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Studies on the Intramolecular Cycloaddition Reaction of Isomünchnones Derived from N-Alkenyl Substituted Diazoimides

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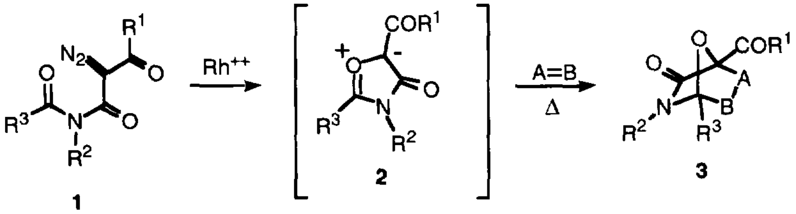
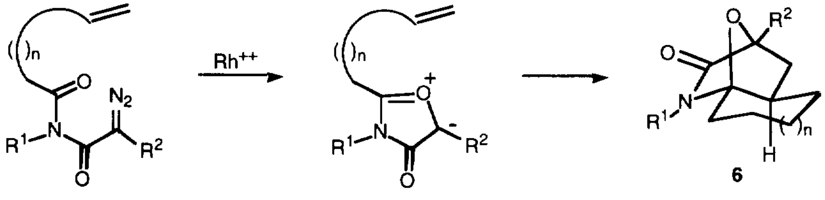
Abstract: A series of N-alkenyl substituted diazoimides were prepared and subjected to Rh(II) catalyzed decomposition. The initially generated rhodium carbenoid undergoes ready cyclization onto the neighboring amide carbonyl oxygen atom to generate an isomünchnone intermediate. Subsequent 1,3-dipolar cycloaddition across the pendant olefin affords the cycloadduct in high yield. The stereochemical assignment of several of the cycloadducts was deduced by X-ray crystallography. The stereochemical outcome of the reaction is the consequence of an *exo*-cycloaddition of the neighboring π-bond across the transient isomünchnone dipole. Molecular mechanics calculations were used to model energy differences between the *exo* and *endo* diastereomers. The calculations reveal that the *exo* diastereomers are significantly (18-20 kcal/mol) lower in energy than the corresponding *endo* isomers thereby providing a rationale for the preferred *exo*-cycloaddition.

The 1,3-oxazolium-4-oxides (isomünchnones) are easily obtained through the catalytic cyclization of a suitable diazoimide.[1] This type of mesoionic oxazolium ylide corresponds to the cyclic equivalent of a carbonyl ylide and readily undergoes 1,3-dipolar cycloaddition.[2-6] The starting diazoimides are constructed by acetoacylation[7] or malonylacylation[8] of the corresponding amides followed by standard diazo transfer techniques.[9] Formation of the isomünchnone ring can be rationalized by initial generation of a metallo-carbenoid species which is then followed by intramolecular cyclization onto the neighboring carbonyl oxygen to form the dipole.[10] The resulting isomünchnone can be trapped with dipolarophiles to give bimolecular cycloadducts in high yield.[11]



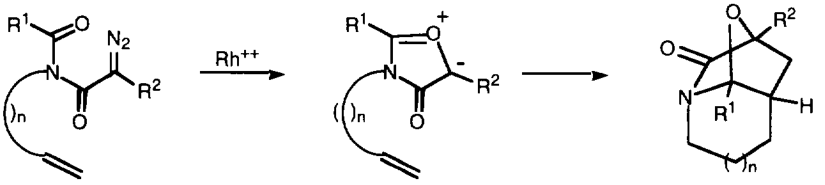
Several years ago our laboratory became interested in using the intramolecular cycloaddition of isomünchnones for the construction of a variety of alkaloid systems.[8] Intramolecular dipolar cycloadditions have been particularly useful in natural product synthesis, since this reaction results in the formation of an extra ring and exhibits increased reactivity due to entropic factors.[12-14] The regiochemistry of the process is complicated by a complex interplay of factors such as the nature of the 1,3-dipole, alkene polarity, ring strain, and other nonbonded interactions. In general, the intramolecular situation can be assessed as a competition between bridged and fused modes of cycloaddition. In previous papers we have outlined a strategy for the synthesis of polyheterocyclic ring systems wherein heterocycle **6** is prepared by an intramolecular dipolar cycloaddition of the isomünchnone dipole **5**.[6,15] Two basic structural variations can be achieved by altering the point of attachment of the alkenyl tether. We refer to these as type I and type II internal cycloaddition routes. To date, all of our studies have dealt with type I cycloadditions. From a synthetic standpoint, we were struck by the ease with which the type II reaction would allow for the preparation of complicated N-hetero tricyclic compounds such as **9**. Provided with this stimulus, we have investigated the Rh(II) catalyzed behavior of a series of N-alkenyl substituted diazoimides. The results described herein summarize various aspects of this study.

