calculated from the analytical data[32] to be 13:1.

The other copolymer were prepared and characterized in a similar manner. AN–QN (20:1), $[\alpha]_D$ −19.7° (DMF, c 1); AN–QD (14:1), $[\alpha]_D$ +30.1° (DMF, c 1); AN–QD (23:1), $[\alpha]_D$ +25.6° (DMF, c 1).

Typical Procedures of Asymmetric Michael Reactions. Reaction 1 at Atmospheric Pressure. Quinine (1, 0.032 mmol), benzenethiol (**3a**, 4 mmol), and cyclohexen-3-one (**4a**, 5 mmol) were dissolved in 7 mL of toluene, and the solution was allowed to stand at ambient temperature. The reaction was almost complete after 5 h. The reaction mixture was extracted, successively, twice with 2 N hydrochloric acid and twice with water and dried over magnesium sulfate. Benzene was added to the solution, if necessary, during the washing procedure. The solvent and the reactants were evaporated completely under reduced pressure to give the addition product **5a** in a almost quantitative yield. For purification of **5a**, a short silica gel column was employed; benzene being an eluent. The optical rotation of **5a** was determined in benzene (c 0.5–1), and compared with the rotation of enantiomerically pure **5a**, $[\alpha]_{365}$ 651°[1] to determine ee %.

Reaction 1 at High Pressure. The reaction solution was prepared in a similar manner as described above and placed in a Teflon tube plugged at the both ends with Teflon stoppers. The tube was placed in a high-pressure reactor and pressurized. Generally it was 4–5 min from a preparation of the reaction mixture to a finish of pressurization operation. After 5 h, the pressure was released and the reaction mixture was worked up as described above.

Products of Reaction 1. 3-(Phenylthio)cyclohexanone (**5a**):[2] colorless oil, IR 1720 cm^{-1}; ^1H NMR (CCl_4) 1.2–2.7 (m, 8 H), 3.0–3.5 (m, 1 H), 6.7–7.3 (m, 5 H). 3-((*p*-Methylphenyl)thio)cyclohexanone (**5b**):[2] colorless oil; IR 1720 cm^{-1}; ^1H NMR (CCl_4) 1.4–2.8 (m, 8 H), 2.24 (s, 3 H), 6.8–7.3 (m, 4 H). 3-((*p*-*tert*-Butylphenyl)-thio)cyclohexanone (**5c**):[2] colorless oil; IR 1710 cm^{-1}; ^1H NMR (CCl_4) 1.32 (s, 9 H), 1.8–2.8 (m, 8 H), 3.3 (m, 1 H), 7.15 (s, 4 H). 3-((*p*-*tert*-Butylphenyl)thio)-6,6-dimethylcyclohexanone (**5d**):[2] colorless oil; ^1H NMR (CCl_4) 1.00 (s, 1 H), 1.08 (s, 1 H), 1.5–2.1 (m, 4 H), 1.29 (s, 9 H), 3.2 (m, 1 H), 7.10 (s, 4 H).

Reaction 2. The reaction **2** at atmospheric or high pressure was performed in a similar manner as described for reaction 1. Chromatographic separation of **8** from **6** was achieved by a short silica gel column (diethyl ether–hexane, 1/9 to 3/7). 1,3-Diphenyl-4-nitrobutan-1-one (**8**):[3] 33–100% yield, depending on pressure; mp 87–89 °C; IR (KBr) 1370, 1550, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 3.38 (d, 2 H), 3.9 (m, 1 H), 4.46 (q, 2 H), 7.0–7.9 (m, 10 H). The ee % was determined polarimetrically. The optical rotation of an enantiomerically pure (−)-**8**, $[\alpha]_D$ −41° was used for calculation.

Reaction 3. The AN–QN- or AN–QD-catalyzed reaction 3 at atmospheric or high pressure was performed in a similar manner as described for reaction 1. For example, methyl 1-oxoindan-2-carboxylate (**9**, 2 mmol) and methyl vinyl ketone (**10**, 2 mmol) were dissolved in toluene (10 mL), and to this solution was added an AN–QN (13:1) catalyst (42 mg, 0.05 mmol as QN). The reaction mixture was allowed to stand without stirring for 2 days or pressurized as described for reaction 1 for 2 days. The mixture was filtered, and the catalyst was washed with a small amount of benzene. The combined filtrate and washings were evaporated to dryness, and the residue was chromatographed on a short silica gel column eluted by dichloromethane to give the adduct **11** in a yield of 72–76%. Methyl 2-(3-oxobutyl)-1-oxoindan-2-carboxylate (**11**):[15] mp 104.5–107 °C; IR (KBr) 1715, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 2.15 (s, 3 H), 2.1–2.8 (m, 4 H), 3.06 and 3.78 (2 d, 2 H), 7.4–8.1 (m, 4 H). The ee was determined polarimetrically by using $[\alpha]_D$ −80.5° for the enantiomerically pure (−)-**11**.[14,15]

Acknowledgment. We are indebted to Professor M. Araki, Kyoto Institute of Technology, for preparation of AN–QN and AN–QD catalysts. This work was supported by Grant-in-Aid for scientific Research (No. 60430008 and 61840017) from the Ministry of Education, Science and Culture of Japan.

N-Dienyl Lactams: Preparation and Selectivity in the Diels–Alder Reaction[1a]

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We have shown that *N*-dienyl lactams are prepared in good yield by reaction of a lactam with an α,β-unsaturated aldehyde. The *N*-dienyl lactam is obtained with good selectivity for the *E,E*-isomer. The *N*-dienyl lactams are excellent enophiles and react with electron-deficient olefins to give exclusively the ortho regioisomer with good selectivity for the endo (*Z*) adduct, similar to results observed for dienyl amides. In addition, the yield of the Diels–Alder adduct can be significantly enhanced by the use of aqueous solvents when compared to traditional aprotic solvents.

In recent years the synthesis of heteroatom-substituted dienes and their use in the Diels–Alder reaction has become an area of major interest. There are a few examples of 1-(dialkylamino)-1,3-butadienes[2] as well as other 1- and 2-amino dienes which were shown to give primarily the *Z* and endo adduct in Diels–Alder reactions.[3-5] There are also several examples of *N*-dienyl amides and carbamates which are excellent enophiles in the Diels–Alder reaction.[6,7] Oppolzer prepared *N*-dienyl amides via treatment of the imine derived from reaction of amines with α,β-unsaturated aldehydes with dimsylsodium and an acid chloride.[6] Overman reported that pyrolysis of acetylenic imino ethers gave the dienyl amide.[7] Overman also prepared *N*-dienyl carbamates from the corresponding dienyl acid and ethyl

(1) (a) Presented in part at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 1986; paper ORGN 174. (b) Smith/Kline and French Research Fellow. (c) Abstracted in part from the Ph.D. thesis of C.A.Z.

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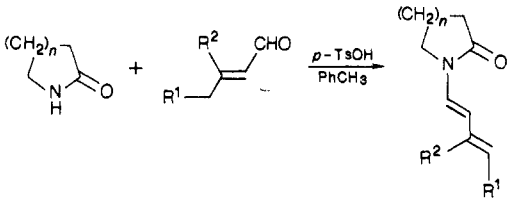
chloroformate[8] and prepared the *N*-dienyl amides by a modified Curtius sequence.[9] *N*-alkyl-2-pyridone derivatives are obvious relatives of *N*-alkenyl lactams and have been prepared by a variety of methods.[10]

Although both dienyl amides and carbamates have been prepared, the analogous *N*-dienyl lactams have been prepared only twice by highly specialized and low yield techniques. Ziegler and Heck reported that *N*-vinyl-2-pyrrolidinone reacted with 2-bromostyrene, in the presence of a palladium catalyst, to give *N*-(4-phenyl-1,3-butadienyl)-2-pyrrolidinone (**1**) in 25% yield.[11] Murata and Terada prepared *N*-(1,3-butadienyl)-2-pyrrolidinone (**2**) from 3-hydroxybut-3-enamine and γ-butyrolactone via pyrolytic amination, acylation, and passage through a hot tube at 550 °C, in 10% yield.[12] Although one can envision the use of derivatives of 4-aminobutanoic acid or 5-aminopentanoic acid in Oppolzer's imine acylation sequence, followed by intramolecular cyclization to the lactam, this approach does not appear straightforward or general. Similarly the acetylenic imino ether or dienyl carbamate technique is not applicable to lactams.

