. [g] Indeterminate result. [h] Determined by HPLC analysis of the crude reaction mixture.

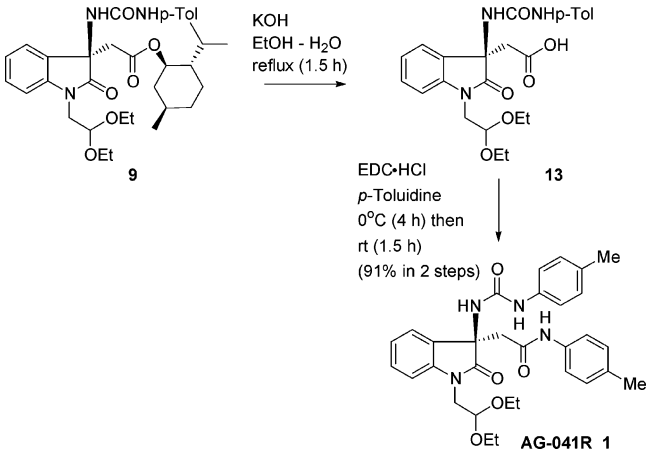
Since the final product was not crystalline, clean conversion from menthol ester **9** to the final compound **1** was required. Hydrolysis of the menthol ester was efficiently performed by using KOH in ethanol/H_2O under reflux conditions. The menthol-free carboxylic acid was obtained from basic water extraction of the intermediate carboxylic acid **13** from hexane followed by the acidic extraction of the compound. In the amidation step, we examined EDC-HCl, thionyl chloride, carbonyl diimidazole, DPPA, and DCC. Among them, EDC-HCl was selected as the coupling agent because it gave the best result in terms of purity of the product affording the final product **1** in 99.1% purity and in 91% yield.

Scope of the Asymmetric Alkylation Reaction. To clarify the generality of the asymmetric reaction, the diastereoselective alkylation of various N-protected oxindole enolates with *l*-menthyl bromoacetate was examined. As shown in Table 2, a substituent at the 1-position did not affect the diastereoselection (Table 2, entry 3). The results confirmed that diethylacetal functionality does not take part in the coordination of the lithium cation and the substituent at the 1-position does not play a role in diastereoselection. After exchanging the protective group of nitrogen at the 3-position for a carbamate, the character of the reaction significantly changed (Table 2, entries 4−7). Both *tert*-butyl and methyl carbamates gave low diastereoselectivity with 1 equiv of base. The selectivity was improved by the use of a slight excess of base and an electrophile, although only a slight increase of selectivity was observed in the case of urea. The

SCHEME 3. Synthesis of Alcohol Derivative 12



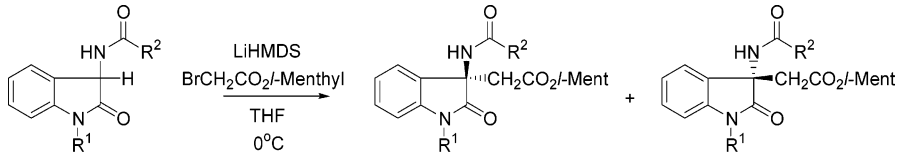
SCHEME 4. Transformation to Target Compound 1



diastereoselectivity increased to a reasonable range with 1.5 equiv of base (Table 2, entry 6). The same trend was observed in the case of the acyl group for the protective group (Table 2, entries 8 and 9). The diastereoselectivity of the benzamide was better than that of acetamide, and therefore, the bulkiness of the protective group is apparently one of the factors of stereoselectivity (Table 2, entries 8−11). Not only the bulkiness of the protective groups but also the basicity order of the carbonyl group, urea > carbamate > amide, appeared to reflect the diastereoselectivity. An increase in the electron density of the carbonyl group in the nitrogen protective group would facilitate the coordination of the carbonyl group in the N-protective group with lithium cation and thus lead to high stereoselection. The use of a slight excess of base would give partially deprotonated nitrogen and raise the electron density of the carbonyl group. This would affect efficient chelation, the probable cause of the high diastereoselectivity observed in entries 9 and 11.