Type I



4 **5** **6**

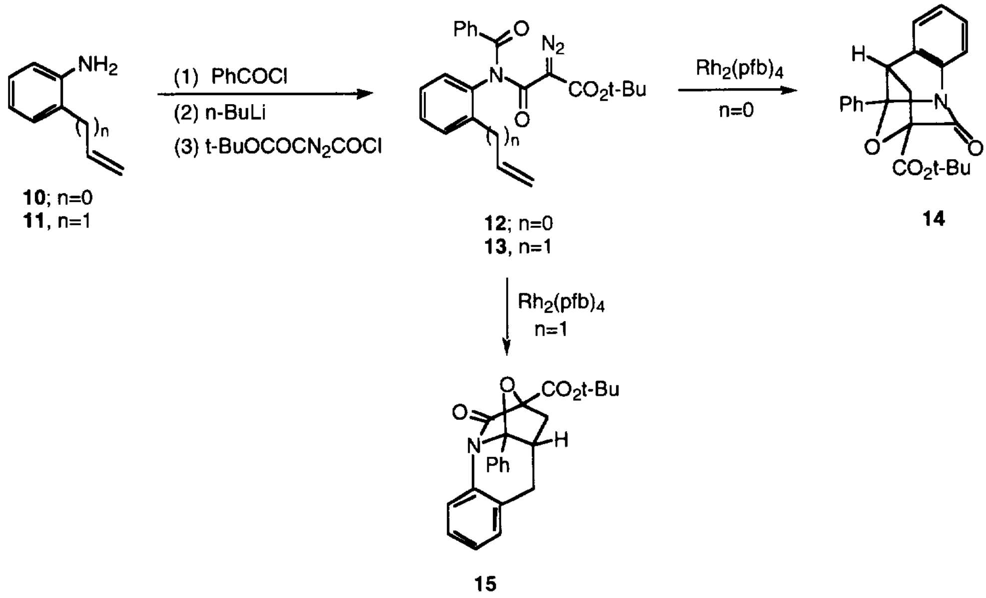
Type II



7 **8** **9**

Results and Discussion

The systems that we initially studied were ultimately derived from *ortho*-substituted anilines, such that the tethered alkene was attached to the benzene backbone. This arrangement provides interatomic distances and bond angles that are ideal for dipole formation. Diazoimides **12** and **13** were prepared by reaction of the appropriately substituted *ortho*-anilines with benzoyl chloride followed by the sequential treatment of the amide with n-butyllithium and t-butyl 2-diazomalonyl chloride.[16] It was necessary to use the lithium salt of the amide in order for reaction to occur. The unactivated amide did not react with the diazomalonyl chloride. The use of this reagent represents a shorter method to prepare diazoimides directly from an amide since diazoacetimidation classically involves two steps, one of which consists of a diazo transfer.[6] Exposure of diazoimides **12** and **13** to a catalytic quantity of Rh(II) perfluorobutyrate at 25°C afforded the polyheterocyclic systems **14** and **15** in excellent yield (93%, 95%) and with complete diastereospecificity. Cycloadduct **15** was initially identified on the basis of its characteristic 300-MHz NMR spectrum ($CDCl_3$) which showed a singlet at 1.53 (9H) for the t-butyl group, a set of doublet of doublets at 1.83 (1H, J=13.2 and 4.6 Hz) and 2.83 (1H, J=13.2 and 10.4 Hz) and multiplets at 3.10 (2H), 3.40 (1H) and 7.30 (9H). This structure was unambiguously established through an X-ray crystallographic study. Assignment of the stereochemistry of the closely related cycloadduct **14** is based on its spectroscopic properties and by analogy to **15**. Note that in both of these cases, the cycloaddition occurs *exo* with respect to the carbonyl ylide dipole and this is in full accord with the lowest energy transition state (*vide infra*).



Diazoimides where the alkenyl substituent was tethered onto the N-atom by a simple methylene chain were also observed to undergo cycloaddition across the isomünchnone dipole. Thus, treatment of diazoimides **16** and **17** with a catalytic quantity of rhodium(II) trifluoroacetate in benzene (80°C) gave cycloadducts **18** and **19**

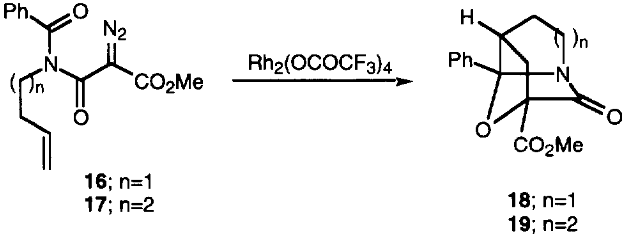
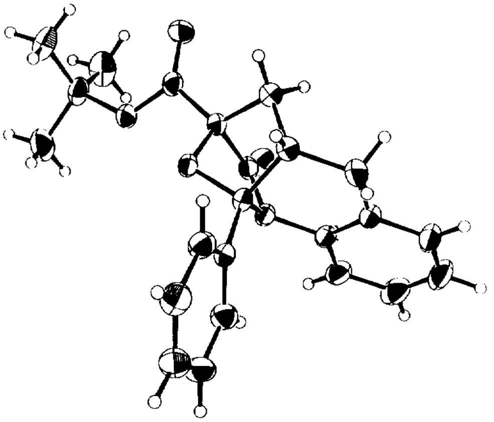
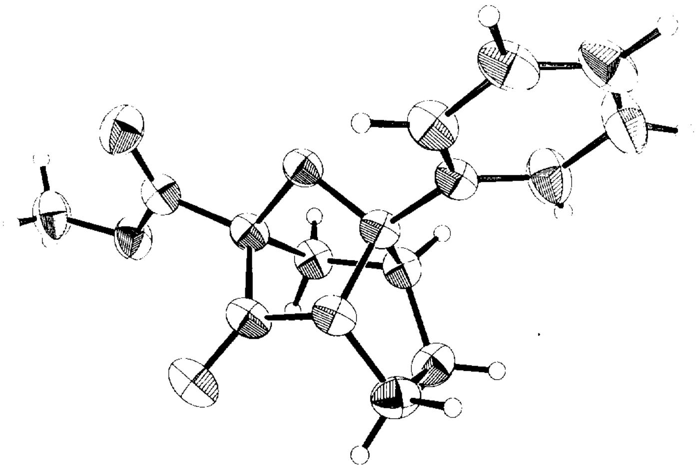