We recently reported that reaction of a lactam with an enolizable aldehyde gave the corresponding (*E*)-*N*-alkenyl lactam.[13] Further investigation of this reaction showed that 2-pyrrolidinone reacted with crotonaldehyde to give **2** in 41% isolated yield under the same conditions. Although the yield of **2** is modest it represents a significant improvement over Heck's[11] or Murata and Terada's[12] synthetic routes. The ready availability of the precursors makes this a very attractive route to **2** and suggested a serious evaluation of **2** and analogues as synthetically useful compounds.

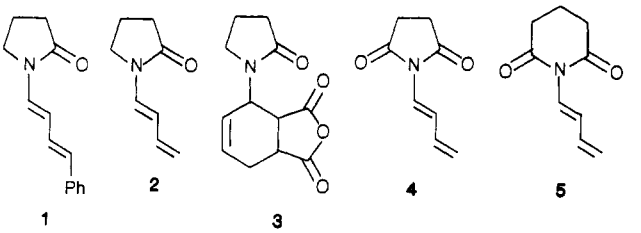
Murata and Terada had reported that **2** reacted with maleic anhydride to give the Diels–Alder adduct **3** in 75% yield[12] but the stereochemistry was not specified. There are several examples of Diels–Alder reactions with *N*-alkyl-2-pyridones, but the chemistry of these compounds[10] is not directly applicable to the dienyl lactams described here. Murata and Terada's work is therefore the only report of a *N*-dienyl lactam in a Diels–Alder reaction. Terada has prepared *N*-1,3-butadienylphthalimide (**4**) and the corresponding succinimide derivative **5**, however, by the same pyrolytic method used for **2** and reported facile Diels–Alder reaction with *p*-benzoquinone, maleic anhydride, acrylic acid, and acrolein.[14] Although 2-pyridones have been used extensively in synthesis the only synthetic applications of dienyl lactams have been as monomers for the preparation of a variety of useful polymers.[15] The difficulty in preparing **1**, **2**, **4**, and **5** has limited other applications. The presence of the preformed lactam ring in the Diels–Alder adduct, however, suggested the possibility of elaboration to tricyclic derivatives by methods not amenable to the dienyl amides or applicable to 2-pyridones. In addition, the effect of the lactam ring on the selectivity of the cycloadducts when compared to dienyl amides and carbamates was of interest. Although one expects similar behavior of dienyl lactams and dienyl amides in the Diels–Alder reaction it was necessary to confirm this reactivity before proceeding.

Table I. Preparation of *N*-Dienyl Lactams via Reaction of Lactams with α,β-Unsaturated Aldehydes



diene[a]	*n*	R^1	R^2	%
2	1	H	H	41
8	1	H	CH_3	66
11	1	CH_3	H	48[b]
12	1	n-C_4H_9	H	56[c]
6	2	H	H	34
9	2	H	CH_3	39
7	3	H	H	20
10	3	H	CH_3	46

[a] All new compounds gave satisfactory analyses. [b] Isolated as an 81:19 mixture of *E,E*/*E,Z* isomers. [c] Isolated as a 75:25 mixture of *E,E*/*E,Z* isomers.



We have shown that reaction of lactams with a variety of α,β-unsaturated aldehydes is general and the *N*-dienyl lactam is produced in modest to good yield as shown in Table I.

Not only the *N*-dienyl-2-pyrrolidiones could be prepared by this method but also derivatives of *N*-1,3-butadienyl-2-piperidone (**6**) and *N*-1,3-butadienyl-1,3,4,5,6,7-hexahydro-2*H*-azepin-7-one (**7**). Reaction of lactams with 2-butenal derivatives gave the corresponding (*E*)-diene possessing a terminal methylene moiety (see **2** and **5–10**). The *Z* isomer was not detected by ^1H NMR, ^{13}C NMR, or gas chromatography. Reaction of more highly substituted aldehydes such as (*E*)-2-pentenal with 2-pyrrolidinone gave 48% of *N*-(1,3-pentadienyl)-2-pyrrolidinone (**11**) as an 81:19 mixture of the *E,E*/*E,Z* isomers. Similarly, (*E*)-2-octenal gave a 75:25 mixture of **12** in 56% yield. The preference for the *E* isomer can be rationalized by thermodynamic arguments analogous to our observations for the preparation of (*E*)-*N*-alkenyl lactams.[13] The isolated yield of the *N*-dienyl lactam generally increased as the volatility and propensity for polymerization of the aldehyde decreased. Although the yield of **2** is modest, the ready availability of crotonaldehyde and 2-pyrrolidinone allows large quantities of the dienyl lactam to be prepared in a convenient manner.

Overman and Houk showed that *N*-dienyl carbamates and *N*-dienyl amides undergo reaction with electron-deficient olefins to give the Diels–Alder adduct in good yield. The reaction gives >98% of the ortho adduct as a 70–83:30–27 endo/exo (*Z*/*E*) mixture.[16] Oppolzer described the intramolecular Diels–Alder reaction of similar

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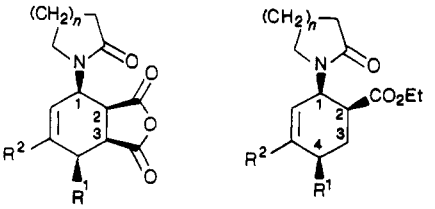
Table II. Reaction of N-Dienyl Lactams with Maleic Anhydride and Ethyl Acrylate to Give Cycloadducts I and II, respectively



I[a] II[a]

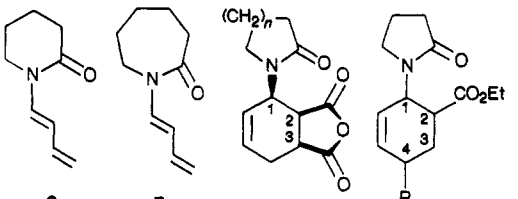
diene	n	R^2	%	I[f]	%	E:Z[g]	solvent	II
2[b]	1	H	70	13	41	(30:70)	toluene	16
					72	(18:82)	dioxane	16
					95	(15:85)	aq EtOH	16
8[b]	1	CH_3	50	20	78	(10:82)	toluene	23
11[c]	1	H			95	(9:91)[h]	aq EtOH	18
12[d]	1	H			92	(2:98)[i]	aq EtOH	19
6[b]	2	H	67	14	93	(21:79)	aq EtOH	24
					74	(26:74)	toluene	24
					82	(24:76)	dioxane	24
					86	(22:78)	EtOH	24
					80	(20:80)	aq THF[e]	24
9[b]	2	CH_3	64	21	77	(22:78)	toluene	25
7[b]	3	H	67	15	95	(26:74)	aq EtOH	26
					72	(39:61)	toluene	26
10[b]	3	CH_3	55	22	91	(40:60)	aq EtOH	27
					55	(44:56)	toluene	27

[a] Satisfactory analyses for each new compound. [b] R^1 = H. [c] R^1 = CH_3. [d] R^1 = n-C_4H_9. [e] Reaction incomplete after 10 days 85 °C and contained ≈20% of unreacted diene. [f] C_1C_2-Z, C_2C_3-Z. [g] C_1C_2. [h] Ratio for C_1C_4 is E,Z (80:20). [i] Ratio for C_1C_4 is E,Z (80:20).

dienes obtaining cycloadducts in 70–97% yield,[17,18] >98% ortho and primarily (76–86%) as the endo (Z) isomer. Additional studies by Overman[19] show that dienyl amides and carbamates react with a wide variety of dienophiles with high regiochemical integrity and good to excellent stereoselectivity. Overman and Houk[16,20] demonstrated the preference for the ortho adduct, which corresponds to the endo (Z) adduct, could be rationalized on the basis of classical frontier orbital analysis.[16,21]

We repeated Terada's reaction of **2** and maleic anhydride and isolated 70% of **13** as a single diastereomer. Homonuclear decoupling in the 5.90–4.50 ppm region of the proton NMR showed $J(H_1–H_2)$ to be 6.2 Hz, indicating a Z relationship analogous to the endo selectivity reported by Overman and Houk.[16] Adduct **13** therefore has the C_1C_2-Z, C_2C_3-Z geometry. As shown in Table II the other N-dienyl lactams react with maleic anhydride to give only the C_1C_2-Z, C_2C_3-Z isomer, including **6** and **7**, which gave adducts **14** and **15**, respectively.