Stereochemistry of the Reaction. From the results shown in Table 1 and because the use of a more coordinatable lithium base gave the best stereoselectivity, the coordination of *l*-menthyl bromoacetate with the lithium enolates at its carbonyl group in the transition state is possible. In the most stable conformer of the *l*-menthyl bromoacetate, the carbonyl group is directed away from the isopropyl group of *l*-menthol and bisects the menthol ring, suggesting that the oxindole enolates approach from the carbonyl group side of the conformer as depicted in Figure 1 coordinating with the lithium cation, and thus the approach of the enolates from the upper side would be eliminated. The results shown in Table 2 indicate that the

TABLE 2. Diastereoselective Alkylation of Various N-Protected Oxindole Enolates with *l*-Menthyl Bromoacetate



2 or **14** **9** or **15** **10** or **16**

entry[a]	substrate	R^1	R^2	LiHMDS (equiv)	product[d]	yield[e] (%)	ratio (major:minor)
1	**2**	$CH_2CH(OEt)_2$	*p*-TolNH	1.0	**9** + **10**	83	92:8[f]
2[b]	**2**	$CH_2CH(OEt)_2$	*p*-TolNH	1.2	**9** + **10**	77	94:6[f]
3	**14a**	Me	*p*-TolNH	1.0	**15a** + **16a**	84	91:9[g]
4	**14b**	Me	*t*-BuO	1.0	**15b** + **16b**	74	56:44[g]
5[b]	**14b**	Me	*t*-BuO	1.2	**15b** + **16b**	64	69:31[g]
6[c]	**14b**	Me	*t*-BuO	1.5	**15b** + **16b**	62	85:15[g]
7	**14c**	Me	MeO	1.0	**15c** + **16c**	58	72:28[g]
8	**14d**	Me	Ph	1.0	**15d** + **16d**	83	88:12[g]
9[b]	**14d**	Me	Ph	1.2	**15d** + **16d**	82	95:5[g]
10	**14e**	Me	Me	1.0	**15e** + **16e**	57	76:24[g]
11[b]	**14e**	Me	Me	1.2	**15e** + **16e**	69	84:16[g]

[a] Unless otherwise noted, the reaction was carried out with 1.1 equiv of *l*-menthyl bromoacetate. [b] 1.3 equiv of *l*-menthyl bromoacetate was used. [c] 1.6 equiv of *l*-menthyl bromoacetate was used. [d] Stereochemistry was tentatively assigned on the basis of the results shown in Table 1. [e] Isolated yield of diastereomixtures. [f] Determined by HPLC analysis of the crude reaction mixture. [g] Determined by ^{1}H NMR analysis of the crude reaction mixture.

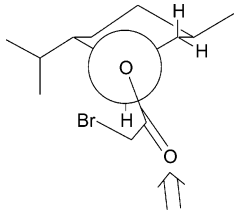


FIGURE 1. Expected direction of the oxindole enolates approach to the *l*-menthyl bromoacetate.

carbonyl group in the nitrogen protective group of the oxindole enolates participates in the coordination with the lithium cation. On the basis of these results, two transition states (Figure 2) are possible. Of the two, transition state A, without the steric interaction between the isopropyl group in the *l*-menthyl group and the nitrogen protective group of transition state B, is preferable. The relatively lower stereoselectivity observed in the carbamates as protective groups (Table 2, entries 4 and 7) would be reasonably explained by the model. The more flexible nature of the carbamates, compared to the ureas and amides, would reduce the steric interaction in the undesirable transition state B and would lead to decreased stereoselectivity.

Conclusion

We have demonstrated a highly efficient asymmetric alkylation of oxindole derivatives using commercially inexpensive *l*-menthol as a chiral auxiliary and found the use of lithium cation is essential for high diastereoselection. Diastereoselective alkylation from a six-step chromatography-free synthesis of the optically pure oxindole derivative **1** was successful and achieved an overall yield of 26%.