Figure 1: Ortep Representation of Cycloadduct **15**

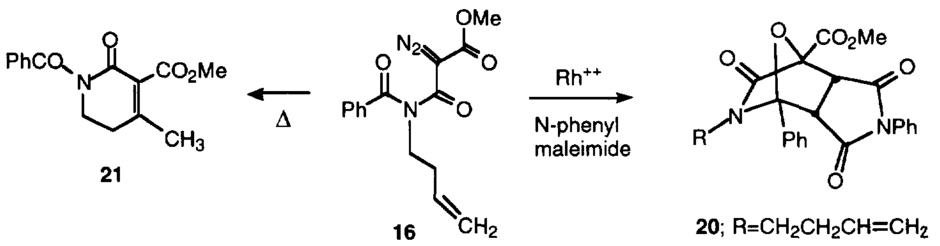


in high yield (95%) as single diastereomers. Their spectroscopic properties support the stereochemical assignment as being the result of *exo*-cycloaddition with respect to the dipole. The structural assignment of **18** was unequivocally established by an X-ray crystal analysis.

Figure 2: Ortep Representation of Cycloadduct **18**

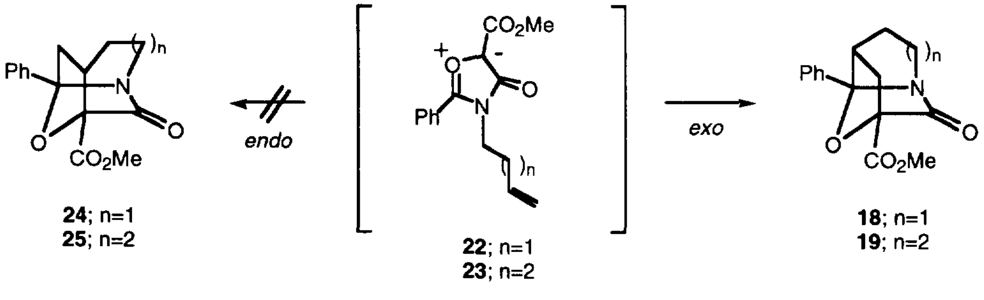


Interestingly, when N-phenyl maleimide was added to the reaction mixture (2 equiv), it was possible to isolate the bimolecular cycloadduct **20** in 85% yield. Apparently there is a high negative $\Delta S^{\neq}$ contribution to the transition state as a consequence of reduction of freedom of internal rotation about the single bonds of the molecular backbone when the disordered open-chain precursor **22** is converted into the cycloadduct. This would account for the ability of N-phenyl maleimide to capture the dipole prior to the internal cycloaddition reaction. With the *type I* dipoles previously studied,[6] intramolecular cycloaddition to the internal π-bond is too rapid to allow bimolecular trapping of the intermediate isomünchnone.

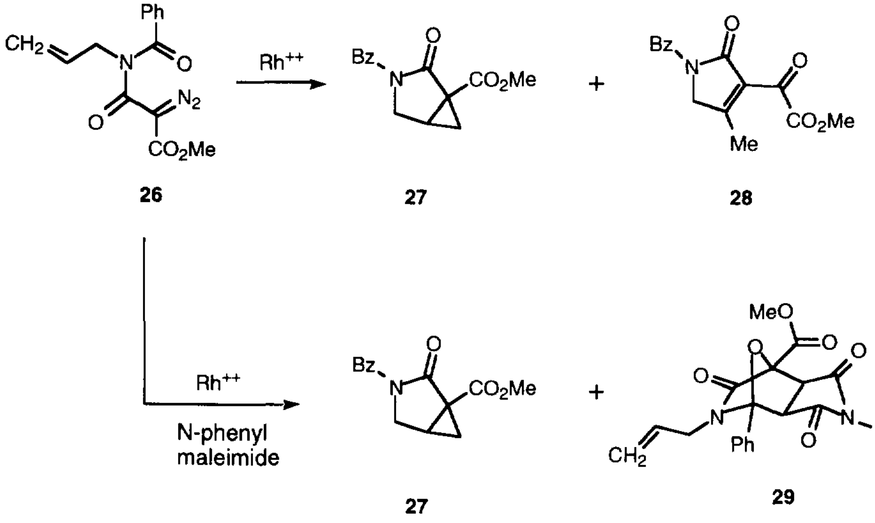


It should also be noted that the thermal reaction of **16** differs considerably from the transition metal-catalyzed process. Thus, heating a benzene solution of **16** at reflux in the absence of the Rh(II) catalyst gave lactam **21** in 86% yield. By analogy with other work on related systems, the formation of **21** can be explained in terms of an intramolecular 1,3-dipolar cycloaddition of the diazo group across the neighboring π-bond followed by nitrogen extrusion and a subsequent 1,2-hydrogen shift.[17,18]