In the Diels–Alder reactions of the analogous N-dienyl imides **4** and **5** with maleic anhydride Terada did not discuss the stereochemical outcome.[14] The reaction of acrolein or acrylic acid with **4** or **5** gave products which were drawn as ortho, but no corroboration or comment on the stereochemistry was offered.[14] There were no previous reports of a Diels–Alder adduct derived from a N-dienyl lactam and alkenes such as ethyl acrylate. When we examined the reaction of ethyl acrylate with the N-dienyl lactams in Table I we found the reaction proceeded with exclusive ortho selectivity and with a high preference for the endo (Z) isomer as shown in Table II, again analogous to Overman and Houk's work.[16] Overman described the chemical shift of the endo proton to be 0.25–0.40 ppm downfield of the exo proton, and we observed a similar chemical shift. Decoupling at 5.6 ppm in **16** collapsed the quartet at 2.8 ppm to a triplet indicating the 1,2-isomer. Irradiation at 5.4 ppm gave a doublet at 5.6 ppm with a coupling constant of 5.8 Hz, consistent with a Z relationship. As shown in Table II only the ortho isomer was detected, as a 70:30 → 80:20 mixture of endo/exo products. The close analogy of the dienyl lactams to the dienyl amides is not surprising, but the size of the lactam ring appears to have an effect on the selectivity. The pyrrolidinone ring exerts little or no effect on the selectivity of the reaction when compared with the dienyl amides. When the ring size is increased a decrease in selectivity is observed with formation of increased amounts of the E isomer (compare **2**, **6**, **7** and **8**, **9**, **10**).



6 **7** **13**, n=1; **14**, n=2; **15**, n=3 **17**

It is noted that the presence of the methyl group on the diene moiety in **11** or the pentyl group in **12** led to an isomeric mixture separable only by gas chromatography. This required that **11** and **12** be reacted as the mixture of (E,E)- and (E,Z)-diene isomers. Analysis by GC/MS, ^1H, and ^{13}C NMR showed four isomeric Diels–Alder adducts which were identified as **17**. The four isomers are **17a** (C_1C_1-Z, C_1C_4-Z), **17b** (C_1C_2-E, C_1C_4-Z), **17c** (C_1C_2-Z, C_1C_4-E), and **17d** (C_1C_2-E, C_1C_4-E). The initial 80:20

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(*E,E*)/(*E,Z*)-diene mixture was reflected in the ≈80:20 **17a,17b/17c,17d** mixture. A slight improvement in the endo selectivity was observed and the ratio of endo/exo (**17a,17c/17b,17d**) was 91:9 for reaction of **11** and 91:2 for reaction of **12**. We examined **11**, **12**, and **17** for thermal isomerization and found them to be completely stable. We therefore assume the observed isomeric ratios of **18** and **19** reflect the actual selectivity of the Diels–Alder reaction of **11** and **12**, respectively.

All Diels–Alder reactions were carried out initially in refluxing toluene but in several cases the yields were disappointing. It has been shown that highly polar and especially aqueous solvents can lead to enhancement of the rate and yield of many Diels–Alder reactions.[22] Berson demonstrated a clear relationship between the endo/exo product ratio and solvent polarity in the Diels–Alder reaction of cyclopentadiene with acrylate derivatives.[23] We therefore examined both the yield of the *N*-dienyl lactam Diels–Alder reaction and the endo selectivity in increasingly polar solvents with the results shown in Table II. The yield of the cycloadduct increases as the polarity of the solvent increases and the use of 50% aqueous ethanol gave the best results. In each case the isolated yield of adduct was over 90% and we observed up to a 20% increase in the yield and up to 6% increase in selectivity relative to the results obtained in toluene.

We have demonstrated the ability to prepare (*E*)-*N*-1,3-dienyl lactams by a simple procedure that gives comparatively good yields of this class of compounds, previously available only by difficult synthetic approaches of limited utility. We have demonstrated the facile intermolecular Diels–Alder reaction of these dienes with maleic anhydride and ethyl acrylate and shown that the endo (*Z*) isomer is obtained in excellent yield, exclusively as the ortho regioisomer. This reaction therefore proceeds with high regioselectivity and good stereoselectivity. We have shown that the use of increasingly polar and protic solvents leads to an increase in the yield and stereoselectivity of the reaction. *N*-Dienyl amides have found extensive use in organic synthesis[24] but the lack of a useful synthetic route to *N*-dienyl lactams has inhibited their synthetic exploitation. Now that the synthetic route is established and the reactivity and selectivity in the Diels–Alder reaction confirmed we can proceed to examine structural modifications of the lactam and Diels–Alder adduct which will allow elaboration to tricyclic alkaloids.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on an IBM WP-200SY spectrometer at 200.13 and 50.3 MHz, respectively, as solutions in deuteriochloroform. Infrared data were recorded with a Perkin–Elmer Model 283 instrument. High-resolution mass spectra were measured on an AEI MS-902 mass spectrometer and are accurate to ±5 ppm. TLC was done on silica gel 60F-254 sheets from E. Merck. Column chromatography was performed with silica gel 60 (70–230 mesh) from E. Merck. The gas chromatography/mass spectrometry (GC/MS) analyses were performed on a Hewlett Packard 5980-B GC/MS system. All lactams and aldehydes were obtained from Aldrich and used without further purification. The 3-methyl-2-butenal[25] was prepared by oxidation of 3-methyl-2-buten-1-ol[26] with pyridinium chlorochromate.

General Procedure for Preparation of *N*-Dienyl Lactams. Approximately 100 mmol of lactam was mixed with 100 mmol of the desired aldehyde in 150–175 mL of dry toluene and treated with about 50 mg of *p*-toluenesulfonic acid. The solution was refluxed until the maximum amount of water was removed by a Dean–Stark trap (2–24 h). The solution was cooled to ambient temperature, washed with 75 mL of saturated $NaHCO_3$ and with 75 mL of water. The aqueous phase was extracted with 3 × 75 mL of ether, dried ($MgSO_4$), and the solution was filtered and concentrated in vacuo.

***N*-1,3-Butadienyl-2-pyrrolidinone (2).** Reaction of 20.0 g (235 mmol) of 2-pyrrolidinone and 16.5 g (235 mmol) of crotonaldehyde for 12 h gave after chromatography (ether/silica gel, R_f 0.29) 13.2 g (96.0 mmol, 41%) of **2** as white flakes: mp 58–59 °C (lit. mp 59.5–61.5 °C);[12,14] ^{1}H NMR($CDCl_3$) δ 2.02–2.23 (m, 2 H), 2.41 (t, 2 H), 3.46 (t, 2 H), 4.93 (d, 1 H, *J* = 10.3 Hz), 5.08 (d, 1 H, *J* = 16.9 Hz), 5.60 (dd, 1 H, *J* = 14.2, 14.1 Hz), 6.23–6.37 (m, 1 H, *J* = 10.4, 16.9 Hz), and 7.03 (d, 1 H, *J* = 14.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.41 (t), 29.81 (t), 43.76 (t), 111.19 (d), 112.74 (t), 125.49 (d), 133.84 (d), and 171.69 (s).

***N*-1,3-Pentadienyl-2-pyrrolidinone (11).** Reaction of 10.0 g (117 mmol) of 2-pyrrolidinone and 9.88 g (117 mmol) of 2-pentenal for 15 h gave after bulb-to-bulb distillation [120–130 °C (0.8 mmHg)] 8.46 g (56.0 mmol, 48%) of **11**. Analysis by capillary GC/MS showed an 81:19 mixture of *E,E/E,Z* isomers:[27] ^{1}H NMR($CDCl_3$) δ 0.99 (m, 3 H), 1.28–1.60 (m, 2 H), 2.49–2.58 (m, 2 H), 3.48–3.59 (m, 2 H), 4.40–4.79 (m, 2 H), 4.90–5.15 (m, 1 H), and 6.95–7.09 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ [*E,E*] 16.89 (q), 17.65 (t), 30.68 (t), 44.64 (t), 112.08 (d), 123.52 (d), 126.29 (d), 128.57 (d), and 172.45 (s), [*E,Z*] 12.74 (q), 17.65 (t), 30.68 (t), 44.69 (t), 107.17 (d), 123.30 (d), 125.34 (d), 126.58 (d), and 172.33 ppm (s); IR (KBr) 2970, 1690, 1640, and 720 cm^{-1}; mass spectrum, *m/z* (relative intensity) 151 (34, P), 98 (60), 96 (28), 81 (22), 68 (28), 67 (40), 53 (21), 41 (100, B), and 39 (64). Anal. Calcd for $C_9H_{13}NO$: 151.0998. Found: 151.1001 (±0.8 mmu).