Experimental Section

1*H*-Indole-2,3-dione 3-(*O*-Methyloxime) (6). To a suspension of isatin (100 g, 0.68 mol) in methanol (1.0 L) were added *O*-methylhydroxylamine hydrochloride (59.6 g, 0.714 mol) and dipotassium hydrogenphosphate (118 g, 0.68 mol). After the mixture was stirred for 2 h at ambient temperature, the solvent was removed in vacuo. Water (1.0 L) was added to the mixture to give yellow crystals. The crystals were collected and dried under reduced pressure over phosphorus oxide to give the title compound **6** as yellow crystals (120 g, 100%): mp 172−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.88 (dd, J = 7.5, 0.6 Hz, 1H), 7.29 (ddd, J = 7.8, 7.8, 1.4 Hz, 1H), 7.00 (ddd, J = 7.8, 7.5, 0.9 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 143.8, 141.9, 132.4, 127.6, 122.8, 116.0, 110.8, 64.7. HRMS *m*/*z* $[M + H]^+$ calcd for $C_9H_9N_2O_2$ 177.0664, found 177.0657.

1-(2,2-Diethoxyethyl)-1*H*-indole-2,3-dione 3-(*O*-Methyloxime) (7). To a solution of **6** (93.3 g, 0.53 mol) in DMA (370 mL) was added potassium *tert*-butoxide (71.2 g, 0.636 mol) followed by the addition of bromoacetaldehyde diethylacetal (131 g, 0.665 mol). The mixture was maintained at 110 °C for 4 h then cooled to ambient temperature. Aqueous ammonium chloride was added and extracted with methyl *tert*-butyl ether (2 × 1 L). The combined organic layers were washed successively with aqueous potassium bisulfate and aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated in vacuo to give a yellow oil. (127 g) The crude product **7** was used without purification for the next step: mp 72−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, J = 7.5, 1.4, 0.8 Hz, 1H), 7.27 (ddd, J = 8.0, 7.6, 1.4 Hz, 1H), 7.00−6.92 (m, 2H), 4.63 (t, J = 5.3 Hz, 1H), 4.22 (s, 3H), 3.77 (d, J = 5.3 Hz, 2H), 3.67 (dq, J = 9.3, 7.0 Hz, 2H), 3.44 (dq, J = 9.3, 7.0 Hz, 2H), 1.07 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 143.9, 143.1, 131.8, 127.2, 122.4, 115.3, 109.8, 100.4, 64.5, 63.5, 43.3, 15.2. HRMS *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_4$ 293.1501, found 293.1490.

***N*-[1-(2,2-Diethoxyethyl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl]-*N*′-(4-methylphenyl)urea (2).** To a solution of **7** (127 g) in acetonitrile (2.0 L) was added 5% palladium on carbon (12.7 g). The mixture was stirred under hydrogen under atmospheric pressure at ambient temperature for 6 h. After removal of the palladium carbon by filtration, *p*-tolyl isocyanate (60.6 g, 0.434 mol) was added at ambient temperature. The mixture was stirred for 1 h during which time a solid was generated. The cake was collected, washed with acetonitrile, and then dried under reduced pressure to yield the title compound **2** as white crystals (109 g, 52% in 3 steps): mp 175−177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (s, 1H), 7.38−7.20 (m, 4H), 7.06 (d, J = 7.8 Hz, 1H), 7.03−6.95 (m, 3H), 6.91 (d, J = 7.8 Hz, 1H), 5.05 (d, J = 7.8 Hz, 1H), 4.69 (t, J = 5.3 Hz, 1H), 3.82 (dd, J = 14.2, 5.5 Hz, 1H), 3.70−3.58 (m, 3H), 3.47