In recent years, molecular mechanics has developed into an important technique for the calculation of molecular properties.[19] We have used the Bakmdl program[20] to model energy differences in the diastereomeric transition states for the two possible cycloadducts (*i.e.*, *exo* (**18**) *vs.* *endo* (**24**)). The stability of the diastereomeric cycloadducts was determined by calculation of their steric energies (*i.e.*, the direct sum of the force field increments). These steric energies represent the thermally averaged energies relative to the same molecule but with all bond lengths, bond angles, and torsional angles set to their strainless values and the atoms having Van der Waals and electrostatic interactions corresponding to infinite separation.[21] We assume that the relative energy differences of the two lowest energy conformations of the regioisomeric cycloadducts will parallel the energy differences in the transition state. The *exo-endo* cycloadducts were subjected to energy minimization within the Model KS 2.94 program. The resulting lowest energy conformations were then submitted to MMX for the calculations of strain energies.[22] The calculations reveal a 18.4 kcal difference between the *exo* and *endo* diastereomers (*i.e.*, **18** *vs.* **24**) and a 20 kcal difference with **19** (*vs.* **25**). The large differences in strain energy between the two diastereomers (and presumably the diastereomeric transition states) provides a reasonable explanation for why these internal isomünchnone reactions proceed exclusively *via* the *exo* orientation.



The facility of an intramolecular cycloaddition reaction depends on the length and nature of the tether connecting the dipole and dipolarophile functionalities. The activation energy of the process will also reflect the strain energy of the ring to be formed and the stereoelectronic interactions in the transition state. In order to probe the limits of tether length on the intramolecular cycloaddition of these N-alkenyl substituted isomünchnones, we examined the Rh(II) catalyzed behavior of diazoimide **26**. Exposure of **26** to a refluxing mixture of $Rh_2(OAc)_4$ in benzene did not produce any detectable quantities of an intramolecular cycloaddition product. Instead, the reaction afforded the intramolecular cyclopropanation product **27** (60%) as well as pyrrolone **28** (17%). The formation of **28** involves an initial 1,3-dipolar cycloaddition of the diazo group across the neighboring π-bond followed by nitrogen extrusion and diradical reorganization.[23] This same rearranged dihydro-1H-pyrrole **28** is also obtained upon heating diazoimide **26** in benzene in the absence of $Rh_2(OAc)_4$ and is analogous to the formation of **21**.



	27	29
$Rh_2(OAc)_4$	40%	60%
$Rh_2(tfa)_4$	0%	100%

When the reaction of **26** was carried out in the presence of N-phenyl maleimide, a mixture of **28** as well as the bimolecular cycloadduct **29** was obtained. Interesting, a variation in product ratio was observed when the catalyst ligand was changed to the more electron withdrawing trifluoroacetamide group ($Rh_2(tfa)_4$). With this catalyst, only the bimolecular cycloadduct **29** was found. The chemoselectivity encountered presumably reflects the differences in electrophilicity between the various rhodium carbenoid intermediates, implying involvement of the metal and its ligands during the formation of the isomünchnone dipole.[24-27] The fact that no dipolar cycloaddition occurs in the absence of a trapping agent suggests that ring strain of the resulting intramolecular cycloadduct is sufficiently reflected in the transition state of cycloaddition so that a substantial kinetic barrier to this process exists.

In conclusion, isomünchnone dipoles generated from the Rh(II) catalyzed reaction of diazoimides undergo successful intramolecular dipolar-cycloaddition across alkenyl π-systems tethered to the nitrogen atom of the imide. The facility of the cycloaddition is critically dependent on conformation factors in the transition state. The structurally diverse group of heterocyclic compounds that have been prepared by the intramolecular dipolar cycloaddition of these mesoionics clearly demonstrates the high potential they have in organic synthesis. We are continuing to explore the scope, generality, and synthetic applications of the intramolecular isomünchnone cycloaddition reaction and will report additional findings at a later date.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in oven dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator. All reaction mixtures were purified on a silica gel column.