***N*-1,3-Octadienyl-2-pyrrolidinone (12).** Reaction of 10.0 g (117 mmol) of 2-pyrrolidinone and 14.7 g (117 mmol) of (*E*)-2-octenal for 16 h gave after chromatography (ether/silica gel, R_f 0.31) 12.6 g (65.5 mmol, 56%) of **12**. Analysis by capillary GC/MS showed a 75:25 mixture of *E,E/E,Z* isomers:[27] ^{1}H NMR ($CDCl_3$) δ 0.99 (m, 3 H), 1.25–1.45 (m, 4 H), 1.98–2.24 (m, 4 H), 2.40–2.64 (m, 2 H), 3.43–3.63 (m, 2 H), 5.28–5.61 (m, 2 H), 5.67–6.18 (m, 1 H), and 7.04–7.15 (m, 1 H); ^{13}C NMR($CDCl_3$) δ [*E,E*] 13.70 (q), 17.27 (t), 22.06 (t), 27.34 (t), 31.50 (t), 45.01 (t), 112.60 (d), 124.24 (d), 127.67 (d), 132.58 (d), and 172.62 (s), [*E,Z*] 13.73 (q), 17.27 (t), 22.15 (t), 27.34 (t), 32.31 (t), 31.67 (t), 45.07 (t), 107.89 (d), 125.95 (d), 126.03 (d), 130.01 (d), and 172.77 (s); IR (neat) 2975, 1680, 1630, 1600, 1420, 1250, 960, and 720 cm^{-1}; mass spectrum, m/*z* (relative intensity) 193 (2, P), 150 (14), 124 (15), 86 (14), 85 (36), 82 (15), 69 (20), 67 (11), 57 (22), 56 (18), 42 (29), 41 (100, B), and 39 (36). Anal. Calcd for $C_{12}H_{19}NO$: 193.1468. Found: 193.1466 (±1.0 mmu).

***N*-(3-Methyl-1,3-butadienyl)-2-pyrrolidinone (8).** Reaction of 7.08 g (83.3 mmol) of 2-pyrrolidinone and 7.03 g (83.3 mmol) of 3-methyl-2-butenal for 11 h gave after bulb-to-bulb distillation [120–130 °C (1.0 mmHg) 8.24 g (54.8 mmol, 66%) of **8** as a white solid: mp 54–55.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 2.08–2.15 (m, 2 H), 2.50 (t, 2 H), 3.52 (t, 2 H), 4.86 (s, 1 H), 4.90 (s, 1 H), 5.72 (d, 1 H, *J* = 14.7 Hz), and 7.06 (d, 1 H, *J* = 14.7 Hz); ^{13}C NMR($CDCl_3$) δ 17.12 (q), 18.43 (t), 30.91 (t), 44.83 (t), 114.03 (d), 114.70 (t), 123.32 (d), 140.29 (s), and 172.98 (s); IR (KBr) 2980, 2960, 1690, 1640, 1400, 1280, 1230, 1050, 950, and 870 cm^{-1}; mass spectrum, *m/z* (relative intensity) 151 (6, P), 138 (13), 110 (38), 85 (39), 82 (60), 70 (30), 67 (21), 54 919), 53 (61), 43 (32), 42 (46), 41 (100, B), and 39 (82). Anal. Calcd for $C_9H_{13}NO$: 151.0998. Found: 151.1004 (±0.8 mmu).

***N*-1,3-Butadienyl-2-piperidone (6).** Reaction of 10.0 g (101

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(27) Although separable by gas chromatography the pure *E,E* or *E,Z* isomers could not be isolated. The isomeric ratio was determined by GC/MS and ^{1}H NMR.

mmol) of 2-piperidone and 7.07 g (101 mmol) of crotonaldehyde for 15 h gave after chromatography (ether/silica gel, R_f 0.35) 5.97 g (39.6 mmol, 39%) of *6* as white flakes: mp 69–71 °C; ^{1}H NMR ($CDCl_3$) δ 1.71–1.94 (m, 4 H), 2.39 (t, 2 H), 3.35 (t, 2 H), 4.84 (d, 1 H, J = 11.0 Hz), 5.02 (d, 1 H, J = 16.7 Hz), 5.62 (dd, 1 H, J = 10.9, 14.5 Hz), 6.11–6.36 (m, 1 H, J = 16.7 Hz), and 7.51 (d, 1 H, J = 14.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.94 (t), 22.02 (t), 32.40 (t), 44.68 (t), 111.42 (d), 113.70 (t), 129.66 (d), 134.95 (d), and 167.86 (s); IR (KBr) 3020, 2970, 2940, 1690, 1660, 1610, 1430, 1350, 1270, 1240, 1100, 1000, 950, and 890 cm^{-1}; mass spectrum, m/z (relative intensity) 151 (38, P), 108 (15), 96 (63), 94 (30), 86 (19), 81 (20), 70 (15), 69 (29), 68 (42), 53 (21), 41 (100,B), and 39 (71). Anal. Calcd for $C_9H_{13}NO$: 151.0998. Found: 151.1001 (±0.8 mmu).

***N*-(3-Methyl-1,3-butadienyl)-2-piperidone (9).** Reaction of 10.0 g (101 mmol) of 2-piperidone and 8.48 g (101 mmol) of 3-methyl-2-butenal for 12 h gave after bulb-to-bulb distillation [97–102 °C (0.5 mmHg)] 6.51 g (39.4 mmol, 39%) of **9** as a white solid: mp 101–102 °C; ^{1}H NMR ($CDCl_3$) δ 1.69–1.87 (m, 4 H), 1.91 (s, 3 H), 2.51 (t, 2 H), 3.46 (t, 2 H), 4.87 (s, 1 H), 4.90 (s, 1 H), 5.81 (d, 1 H, J = 15.0 Hz), and 7.63 (d, 1 H, J = 15.0 Hz); ^{13}C NMR ($CDCl_3$) δ 17.91 (q), 18.23 (t), 32.56 (t), 44.77 (t), 114.04 (d), 114.60 (d), 123.67 (d), 140.55 (s), and 167.98 (s); IR (KBr) 2970, 1670, 1630, 1425, 1180, 1085, 970, and 865 cm^{-1}; mass spectrum, m/z (relative intensity) 165 (50, P), 150 (78), 122 (59), 110 (38), 99 (28), 95 (4), 94 (56), 82 (47), 81 (34), 67 (56), 55(49), 53 (40), 41 (100, B), and 39 (75). Anal. Calcd for $C_{10}H_{15}NO$ 165.1155. Found: 165.1154 (±0.8 mmu).

***N*-1,3-Butadienyl-1,3,4,5,6,7-hexahydro-2*H*-azepin-7-one (7).** Reaction of 10.0 g (88.0 mmol) of 1,3,4,5,6,7-hexahydro-2*H*-azepin-7-one and 6.16 g (88.0 mmol) of crotonaldehyde for 12 h gave after bulb-to-bulb distillation [96–102 °C (0.5 mmHg)] 2.87 g (17.4 mmol, 20%) of **7** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.68–1.87 (br m, 6 H), 2.58 (t, 2 H), 3.54 (t, 2 H), 4.90 (d, 1 H, J = 10.2 Hz), 5.04 (d, 1 H, J = 16.8 Hz), 5.60–5.72 (m, 1 H, J = 14.4, 10.3 Hz), 6.23–6.37 (m, 1 H, J = 10.2, 16.8 Hz), and 7.35 (d, 1 H, J = 14.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.41 (t), 27.35 (t), 29.25 (t), 37.10 (t), 45.21 (t), 111.50 (d), 113.60 (t), 130.47 (d), 135.47 (d), and 174.09 (s); IR (neat) 2970, 1650, 1620, 1440, 1390, 1205, 1080, 995, 970, and 880 cm^{-1}; mass spectrum, m/z (relative intensity) 165 (8, P), 122 (12), 108 (11), 97 (20), 95 (17), 82 (38), 80 (30), 68 (27), 55 (29), 53 (36), 41 (100, B), and 39 (92). Anal. Calcd for $C_{10}H_{15}NO$: 165.1154. Found: 165.1164 (±1.2 mmu).