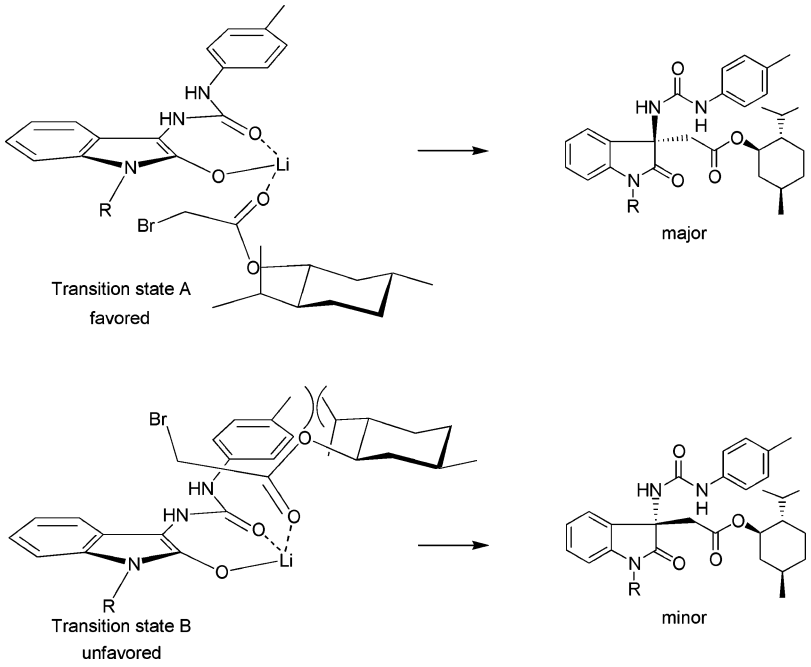


FIGURE 2. Plausible favored and unfavored transition states for the alkylation reaction.

(dq, J = 9.5, 7.0 Hz, 2H), 2.19 (s, 3H), 1.05 (t, J = 7.0 Hz, 3H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.6, 154.2, 143.0, 137.1, 129.8, 128.7, 127.7, 127.5, 122.9, 121.6, 117.6, 109.0, 99.4, 62.3, 62.0, 52.3, 43.0, 20.2, 15.2. HRMS *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{28}N_3O_4$ 398.2080, found 398.2076.

General Procedure for the Asymmetric Alkylation Reaction (Table 1). To a solution of **2** (39.7 mg, 0.10 mmol) in a solvent (0.40 mL) was added a base at 0 °C followed by the addition of *l*-menthyl bromoacetate[9] at the indicated temperature. After stirring until no urea **2** could be detected by TLC, aqueous NH_4Cl was added and the mixture was extracted with methylene chloride (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The diastereomeric ratio of the crude products was determined by ^{1}H NMR analysis or HPLC assay.

[(*R*)-1-(2,2-Diethoxyethyl)-2-oxo-3-(3-*p*-tolylureido)-2,3-dihydro-1*H*-indol-3-yl]acetic Acid (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl Ester (9). (a) For Small Scale. To a suspension of **2** (39.7 mg, 0.10 mmol) in THF (0.40 mL) was added LiHMDS (0.90 M in THF, 0.111 mL, 0.10 mmol) at 0 °C followed by the addition of *l*-menthyl bromoacetate (30.5 mg, 0.110 mmol). After stirring for 5 h, aqueous NH_4Cl was added and the mixture was extracted with methylene chloride (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The crude mixture was purified by silica gel chromatography to give the title compound **9** as white crystals (49.4 mg, 83% yield). The diastereomeric ratio of the crude products was 92:8 determined by HPLC assay (YMC-Pack CN 4.6 × 300, *n*-hexane/*i*-PrOH = 99:1, 0.9 mL/min, major t_R = 19.0 min, minor t_R = 21.2 min).