Preparation and Rhodium(II) Catalyzed Cycloaddition of 3-[(2-Vinyl-phenyl)-benzoylamino]-2-diazo-3-oxo-propionic acid tert-Butyl Ester (12). A stirred solution containing 1.50 g (12.6 mmol) of o-vinyl aniline[28] in 30 mL of CH_2Cl_2 at 0°C was treated with 3.54 g (25 mmol) of benzoyl chloride. The solution was allowed to warm to rt while stirring for 1h. The reaction was quenched with a saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to give N-(2-vinyl-phenyl)benzamide as a white solid (95%); mp 134-135°C; IR (KBr) 1644, 1518, 1472, and 1300 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 5.43 (d, 1H, J=11.0 Hz), 5.69 (dd, 1H, J=17.5 and 0.9 Hz), 6.84 (dd, 1H, J=17.5 and 11.0 Hz), and 7.10-8.10 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 118.3, 123.5, 125.3, 127.0, 128.5, 128.7, 130.6, 131.8, 132.3, 134.4, 134.7, and 165.5.

A solution containing 0.28 g (1.25 mmol) of the above amide in 15 mL of THF was cooled to -78°C. To this solution was added 1.0 mL (1.5 mmol) of a 1.6 M n-butyllithium solution in hexane. The reaction was allowed to stir for 30 min at -78°C and then 0.30 g (1.5 mmol) of tert-butyl diazo-malonylchloride[16] was added dropwise. The solution was allowed to stir at -78°C for 1 h and was then quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-[(2-vinyl-phenyl)-benzoylamino]-2-diazo-3-oxo-propionic acid tert-butyl ester (**12**) (48%) as a bright yellow oil; IR (neat) 2130, 1705, 1654, 1448, and 1331 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H), 5.37 (d, 1H, J=11.0 Hz), 5.75 (d, 1H, J=17.4 Hz), 6.95 (dd, 1H, J=17.4 and 11.0 Hz), and 7.00-7.60 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.1, 41.0, 83.4, 117.5, 126.4, 127.9, 128.4, 128.5, 129.3, 129.6, 131.7, 131.8, 134.6, 135.8, 137.2, 159.3, 166.3, and 171.7.

To a solution containing 2 mg of rhodium(II) acetate in 5 mL of benzene at 80°C was added dropwise 0.10 g (0.27 mmol) of **12** in 1 mL benzene. The solution was allowed to stir at 80°C for an additional 15 min following the addition. The solution was concentrated under reduced pressure and the residue was subjected to flash silica chromatography to give 1-aza-13-oxa-11-oxo-12-phenyltricyclo[6.3.1.0^{2,7}]dodecane-2,4,6 triene-10-carboxylic acid tert-butyl ester (**14**) (93%) as a white solid; mp 157-158°C; IR (neat) 1768, 1739, 1549, 1337, and 1110 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 9H), 2.15 (dd, 1H, J=13.1 and 1.4 Hz), 2.72 (dd, 1H, J=13.1 and 9.4 Hz), 3.72 (d, 1H, J=9.4 Hz), and 7.00-7.60 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.9, 40.9, 48.6, 83.8, 90.6, 110.1, 121.1, 124.5, 127.0, 128.3, 128.7, 129.7, 132.9, 141.2, 146.3, 162.8, and 178.6; Anal, Calcd. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found C, 72.61; H, 5.84; N, 3.84.

Preparation and Rhodium(II) Catalyzed Cycloaddition of 3-[(2-Allyl-phenyl)-benzoylamino]-2-diazo-3-oxo-propionic acid tert-Butyl Ester (13). A stirred solution containing 1.0 g (7.51 mmol) of O-allyl aniline[29] in 30 mL of CH_2Cl_2 at 0°C was treated with 1.74 mL (15.0 mmol) of benzoyl chloride. The solution was allowed to warm to rt while stirring for 1h. The reaction was quenched with a saturated $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to give N-(2-allyl-phenyl)-benzamide as a white solid (85%); mp 118-119°C; IR (KBr) 1644, 1525, 1478, and 1300 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.43 (d, 2H, J=6.0 Hz), 5.06-5.25 (m, 2H), 5.90-6.10 (m, 1H), and 7.10-8.00 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 36.9, 116.7, 123.6, 125.3, 127.0, 127.4,128.6, 130.2, 131.7, 134.8, 136.2, and 165.5.

A solution containing 0.50 g (2.10 mmol) of the above amide in 20 mL of THF was cooled to -78°C. To this solution was added 1.58 mL (2.5 mmol) of a 1.6 M n-butyllithium solution in hexane. The reaction was allowed to stir for 30 min at -78°C and then 0.75 g (3.7 mmol) of tert-butyl diazo-malonylchloride was added dropwise. The solution was stirred at -78°C for 2 h and then quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-[(2-allyl-phenyl)-benzoylamino]-2-diazo-3-oxo-propionic acid tert-butyl ester (**13**) (60%) as a bright yellow oil; IR (neat) 2129, 1709, 1659, and 1254 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H), 3.40-3.50 (m, 2H), 5.07-5.12 (m, 2H), 5.80-6.00 (m, 1H), and 7.00-7.70 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.7, 28.1, 35.2, 83.4, 116.8, 127.1, 128.0, 128.6, 128.7, 129.3, 129.4, 130.1, 131.8, 134.8, 135.7, 137.9, 159.2, 166.3, and 171.4.