***N*-(3-Methyl-1,3-butadienyl)-1,3,4,5,6,7-hexahydro-2*H*-azepin-7-one (10).** Reaction of 20.0 g (176 mmol) of 1,3,4,5,6,7-hexahydro-2*H*-azepin-7-one and 14.7 g (176 mmol) of 3-methyl-2-butenal for 13 h gave after bulb-to-bulb distillation [108–113 °C (0.5 mmHg)] 14.5 g (80.9 mmol, 46%) of **10** as a white solid: mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 1.69–1.83 (m, 6 H), 1.90 (s, 3 H), 2.64 (t, 2 H), 3.63 (t, 2 H), 4.85 (s, 1 H), 4.89 (s, 1 H), 5.80 (d, 1 H, J = 14.9 Hz), and 7.38 (d, 1 H, J = 14.9 Hz); ^{13}C NMR($CDCl_3$) δ 18.90 (q), 23.39 (t), 27.30 (t), 29.24 (t), 37.12 (t), 45.11 (t), 113.23 (d), 113.76 (t), 126.99 (d), 141.06 (s), and 174.21 (s); mass spectrum, m/z (relative intensity) 179 (20, P), 136 (37), 108 (18), 96 (44), 82 (46), 67 (43), 55 (50), 41 (100, B), and 39 (54). Anal. Calcd for $C_{11}H_{17}NO$: 179.1311. Found: 179.1309 (±0.9 mmu).

General Procedure for Diels–Alder Reaction of Lactams. Approximately 300 mmol of a *N*-dienyl lactam was mixed with about 300 mmol of maleic anhydride or ethyl acrylate and refluxed for the indicated time in the appropriate solvent. The solution was cooled to ambient temperature, and the solvents were removed in vacuo. The ratio of stereoisomers was determined by GC/MS (12 m × 0.2 mm methyl silicon capillary column) as well as ^{1}H NMR and ^{13}C NMR.

Reaction of 2. (a) With Maleic Anhydride. Reaction of 0.500 g (36.5 mmol) of **2** with 0.358 g (36.5 mmol) of maleic anhydride gave after recrystallization (benzene/hexane) 0.600 g (25.5 mmol, 70%) of 4-, (5-oxo-3,4-dihydro-2*H*-pyrrolyl)-4,7-dihydro-2,9-benzofurandione (**13**) as a tan solid: mp 120–121 °C (lit. mp 122–124 °C);[12,14] ^{1}H NMR($CDCl_3$) δ 1.69–1.89 (m, 2 H), 2.01–2.27 (m, 2 H), 2.45–2.69 (m, 2 H), 2.77–2.96 (m, 3 H), 3.86 (m, 1 H), 4.69–4.80 (m, 1 H), and 6.07–6.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.70 (t), 23.35 (t), 30.93 (t), 39.30 (d), 42.24 (d), 45.94 (t), 47.34 (d), 126.23 (d), 129.30 (d), 170.87 (s), 173.59 (s), and 175.89 (s); IR (KBr) 2980, 1835, 1780, 1680, 1410, 1270, 970, and 950 cm^{-1}.

(b) With Ethyl Acrylate in Chlorobenzene. Reaction of 2.00 g (145 mmol) of **2** and 1.45 g (145 mmol) of ethyl acrylate for 96 h in chlorobenzene gave after chromatography (ether/silica gel, R_f 0.31) 1.38 g (58.3 mmol, 40%) of 6-carbethoxy-1-(5-oxo-3,4-dihydro-2*H*-pyrrolyl)-2-cyclohexene (**16**) as a mixture of diastereomers: ^{1}H NMR($CDCl_3$) δ [*Z*] 1.24 (t, 3 H), 2.19–2.00 (m, 6 H), 2.32 (t, 2 H), 2.78–2.87 (m, 1 H), 3.37 (t, 1 H), 3.51 (t, 1 H), 4.11 (q, 2 H), 5.04–5.09 (m, 1 H), 5.44–5.51 (m, 1 H), and 6.02–6.09 (m, 1 H), [*E*] 1.15 (t, 3 H), 1.70–1.97 (m, 6 H), 2.23 (t, 2 H), 2.45–2.61 (m, 1 H), 3.23–3.35 (m, 2 H), 4.03 (q, 2 H), 4.80–4.91 (m, 1 H), 5.25–5.33 (m, 1 H), and 5.75–5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.82 (q), 18.33 (t), 20.98 (t), 23.66 (t), 30.79 (t), 43.66 (d), 45.14 (d), 45.24 (t), 60.32 (t), 123.94 (d), 131.84 (d), 173.07 (s), and 174.51 ppm (s); IR (neat) 2990, 1730, 1680, 1410, 1270, 1170, and 700 cm^{-1}; mass spectrum, m/z (relative intensity) 237 (2, P), 163 (14), 162 (50), 137 (29), 122 (29), 107 (39), 105 (28), 79 (100, B), 77 (79), 41 (64), and 39 (43). Anal. Calcd for $C_{13}H_{19}NO_3$: 237.1366. Found: 237.1368 (±1.2 mmu).

(c) With Ethyl Acrylate in Dioxane. Reaction of 0.250 g (1.82 mmol) of **2** with 0.182 g (1.82 mmol) of ethyl acrylate in dioxane for 96 h gave after chromatography as in b 0.311 g (1.31 mmol, 72%) of **16**. GC/MS analysis showed the *Z*:*E* ratio to be 82:18.

Reaction of 8. (a) With Maleic Anhydride. Reaction of 0.500 g (3.31 mmol) of **8** with 0.324 g (3.31 mmol) of maleic anhydride gave after recrystallization (benzene/hexane) 0.413 g (1.66 mmol, 50%) of 4-(5-oxo-3,4-dihydro-2*H*-pyrrolyl)-6-methyl-4,7-dihydro-2,9-benzofurandione (**20**) as a tan solid: mp 194–196 °C; ^{1}H NMR($CDCl_3$) δ 1.69 (s, 3 H), 1.77–1.94 (m, 2 H), 2.04–2.29 (m, 2 H), 2.47–2.69 (m, 2 H), 2.81–2.97 (m, 1 H), 3.03–3.16 (m, 1 H), 3.18–3.29 (m, 1 H), 3.33–3.47 (m, 1 H), 4.76 (br s, 1 H), and 5.29 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.36 (t), 23.06 (t), 29.04 (t), 39.49 (t), 40.33 (d), 44.20 (t), 50.17 (d), 117.55 (d), 136.52 (d), 172.70 (s), 174.06 (s), and 174.36 (s); mass spectrum, m/z (relative intensity) 249 (7, P), 221 (13), 176 (39), 151 969), 136 (8), 122 (25), 118 (41), 108 (25), 91 (88), 87 (77), 77 (28), 65 (32), 41 (100, B), and 39 (68). Anal. Calcd for $C_{13}H_{15}NO_4$ 249.1001. Found: 249.0995 (±1.2 mmu).

(b) With Ethyl Acrylate in Toluene. Reaction of 0.558 g (3.70 mmol) of **8** and 0.370 g (3.70 mmol) of ethyl acrylate for 100 h gave after chromatography (ether/silica gel, R_f 0.18) 0.731 g (2.91 mmol, 78%) of 6-carbethoxy-3-methyl-1-(5-oxo-3,4-dihydro-2*H*-pyrrolyl)-2-cyclohexene (**23**) as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H), 1.75 (s, 3 H), 1.90–2.12 (m, 6 H), 2.31 (t, 2 H), 2.69–2.81 (m, 1 H), 3.47 (t, 2 H), 4.09 (q, 2 H), 5.02 (m, 1 H), and 5.20 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.97 (q), 18.38 (t), 21.66 (q), 23.46 (t), 28.79 (t), 31.04 (t), 43.47 (d), 45.38 (t), 45.87 (d), 60.48 (t), 118.42 (d), 139.79 (s), 173.46 (s), and 174.67 (s); IR (KBr) 2980, 1730, 1670, 1420, 1280, 1170, and 910 cm^{-1}; mass spectrum, m/z (relative intensity) 251 (3, P), 208 (11), 177 (21), 151 (28), 136 (26), 121 (43), 119 (48), 93 (83), 91 (95), 86 (42), 85 (28), 79 (45), 77 (65), 67 (30), 65 (35), 53 (29), 51 (23), 41 (100, B), and 39 (65). Anal. Calcd for $C_{14}H_{21}NO_3$: 251.1522. Found: 251.1522 (±1.3 mmu).