(b) For Large Scale. To a suspension of **2** (100 g, 0.252 mol) in THF (500 mL) was added LiHMDS (1 M in THF, 277 mL, 0.277 mol) at 0 °C followed by the addition of *l*-menthyl bromoacetate (83.7 g, 0.302 mol). After stirring for 3 h, aqueous NH_4Cl (200 mL) was added and extracted with *tert*-butyl methyl ether (500 mL). The organic layer was washed with aqueous NH_4Cl (2 × 200 mL) and with saturated NaCl solution, dried over Na_2SO_4, and then concentrated in vacuo. To the crude mixture were added methanol (1.5 L) and water (340 mL) followed by seeding. After standing for 2 h, the crystals formed were collected, washed with methanol/water (75/25, 500 mL), and then dried under vacuum to give diastereomerically pure product **9** as white crystals (82.2 g, 55%). The diastereomeric ratio of the products was >99:1 determined by HPLC assay (YMC-Pack CN 4.6 × 300, *n*-hexane/*i*-PrOH = 99:1, 0.9 mL/min, major t_R = 19.0 min, minor t_R = 21.2 min): mp 153−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 7.3, 0.9 Hz, 1H), 7.25 (ddd, J = 7.8, 7.6, 1.4 Hz, 1H), 7.14−7.05 (m, 4H), 7.02−6.95 (m, 3H), 6.77 (s, 1H), 4.75 (t, J = 4.9 Hz, 1H), 4.62 (ddd, J = 11.0, 10.8, 4.4 Hz, 1H), 3.94 (dd, J = 14.2, 5.8 Hz, 1H), 3.82 (dd, J = 14.2, 5.9 Hz, 1H), 3.78−3.65 (m, 2H), 3.62−3.48 (m, 2H), 3.05 (d, J = 15.3 Hz, 1H), 2.63 (d, J = 15.1 Hz, 1H), 2.25 (s, 3H), 1.90−1.81 (m, 1H), 1.74−1.58 (m, 3H), 1.52−1.32 (m, 1H), 1.30−0.72 (m, 4H), 1.16 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.63 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 169.3, 153.8, 142.8, 135.6, 132.7, 129.25, 129.20, 128.7, 122.4, 120.6, 110.1, 100.8, 75.4, 63.7, 63.5, 59.3, 46.7, 44.2, 41.2, 40.7, 34.1, 31.4, 26.1, 23.3, 22.0, 20.9, 20.8, 16.2, 15.44, 15.42. HRMS *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{48}N_3O_6$ 594.3543, found 594.3545.

2-[(*R*)-1-(2,2-Diethoxyethyl)-2-oxo-3-(3-*p*-tolylureido)-2,3-dihydro-1*H*-indol-3-yl]-*N*-*p*-tolylacetamide (1). To a solution of **9** (12.0 g, 20.2 mmol) in EtOH (240 mL) was added 1 N KOH (24 mL). The mixture was refluxed for 1.5 h, followed by addition of 0.16 N HCl (174 mL). The solvent was removed in vacuo. To the mixture was added 0.24 N KOH (186 mL) to basify the solution. The mixture was washed with hexane (4 × 250 mL) to remove the menthol. The water layer was acidified with 0.2 N HCl (187 mL). Then the mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with saturated NaCl, dried with $MgSO_4$, and then concentrated in vacuo to give **13** (9.7 g). To a solution of **13** were added EDC-HCl (5.03 g, 26.2 mmol) and *p*-toluidine (2.82 g, 26.4 mmol) at 0 °C. The mixture was stirred for 4 h at 0 °C, and then for 1.5 h at room temperature. The mixture was washed with 1 N HCl (2 × 400 mL), followed by saturated NaCl solution (400 mL). The organic layer was dried with $MgSO_4$, and then the solvent was removed in vacuo. The resultant product was dried under vacuum for 2 days at 30 °C to give the title product **1** (10.0 g, 91%). The purity of the product was 99.1% determined by HPLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.35−7.19 (m, 5H), 7.14 (s, 1H), 7.08−6.95 (m, 6H), 6.99 (d, J =

(9) Burgess, K.; Henderson, I. *Tetrahedron* **1991**, *47*, 6601.

8.4 Hz, 2H), 4.77 (dd, J = 5.8, 5.2 Hz, 1H), 3.98 (dd, J = 14.2, 8.2 Hz, 1H), 3.78 (dd, J = 14.2, 4.3 Hz, 1H), 3.78−3.46 (m, 4H), 2.99 (d, J = 14.8 Hz, 1H), 2.62 (d, J = 14.6 Hz, 1H), 2.27 (s, 3H), 2.20 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 167.2, 153.8, 142.3, 135.7, 134.6, 134.4, 132.2, 130.0, 129.3, 129.1, 128.7, 122.8, 122.7, 120.4, 119.8, 110.1, 100.5, 63.4, 59.8, 43.9, 43.8, 20.9, 20.8, 15.3. HRMS m/z $[M + H]^+$ calcd for $C_{31}H_{37}N_4O_5$ 545.2764, found 545.2784.