To a solution containing 2 mg of rhodium(II) acetate in 5 mL of benzene at 80°C was added dropwise 0.04 g of **13** in 1 mL of benzene. The solution was allowed to stir at 80°C for 15 min and was then concentrated under reduced pressure . The residue was subjected to flash silica gel chromatography to give 12-oxa-2-oxo-11-phenyl-3,4,5,6-tetrahydro-2H-1,5-methanobenzo[b]azocine-3-carboxylic acid tert-butyl ester (**15**) (93%) as a white solid; mp 143-144°C; IR (neat) 1744, 1662, 1365, and 1217 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 9H), 1.83

(dd, 1H, J=13.2 and 4.6 Hz), 2.83, (dd, 1H, J=13.2 and 10.4 Hz), 3.00-3.15 (m, 2H), 3.35-3.45 (m, 1H), and 7.03-7.60 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.9, 28.3, 38.2, 39.3, 83.6, 85.5, 95.3, 126.4, 126.7, 127.0, 127.4, 128.5, 128.7, 129.8, 132.5, 137.8, 164.2, and 174.6; Anal. Calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found C, 73.25; H, 6.16; N, 3.71.

Crystals suitable for an X-ray crystallographic structure determination were grown from a methylene chloride-hexane solution. A single crystal of approximately 0.4x0.6x0.8 mm was mounted on a quartz fiber such that the longest crystal dimension was parallel to the fiber axis. Unit cell parameters were determined on a Syntex $P2_1$ automated diffractometer using Mo Ka radiation. Twenty-four reflections were machine centered and used in the least-squares refinement of the lattice parameters and orientation matrix. The unit cell parameters obtained were a = 11.582 (2) Å, b = 31.907 (6) Å, c = 10.942 (2) Å, V = 4043 (1) Å^3, d_{calcd} =1.24 g cm^{-3}, F(000) = 1600, Z = 8, and space group Pccn. Intensity data were collected by using the theta-two theta scan technique with a variable scan rate of 2.0-24.0 deg min^{-1} in 2θ. A scan width of 2.1° was sufficient to collect all of the peak intensity data. Check reflections, monitored after each set of 100 scans, showed no significant change during the course of data collection. Lorentz and polarization corrections were made in the usual manner and no absorption correction was applied. Of the 3451 reflections collected with $3° < 2\theta < 45°$, 2647 were found to be unique and 2022 with $I \geq 3\sigma(I)$. The structure was solved by direct methods using the SHELXTL program. Following anisotropic refinement of the skeleton atoms, the hydrogen atoms were fixed into position and held isotropic. The final discrepancy index and weighted discrepancy index were R = 0.042 and R_w = 0.051, respectively, where $R_w = \Sigma_w{}^{1/2}(F_o - F_c) / \Sigma_w{}^{1/2}F$.

Preparation of N-(3-Butenyl)-N-(methyl 2-diazo-3-oxopropanoyl)-benzamide (16). To a flask containing 9.4 g (67 mmol) of benzoyl chloride in 100 mL of ether and 100 mL of 0.5 M KOH was added 5.8 g (54 mmol) of 4-amino-1-butene hydrochloride salt at 0°C. After stirring at rt for 2 h, the solution was washed with 10% HCl, dried over $MgSO_4$, and concentrated under reduced pressure to give 9.0 g (96%) of N-(3-butenyl)-benzamide as a thick yellow oil; IR (neat) 1787 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.37 (q, 2H, J=6.5 Hz), 3.53 (q, 2H, J=6.5 Hz), 5.09-5.17 (m, 2H), 5.77-5.86 (m, 1H), 6.27 (s, 1H), and 7.40-7.80 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.7, 39.1, 116.7, 127.0, 128.3, 131.1, 134.7, 135.4, and 167.7.

A solution containing 5.0 g (29 mmol) of the above amide and 6.1 mL (57 mmol) of methyl malonylchloride in 50 mL of benzene was heated at reflux for 3 h. The crude reaction mixture was concentrated under reduced pressure and chromatographed on silica gel to give 5.3 g (68%) of N-(3-butenyl)-N-(methyl 3-oxopropanoyl)-benzamide as a clear oil; IR (neat) 1748, 1601, and 1437 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.30-2.35 (m, 2H), 3.69 (s, 3H), 3.73 (s, 2H), 3.77-3.83 (m, 2H), 4.97-5.03 (m, 2H), 5.54-5.63 (m, 1H), and 7.43-7.62 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.0, 44.5, 46.2, 52.5, 117.8, 128.3, 128.7, 132.3, 134.1, 134.6, 167.6, 168.6, and 174.4.

To a solution containing 3.0 g (11 mmol) of the above imide and 1.4 g (12 mmol) of mesyl azide in 25 mL of THF was added 5.0 mL (36 mmol) of Et_3N under N_2 at 0°C. After warming to rt over 12 h, the crude reaction mixture was concentrated under reduced pressure and chromatographed on silica gel to give 2.3 g (72%) of N-(3-butenyl)-N-(methyl 2-diazo-3-oxopropanoyl)-benzamide (**16**) as a bright yellow oil; IR (neat) 2135, 1725, 1700, and 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.46 (dt, 2H, J=7.2 and 7.0 Hz), 3.59 (s, 3H), 3.92 (t, 2H, J=7.0 Hz), 5.02-5.09 (m, 2H), 5.70-5.81 (m, 1H), and 7.34-7.58 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.8, 46.8, 52.5, 66.0, 117.5, 128.4, 129.0, 132.3, 135.1, 135.9, 160.9, 166.5, and 172.3.