Reaction of 11 with Ethyl Acrylate in 50% Aqueous Ethanol. Reaction of 0.500 g (3.31 mmol) of **11** and 0.331 g (3.31 mmol) of ethyl acrylate for 100 h in 50% aqueous ethanol gave after chromatography (ether/silica gel, R_f 0.17) 0.789 g (3.14 mmol, 95%) of 6-carbethoxy-4-methyl-1-(5-oxo-3,4-dihydro-2*H*-pyrrolyl)-2-cyclohexene (**18**) as a clear oil. GC/MS analysis showed a mixture of four isomers in a ratio of 72.8:18.2:7.2:1.8: ^{1}H NMR ($CDCl_3$) δ [C_1C_2-*Z*] 1.08 (d, 3 H, J = 7.1 Hz), 1.24 (t, 3 H), 1.86–2.03 (m, 4 H), 2.16–2.35 (m, 3 H), 2.79–2.84 (m, 1 H), 3.32–3.51 (m, 2 H), 4.09 (q, 2 H), 5.03–5.10 (m, 1 H), 5.38–5.44 (m, 1 H), and 5.82–5.89 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ [C_1C_2-*Z*] 13.96 (q), 18.44 (q), 21.02 (t), 29.83 (d), 30.02 (t), 30.96 (t), 43.80 (d), 45.05 (d), 45.34 (t), 60.53 (t), 123.17 (d), 138.46 (d), 173.19 (s), and 174.72 (s); IR (KBr) 2970, 1730, 1690, 1410, 1270, 1100, 1030, and 720 cm^{-1}; mass spectrum, m/z (relative intensity) 251 (4, P), 177 (19), 151 (100, B), 122 (33), 121 (35), 96 (37), 93 (74), 91 (44), 86 (78), 84 (76), 79 (39), 78 (48), 55 (26), 41 (82), and 39 (34). Anal. Calcd for $C_{14}H_{21}NO_3$ 251.1521; Found: 251.1522 (±1.3 mmu).

Reaction of 12 with Ethyl Acrylate in 50% Aqueous Ethanol. Reaction of 0.500 g (2.59 mmol) of **12** and 0.259 g (2.59 mmol) of ethyl acrylate for 104 h gave after chromatography (ether/silica gel, R_f 0.28) 0.698 g (2.38 mmol, 92%) of 6-carb-

ethoxy-4-*n*-butyl-1-(5-oxo-3,4-dihydro-2*H*-pyrrolyl)-2-cyclohexene (**19**) as a clear oil. GC/MS indicated a mixture of four isomers in a ratio of 78.4:19.6:19.6:0.4: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.12–1.42 (m, 6 H), 1.18 (t, 3 H), 1.91–2.04 (m, 3 H), 2.21–2.36 (m, 2 H), 2.70–2.90 (m, 1 H), 3.16–3.36 (m, 2 H), 4.05 (q, 2 H), 4.98–5.08 (m, 1 H), 5.21–5.44 (m, 1 H), and 5.61–5.77 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.90 (q), 14.03 (t), 18.54 (t), 22.69 (t), 27.91 (t), 29.73 (d), 31.25 (t), 35.37 (t), 43.22 (t), 43.89 (d), 45.50 (t), 60.06 (t), 125.85 (d), 137.46 (d), 172.11 (s), and 173.48 (s); IR (neat) 2990, 1725, 1690, 1400, 1250, 1110, 1020, and 735 cm^{-1}; mass spectrum, *m/z* (relative intensity) 293 (0.2, P), 163 (15), 150 (28), 124 (15), 86 (67), 81 (72), 79 (48), 69 (24), 57 (34), 41 (100, B), and 39 (33). Anal. Calcd for $C_{17}H_{27}NO_3$: 293.1992. Found: 293.1990 (±1.5 mmu).

Reaction of 6. (a) With Maleic Anhydride. Reaction of 0.500 g (3.31 mmol) of **6** and 0.324 g (3.31 mmol) of maleic anhydride gave after recrystallization (benzene/hexane) 0.404 g (1.62 mmol, 49%) of 4-(2-oxo-3,4,5,6-tetrahydropyridyl)-4,7-dihydro-2,9-benzofurandione (**14**) as a tan solid: mp 209–213 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.69–2.09 (m, 4 H), 2.14–2.62 (m, 4 H), 3.11–3.51 (m, 3 H), 3.55–3.72 (m, 1 H), 4.72–4.85 (m, 1 H), and 5.81–6.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.07 (t), 23.37 (t), 29.44 (t), 29.55 (t), 37.31 (d), 40.06 (d), 44.83 (t), 54.08 (d), 118.37 (d), 136.30 (d), 173.27 (s), 174.18 (s), and 175.15 (s); IR (KBr) 2995, 1865, 1780, 1560, 1410, 1200, and 890 cm^{-1}; mass spectrum, *m/z* (relative intensity) 249 (4, P), 176 (11), 151 (10), 106 (11), 105 (31), 99 (61), 91 (22), 82 (11), 78 (32), 76 (100, B), 54 (47), 50 (67), 41 (72), and 39 (50). Anal. Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1000 (±1.2 mmu).

(b) With Ethyl Acrylate in Toluene. Reaction of 0.500 g (3.31 mmol) of **6** and 0.331 g (3.31 mmol) of ethyl acrylate for 73 h in toluene gave after chromatography (ether/silica gel, R_f 0.21) 0.615 g (2.45 mmol, 74%) of a clear oil, 6-carbethoxy-1-(2-oxo-3,4,5,6-tetrahydropyridyl)-2-cyclohexene (**24**) as a mixture of isomers: ^{1}H NMR ($CDCl_3$) δ [*Z*] 1.22 (t, 3 H), 1.56–1.93 (m, 8 H), 2.37 (t, 2 H), 2.80–2.87 (m, 1 H), 3.26 (t, 2 H), 4.11 (q, 2 H), 5.42–5.49 (m, 1 H), 5.54–5.60 (m, 1 H), and 6.02–6.07 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.00 (q), 20.90 (t), 21.48 (t), 23.45 (t), 23.71 (t), 32.48 (t), 43.85 (d), 44.95 (d), 46.50 (t), 60.51 (t), 124.70 (d), 132.24 (d), 170.02 (s), and 173.63 (s); ^{1}H NMR ($CDCl_3$) δ [*E*] 1.18 (t, 3 H), 1.66–1.96 (m, 8 H), 2.37 (m, 2 H), 2.52–2.65 (m, 1 H, *J* = 4.9, 10.4 Hz), 3.15 (t, 2 H), 4.10 (q, 2 H), 5.28–5.45 (m, 2 H), and 5.78–5.82 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.12 (q), 21.00 (t), 21.34 (t), 24.10 (t), 24.67 (t), 32.40 (t), 42.16 (d), 42.56 (t), 52.23 (d), 60.44 (t), 127.52 (d), 130.44 (d), 169.79 (s), and 173.58 (s); IR (neat) 2980, 1720, 1630, 1420, 1300, 1180, and 740 cm^{-1}; mass spectrum, *m/z* (relative intensity) 251 (6, P), 223 (10), 178 (13), 177 (22), 176 (14), 151 (22), 150 (12), 108 (36), 106 (26), 100 (26), 99 (19), 98 (21), 79 (100, B), 77 (63), 55 (38), 41 (34), and 39 (25). Anal. Calcd for $C_{14}H_{21}NO_3$: 251.1522. Found: 251.1533 (±1.2 mmu).

(c) With Ethyl Acrylate in Dioxane. Reaction of 0.250 g (1.65 mmol) of **6** with 0.165 g (1.65 mmol) of ethyl acrylate in dioxane for 88 h gave after chromatography as in b 0.340 g (1.13 mmol, 82%) of **24**. GC/MS analysis showed the *Z*:*E* ratio to be 76:24.

(d) With Ethyl Acrylate in Aqueous THF. Reaction of 0.250 g (1.65 mmol) of **6** with 0.165 g (1.65 mmol) of ethyl acrylate in 50% aqueous THF at 85 °C for 240 h gave after chromatography as in b 0.332 g (1.32 mmol, 80%) of **24**. GC/MS analysis showed the *Z*:*E* ratio to be 80:20.