Typical Procedure for the Asymmetric Alkylation of Ureas: [1-Methyl-2-oxo-3-(3-*p*-tolylureido)-2,3-dihydro-1*H*-indol-3-yl]-acetic Acid (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl Ester (15a + 16a). To a suspension of **14a** (29.5 mg, 0.10 mmol) in THF (0.40 mL) was added LiHMDS (0.90 M in THF, 0.111 mL, 0.10 mmol) at 0 °C followed by the addition of *l*-menthyl bromoacetate (30.5 mg, 0.110 mmol). After stirring for 4 h, aqueous NH_4Cl was added and the mixture was extracted with methylene chloride (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The diastereomeric ratio was determined to be 91:9 by comparison of one of the geminal protons in ^{1}H NMR analysis of the crude product ($-CH_2-CO_2-$*l*-Menthyl, major δ 2.99 ppm, minor δ 2.97 ppm). The crude mixture was purified by silica gel chromatography to give the title compound **15a** and **16a** as an inseparable mixture of diastereomers as a colorless oil (41.2 mg, 84% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.5, 0.8 Hz, 1H), 7.26 (dd, J = 7.6, 1.2 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.03 (ddd, J = 7.6, 7.2, 0.9 Hz, 1H), 6.97 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 7.8 Hz, 1H), 6.78 (s, 1H), 4.58 (ddd, J = 11.0, 10.8, 4.3 Hz, 1H), 3.27 (s, 3H), 2.99 (d, J = 15.0 Hz, 1H), 2.63 (d, J = 15.0 Hz, 1H), 2.24 (s, 3H), 1.91 (br s, 1H), 1.83−1.76 (m, 1H), 1.69−1.56 (m, 3H), 1.48−1.30 (m, 1H), 1.28−1.16 (m, 1H), 1.05−0.70 (m, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H), 0.60 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 169.1, 154.0, 143.4, 135.6, 132.6, 129.4, 129.3, 129.1, 123.1, 122.6, 120.4, 108.6, 75.3, 59.3, 46.7, 41.2, 40.7, 34.1, 31.4, 26.8, 26.1, 23.3, 22.0, 20.81, 20.77, 16.2. HRMS m/z $[M + H]^+$ calcd for $C_{29}H_{38}N_3O_4$ 492.2862, found 492.2863.

Typical Procedure for the Asymmetric Alkylation of Carbamates: (3-*tert*-Butoxycarbonylamino-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic Acid (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl Ester (15b + 16b). To a solution of **14b** (26.2 mg, 0.10 mmol) in THF (0.40 mL) was added LiHMDS (0.90 M in THF, 0.167 mL, 0.15 mmol) at 0 °C followed by the addition of *l*-menthyl bromoacetate (44.4 mg, 0.16 mmol). After stirring for 4 h, aqueous NH_4Cl was added and the mixture was extracted with methylene chloride (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The diastereomeric ratio was determined to be 85:15 by comparison of one of the geminal protons in ^{1}H NMR analysis of the crude product ($-CH_2CO_2-$*l*-Menthyl: major δ 2.53 ppm, minor δ 2.47 ppm). The crude mixture was purified by silica gel chromatography to give the title compound **15b** and **16b** as an inseparable mixture of diastereomers as a colorless oil (28.5 mg, 62% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (m, 1H), 7.02 (ddd, J = 7.6, 7.5, 1.1 Hz, 1H), 6.83 (dd, J = 7.3, 1.1 Hz, 1H), 6.23 (br s, 1H), 4.66 (ddd, J = 11.0, 10.8, 4.4 Hz, 1H), 3.25 (s, 3H), 2.96 (d, J = 14.8 Hz, 1H), 2.53 (d, J = 15.0 Hz, 1H), 1.96−1.86 (m, 1H), 1.78−1.58 (m, 3H), 1.54−1.20 (m, 2H), 1.25 (br s, 9H), 1.10−0.70 (m, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.68 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 169.0, 153.5, 143.1, 129.1, 123.1, 122.8, 122.5, 108.2, 80.2, 75.6, 59.2, 46.8, 41.1, 40.8, 34.1, 31.4, 28.2, 26.7, 26.2, 23.4, 22.1, 20.8, 16.3. HRMS m/z $[M + H]^+$ calcd for $C_{26}H_{39}N_2O_5$ 459.2859, found 459.2867.

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Supporting Information Available: Complete experimental procedures, product characterization, and NMR spectra for all compounds, as well as an ORTEP drawing and a CIF file for the X-ray structure of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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