Rhodium (II) Catalyzed Reaction of N-(3-Butenyl)-N-(methyl-2-diazo-3-oxopropanoyl)-benzamide (16). To a refluxing solution containing 1 mg of the Rh(II) catalyst in 10 mL benzene was slowly added 0.01 g (0.03 mmol) of α-diazo ketone 16. The mixture was stirred under N_2 for 4 h and the solvent was removed under reduced pressure. The crude product mixture was chromatographed on silica gel to give methyl 2-oxo-7-phenyl-8-oxa-3-azatricyclo-[4.2.1.0^{3,7}]nonane-1-carboxylate (**18**) (100%); mp 98-99°C; IR (neat) 1759 and 1367 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.70 (dd, 1H; J=13.0 and 1.5 Hz), 2.01 (ddd, 1H, J=13.0, 9.6 and 6.2 Hz), 2.10-2.21 (m, 1H), 2.53 (dd, 1H, J=13.0 and 9.5 Hz), 2.94 (ddd, 1H, J=12.5, 9.4 and 6.2 Hz), 3.07 (dd, 1H, J=13.0 and 4.3 Hz), 3.62 (ddd, 1H, J=12.5, 9.6 and 4.3 Hz), 3.88 (s, 3H), and 7.40-7.64 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.0, 40.4, 41.2, 44.5, 52.9, 85.8, 105.1, 127.4, 128.7, 130.1, 131.9, 165.4, and 180.1; Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 66.02; H, 5.58; N, 4.85.

Crystals suitable for an X-ray crystallographic structure determination were grown from a CH_2Cl_2-hexane solution. A single crystal of approximately 0.1x0.2x0.2 mm was mounted on a quartz fiber such that the longest crystal dimension was parallel to the fiber axis. Unit cell parameters were determined on a Siemens automated diffractometer using Cu Ka radiation. Thirty-eight reflections were machine centered and used in the least-squares refinement of the lattice parameters and orientation matrix. The unit cell parameters obtained were a = 18.373 (4) Å, b = 7.478 (2) Å, c = 19.529(4) Å, β=91.88 (3)°, V = 2682(1) Å^3, d_{calcd} = 1.35 g cm^{-3}, F(000) = 1152, Z = 8, and space group C2/c. Intensity data were collected by using the Wycoff Omega scan technique with a variable scan rate of 30.0-60.0 deg min^{-1} in 2θ. Check reflections, monitored after each set of 100 scans, showed no significant change during the course of data collection. Lorentz and polarization corrections were made in the usual manner and no absorption correction was applied. Of the 4241 reflections collected with $2.0° < 2θ < 113.5°$, 1553 were found to be unique and have $I \geq 3β(I)$. The structure was solved by direct methods using the SHELXTL-PLUS program. Following anisotropic refinement of the skeleton atoms, the hydrogen atoms were fixed into position and held isotropic. The final discrepancy index and weighted discrepancy index were R = 4.96 % and R_w = 7.15 %, respectively, where $R_w = Σ_w^{1/2}(F_o - F_c) / Σ_w^{1/2}F$.

The Rh(II) reaction was also carried out in the presence of a trapping agent. To a refluxing solution containing 5 mg of the Rh(II) catalyst and 0.30 g (1.7 mmol) of N-phenylmaleimide in benzene was slowly added 0.25 g (0.87 mmol) of α-diazo ketone 16. The mixture was stirred under N_2 for 3 h and the solvent was removed under reduced pressure. The crude product mixture was chromatographed on silica gel. The major fraction isolated corresponded to hexahydro-7-carbomethoxy-4,7-epoxy-5-(3-butenyl)-1,3,6-trioxo-2,4-diphenyl-1H-pyrrolo[3,4-c]pyridine (**20**) (85%); mp 167-168°C; IR (neat) 1759 and 1718 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.75-1.89 (m, 2H), 3.06-3.18 (m, 2H), 3.84 (d, 1H, J=6.8 Hz), 3.99 (s, 3H), 4.04 (d, 1H, J=6.8 Hz), 4.85-4.97 (m, 2H), 5.44-5.55 (m, 1H), 7.07-7.87 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.6, 39.8, 49.1, 53.2, 53.3, 86.5, 99.3, 117.6, 126.2, 128.2, 128.3, 128.4, 128.9, 129.0, 130.9, 131.1, 134.2, 162.8, 166.6, 170.2, and 171.1; Anal.

Calcd. for $C_{25}H_{22}N_2O_5$: C, 67.24; H,4.97; N, 6.28. Found: C, 67.11; H, 5.03; N, 6.22.