(e) With Ethyl Acrylate in Ethanol. Reaction of 0.250 g (1.65 mmol) of **6** with 0.165 g (1.65 mmol) of ethyl acrylate for 92 h gave after chromatography as in b 0.357 g (1.42 mmol, 86%) of **24**. GC/MS analysis showed the *Z*:*E* ratio to be 78:22.

(f) With Ethyl Acrylate in 50% Aqueous Ethanol. Reaction of 0.250 g (1.65 mmol) of **6** with 0.165 g (1.65 mmol) of ethyl acrylate for 76 h gave after chromatography as in b 0.386 g (1.53 mmol, 93%) of **24**. GC/MS analysis showed the *Z*:*E* ratio to be 79:21.

Reaction of 9. (a) With Maleic Anhydride. Reaction of 0.500 g (3.30 mmol) of **9** with 0.297 g (3.03 mmol) of maleic anhydride gave after recrystallization (benzene/hexane) 0.510 g (1.94 mmol, 64%) of 4-(2-oxo-3,4,5,6-tetrahydropyridyl)-6-methyl-4,7-dihydro-2,9-benzofurandione (**21**) as a tan solid: mp 162–164 °C; ^{1}H NMR (DMSO-d_6) δ 1.45–1.59 (m, 2 H), 1.61–1.74 (m, 2 H), 2.30–2.59 (m, 3 H), 3.14–3.44 (m, 2 H), 3.60–3.69 (m, 1 H), 4.69–4.78 (m, 1 H), 5.78–5.88 (m, 1 H), and 5.95–6.05 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 21.64 (q), 22.49 (t), 28.46 (t), 36.59 (t), 38.89 (d), 41.93 (t), 47.78 (d), 51.20 (d), 126.76 (d), 127.74 (s), 171.25 (s), 174.67 (s), and 174.98 (s); IR (KBr) 2970, 1845, 1765, 1660, 1420, 1260, and 910 cm^{-1}; mass spectrum, *m/z* (relative intensity): 263 (1, P), 190 (16), 120 (17), 119 (33), 118 (100, B), 105 (20), 100 (25), 99 (51), 98 (18), 91 (95), 90 (88), 89 (67), 77 (48), 65 (33), 63 (55), 55 (44), 51 (42), 43 (89), 41 (96), and 39 (98). Anal. Calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1157 (±1.3 mmu).

(b) Ethyl Acrylate in Toluene. Reaction of 0.500 g (3.03 mmol) of **9** and 0.303 g (3.03 mmol) of ethyl acrylate for 124 h gave after chromatography (ether/silica gel, R_f 0.28) 0.618 g (2.33 mmol, 77%) of 6-carbethoxy-3-methyl-1-(2-oxo-3,4,5,6-tetrahydropyridyl)-2-cyclohexene (**25**) as a clear oil: ^{1}H NMR($CDCl_3$) δ [*Z*] 1.18 (t, 3 H), 1.60–1.87 (m, 6 H), 1.66 (s, 3 H), 1.85 (t, 2 H), 2.26 (t, 2 H), 2.63–2.79 (m, 1 H), 3.23 (t, 2 H), 4.10 (q, 2 H), 5.12 (s, 1 H), and 5.52 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.68 (q), 20.48 (q), 21.55 (t), 23.03 (t), 23.28 (t), 28.26 (t), 32.03 (t), 43.03 (d), 44.38 (t), 46.64 (d), 59.98 (t), 118.46 (d), 139.55 (s), 169.51 (s), and 173.28 (s); ^{1}H NMR ($CDCl_3$) δ [*E*] 1.13 (t, 3 H), 1.53 (s, 3 H), 1.55–1.80 (m, 6 H), 2.26 (t, 3 H), 2.39–2.59 (m, 1 H), 3.13 (t, 2 H), 4.07 (q, 2 H), 5.00 (s, 1 H), and 5.40 (s, 1 H); IR (neat) 2980, 1720, 1680, 1425, 1270, 1150, 1010, and 870 cm^{-1}; mass spectrum, *m/z* (relative intensity) 265 (8, P), 236 (29), 208 (35), 191 (38), 190 (25), 164 (17), 150 (38), 137 (71), 121 (63), 108 (29), 100 (71), 93 (100, B), 91 (67), 79 (50), 77 (60), 55 (54), 41 (52), and 39 (42). Anal. Calcd for $C_{15}H_{23}NO_3$: 265.1679. Found: 265.1681 (±1.3 mmu).

Reaction of 7. (a) With Maleic Anhydride. Reaction of 0.500 g (3.03 mmol) of **7** with 0.297 g (3.03 mmol) of maleic anhydride gave after recrystallization (benzene/hexane) 0.534 g (2.03 mmol, 67%) of 4-(7-oxo-1,3,4,5,6,7-hexahydro-2*H*-azepin-1-yl)-4,7-dihydro-2,9-benzofurandione (**15**) as a tan solid: mp 162–164 °C; ^{1}H NMR (DMSO-d_6) δ 1.29–1.52 (m, 4 H), 1.59–1.79 (m, 2 H), 2.16–2.63 (m, 3 H), 3.09–3.48 (m, 3 H), 3.57–3.71 (m, 1 H), 4.73–4.81 (m, 1 H), and 5.72–6.06 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 21.64 (t), 22.49 (t), 28.46 (t), 28.68 (t), 36.59 (t), 39.28 (d), 41.93 (t), 47.75 (d), 51.20 (d), 126.76 (d), 127.74 (d), 171.25 (s), 174.67 (s), and 174.98 (s); IR (KBr) 2970, 1810, 1750, 1640, 1425, 1280, and 900 cm^{-1}; mass spectrum, *m/z* (relative intensity) 263 (1, P), 113 (11), 106 (11), 105 (12), 92 (21), 91 (35), 86 (27), 79 (39), 77 (41), 69 (19), 56 (28), 55 (51), 43 (100, B), 41 (44), 39 (29). Anal. Calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1166 (±1.3 mmu).

(b) With Ethyl Acrylate in Toluene. Reaction of 0.500 g (2.79 mmol) of **7** with 0.279 g (2.79 mmol) of ethyl acrylate for 110 h gave after chromatography (ether/silica gel, R_f 0.29) 0.567 g (2.03 mmol, 73%) of a clear oil, 6-carbethoxy-1-(1,3,4,5,6,7-hexahydro-2*H*-azepin-1-yl)-2-cyclohexene (**26**) as a mixture of isomers: ^{1}H NMR ($CDCl_3$) δ [*Z*] 1.22 (t, 3 H), 1.56–1.97 (m, 8 H), 2.37 (t, 2 H), 2.80–2.87 (m, 1 H), 3.26 (t, 2 H), 4.11 (q, 2 H), 5.42–5.49 (m, 1 H), 5.54–5.60 (m, 1 H), and 6.02–6.07 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.09 (q), 20.85 (t), 21.50 (t), 23.43 (t), 23.70 (t), 32.45 (t), 43.38 (t), 44.92 (d), 48.56 (d), 60.48 (t), 124.70 (d), 137.19 (d), 170.03 (s), and 173.61 (s); ^{1}H NMR ($CDCl_3$) δ [*E*] 1.18 (t, 3 H), 1.66–1.96 (m, 8 H), 2.33 (t, 2 H), 2.52–2.65 (m, 1 H), 3.15 (t, 2 H), 4.10 (q, 2 H), 5.28–5.45 (m, 2 H), and 5.78–5.82 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.12 (q), 21.09 (t), 23.33 (t), 24.10 (t), 24.67 (t), 32.40 (t), 42.34 (t), 42.47 (d), 52.41 (d), 60.54 (t), 127.67 (d), 130.50 (d), 169.79 (s), and 173.58 (s); IR (neat) 2980, 1710, 1625, 1300, 1170, and 780 cm^{-1}; mass spectrum, *m/z* (relative intensity) 265 (31, P), 237 (97), 191 (68), 165 (11), 137 (100, B), 121 (62), 100 (52), 93 (57), 77 (34), 55 (75), and 41 (48). Anal. Calcd for $C_{14}H_{21}NO_3$: 265.1679. Found: 265.1677 (±1.3 mmu).

(c) With Ethyl Acrylate in 50% Aqueous Ethanol. Reaction of 0.100 g (6.06 mmol) of **7** with 0.0606 g (6.06 mmol) of ethyl acrylate for 77 h gave after chromatography as in b 0.157 g (5.76 mmol, 95%) of **26**. GC/MS analysis showed the *Z*:*E* ratio to be 74:26.

Reaction of 10. (a) With Maleic Anhydride. Reaction of 0.500 g (2.79 mmol) of **10** with 0.273 g (2.79 mmol) of maleic anhydride gave after recrystallization (benzene/hexane) 0.423 g (1.53 mmol, 54%) of 4-(1,3,4,5,6,7-hexahydro-2*H*-azepin-1-yl)-6-methyl-4,7-dihydro-2,9-benzofurandione (**22**) as a tan solid: mp 210–212 °C; ^{1}H NMR (DMSO-d_6) δ 1.24–1.57 (m, 6 H), 1.71 (s,

3 H), 1.97–2.16 (m, 1 H), 2.26–2.56 (m, 2 H), 2.77–2.92 (m, 2 H), 3.10–3.21 (m, 2 H), 3.21–3.30 (m, 1 H), and 5.06–5.23 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 22.54 (q), 22.71 (t), 28.49 (t), 28.80 (t), 29.03 (t), 36.78 (d), 40.27 (d), 44.28 (t), 53.60 (d), 117.92 (d), 136.14 (s), 172.49 (s), 173.44 (s), and 174.50 (s); IR (KBr) 2960, 1850, 1750, 1640, 1420, 1250, and 910 cm^{-1}; mass spectrum, m/z (relative intensity) 277 (2, P), 204 (12), 146 (20), 91 (41), 77 (46), 65 (20), 56 (63), 55 (65), 54 (50), 43 (100, B), 41 (70), and 39 (59). Anal. Calcd for $C_{15}H_{19}NO_4$: 277.1315. Found: 277.1307 (±1.4 mmu).

(b) With Ethyl Acrylate in Toluene. Reaction of 0.500 g (2.79 mmol) of **10** and 0.279 g (2.79 mmol) of ethyl acrylate for 130 h gave after chromatography (ether/silica gel, R_f 0.17) 0.560 g (2.00 mmol, 72%) of 6-carbethoxy-3-methyl-1-(1,3,4,5,6,7-hexahydro-2*H*-azepin-1-yl)-2-cyclohexene (**27**) as a clear oil: ^{1}H NMR ($CDCl_3$) δ [*Z*] 1.22 (t, 3 H), 1.71 (s, 3 H), 1.49–1.82 (m, 8 H), 1.87–1.99 (m, 2 H), 2.44 (t, 2 H), 2.63–2.82 (m, 1 H), 3.32 (t, 2 H), 4.08 (q, 2 H), 5.22 (s, 1 H), and 5.39 (s, 1 H); ^{1}H NMR ($CDCl_3$) δ [*E*] 1.20 (t, 3 H), 1.64 (s, 3 H), 1.54–1.76 (m, 8 H), 2.28–2.43 (m, 1 H), 2.53 (t, 2 H), 3.21 (t, 2 H), 4.09 (q, 2 H), 5.06 (s, 1 H), and 5.43 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.00 (q), 21.36 (q), 23.17 (t), 23.57 (t), 28.80 (t), 28.94 (t), 29.82 (t), 37.57 (t), 43.46 (d), 45.59 (t), 49.17 (d), 60.29 (t), 119.27 (d), 139.49 (s), 173.69 (s), and 175.06 (s); IR (neat) 2970, 1720, 1630, 1290, 1190, and 860 cm^{-1}; mass spectrum, m/z (relative intensity) 279 (2, P), 251 924), 208 (38), 121 (43), 113 (29), 96 (44), 93 (96), 91 (72), 84 (26), 79 (44), 77 (58), 55 (91), 41 (100, B), and 39 (52). Anal. Calcd for $C_{16}H_{25}NO_3$: 279.1836. Found: 279.1827 (±1.4 mmu).

(c) With Ethyl Acrylate in 50% Aqueous Ethanol. Reaction of 0.200 g (1.12 mmol) of **10** with 0.112 g (1.12 mmol) of ethyl acrylate for 84 h gave after chromatography as in b 0.284 g (1.02 mmol, 91%) **27**. GC/MS analysis showed the *Z*:*E* ratio to be 60:40.

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Registry No. **2**, 112682-86-7; **6**, 112682-88-9; **7**, 112682-87-8; **8**, 112682-83-4; **9**, 112682-84-5; **10**, 112682-85-6; (*E*,*E*)-**11**, 112682-89-0; (*E*,*Z*)-**11**, 112682-90-3; (*E*,*E*)-**12**, 112682-91-4; (*E*,*Z*)-**12**, 112682-92-5; **13**, 112682-96-9; **14**, 112682-97-0; **15**, 112682-98-1; (*E*)-**16**, 112682-99-2; (*Z*)-**16**, 112683-00-8; **18a**, 112683-03-1; **18b**, 112683-04-2; **18c**, 112683-05-3; **18d**, 112683-06-4; **19a**, 112683-15-5; **19b**, 112683-18-8; **19c**, 112683-17-7; **19d**, 112683-16-6; **20**, 112682-93-6; **21**, 112682-94-7; **22**, 112682-95-8; (*E*)-**23**, 112683-01-9; (*Z*)-**23**, 112683-02-0; (*E*)-**24**, 112683-07-5; (*Z*)-**24**, 112683-08-6; (*E*)-**25**, 112683-09-7; (*Z*)-**25**, 112683-10-0; (*E*)-**26**, 112683-11-1; (*Z*)-**26**, 112683-12-2; (*E*)-**27**, 112683-13-3; (*Z*)-**27**, 112683-14-4; 2-pyrrolidinone, 616-45-5; crotonaldehyde, 4170-30-3; (*E*)-2-pentenal, 1576-87-0; (*E*)-2-octenal, 2548-87-0; 3-methyl-2-butenal, 107-86-8; 2-piperidone, 675-20-7; hexahydro-2*H*-azepin-2-one, 105-60-2; maleic anhydride, 108-31-6; ethyl acrylate, 140-88-5.

Absolute Configuration of the Enantiomers of 7-Chloro-4-[[4-(diethylamino)-1-methylbutyl]amino]quinoline (Chloroquine)

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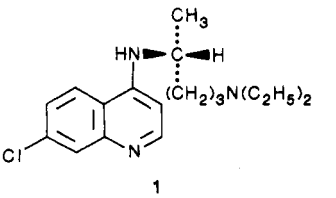
(*R*)-(−)-4-[[4-(Diethylamino)-1-methylbutyl]amino]-7-chloroquinoline [(*R*)-(−)-chloroquine] was prepared in a 10-step synthesis starting from L-glutamic acid via *N*,*N*-phthaloyl-L-glutamic acid, N^{γ},N^{γ}-diethyl-N^{α},N^{α}-phthaloyl-L-glutamine, and *N*,*N*-diethyl-L-glutamine. Reductive conversion of the α-carboxyl group to a methyl group led to *R*-(−)-4-amino-1-(diethylamino)pentane of >90% optical purity, which on condensation with 4,7-dichloroquinoline gave (*R*)-(−)-chloroquine.

Drugs possessing asymmetric centers generally exhibit marked differences in the biological activities of their optical isomers. One isomer may be preferentially metabolized by stereospecific enzymes, or there may be differences in the interactions of the enantiomers with the putative receptor. The report[1] that resolved enantiomers of chloroquine of equal and opposite rotation had identical activity against *Plasmodium lophurae* in mice[2] was therefore unexpected. Recently the two enantiomers of chloroquine, obtained from resolved[3] 4-amino-1-(diethylamino)pentane, have been found to possess specific rotations of about 9 times the magnitude reported earlier,[1] and to differ significantly in their activities on both *Plasmodium berghei*[4] and *P. vinckei*[5] in mice, and also in their binding affinity to DNA.[5] In order to carry out studies on the putative receptor, a knowledge of the absolute configuration of the two enantiomers of chloroquine was needed. This was accomplished by condensing *R*-(−)-4-amino-1-(diethylamino)pentane (**6c**), obtained from L-glutamic acid, with 4,7-dichloroquinoline to give *R*-(−)-chloroquine (**1**) of known absolute configuration.



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Diethyl *N*-(2-carboxybenzoyl)-L-glutamate,[6] prepared from diethyl-L-glutamate,[7] was converted to diethyl *N*,*N*-

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