Thermolysis of N-(3-Butenyl)-N-(methyl-2-diazo-3-oxopropanoyl)-benzamide (16). A solution containing 0.25 g (0.87 mmol) of α-diazo ketone **16** in 5 mL of benzene was heated at reflux for 36 h under N_2. Concentration under reduced pressure followed by silica gel chromatography gave 0.20 g (86%) of methyl 1-benzoyl-4-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (**21**) as a clear oil; IR (neat) 1738, 1690, and 1601 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 2.59 (t, 2H, J=6.4 Hz), 3.75 (s, 3H), 3.94 (t, 2H, J=6.4 Hz), 7.32-7.55 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.2, 30.7, 42.3, 52.3, 127.2, 128.0, 128.1, 131.6, 135.7, 156.4, 162.6, 165.6, and 173.4; HRMS Calcd. for $C_{15}H_{15}NO_4$: 273.1002. Found: 273.1001.

Preparation of N-(4-Pentenyl)-N-(methyl-2-diazo-3-oxopropanoyl)-benzamide (17). To a flask containing 16 g (115 mmol) of benzoyl chloride in 250 mL of ether and 250 mL of 0.5 M KOH was added 14 g (115 mmol) of 5-amino-1-pentene at 0°C. After stirring at rt for 2 h, the solution was washed with 10% HCl, dried over $MgSO_4$, and concentrated under reduced pressure to give 6.7 g (30%) of N-(4-penten-yl)-benzamide as a clear liquid; IR (neat) 1603 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.66-1.75 (m, 2H), 2.01-2.17 (m, 2H), 3.42-3.48 (m, 2H), 4.97-5.07 (m, 2H), 5.75-5.88 (m, 1H), 6.22 (brs, 1H), 7.36-7.49 (m, 3H), and 7.72-7.74 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.7, 31.2, 39.7, 115.0, 127.1, 128.3, 131.1, 134.7, 137.8, and 167.8.

A solution containing 5.7 g (30 mmol) of the above amide and 6.5 mL (60 mmol) of methyl malonylchloride in 50 mL of benzene was heated at reflux for 3 h. The crude reaction mixture was concentrated under reduced pressure and chromatographed on silica gel to give 7.1 g (81%) of N-(4-pentenyl)-N-(methyl 3-oxopropanoyl)-benzamide as a clear liquid; IR (neat) 1748 and 1601 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.59-1.69 (m, 2H), 1.89-2.01 (m, 2H), 3.68 (s, 3H), 3.71-3.76 (m, 2H), 3.73 (s, 2H), 4.83-4.92 (m, 2H), 5.54-5.65 (m, 1H), and 7.52-7.61 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.7, 30.5, 44.5, 46.4, 52.1, 115.1, 128.2, 132.2, 134.6, 137.0, 167.5, 168.4, and 174.3.

To a solution containing 5.0 g (17 mmol) of the above imide and 3.1 g (26 mmol) of mesyl azide in 15 mL of THF was added 7.9 mL (57 mmol) of Et_3N under N_2 at 0°C. After warming to rt over 12 h, the crude reaction mixture was concentrated under reduced pressure and chromatographed on silica gel to give 5.4 g (99%) of N-(4-pentenyl)-N-(methyl 2-diazo-3-oxopropanoyl)-benzamide (**17**) as a bright yellow oil; IR (neat) 2134, 1700, 1710, and 1642 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.55-1.83 (m, 2H), 2.04-2.51 (m, 2H), 3.61 (s, 3H), 3.85 (t, 2H, J=7.5 Hz), 4.92-4.97 (m, 2H), 5.02-5.83 (m, 1H), and 7.35-7.57 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.0, 30.9, 47.0, 52.5, 73.2, 115.1, 128.2, 128.7, 132.1, 135.6, 137.4, 160.8, 166.3, and 172.3.

Rhodium (II) Catalyzed Reaction of N-(4-Pentenyl)-N-(methyl-2-diazo-3-oxopropanoyl)-benzamide (17). To a refluxing solution containing 2 mg of the Rh(II) catalyst in benzene was slowly added 0.10 g (0.32 mmol) of α-diazo ketone 17. The mixture was stirred under N_2 for 3 h and then the solvent was removed under reduced pressure. The crude product mixture was chromatographed on silica gel. The major product isolated corresponded to methyl 2-oxo-8-phenyl-9-oxa-3-azatricyclo-[5.2.1.$0^{3,8}$]decane-1-carboxylate (**19**) (98%); mp 150-151°C; IR (neat) 1750 and 1725 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.11-1.20 (m, 1H), 1.47-1.78 (m, 3H), 1.83 (dd, 1H, J=12.0 and 4.0 Hz), 2.45 (dd, 1H, J=13.0 and 10.2 Hz), 2.59 (ddd, 1H, J=13.5, 13.0 and 3.0 Hz), 3.17-3.23 (m, 1H), 3.75 (dd, 1H, J=13.5 and 4.5 Hz), 3.79 (s, 3H), and 7.32-7.56 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.3, 23.1, 34.4, 39.3, 42.4, 52.9, 86.7, 96.0, 128.5, 128.9, 130.0, 131.4, 165.8, and 175.3; Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.76; H, 6.01; N, 4.82.

Preparation of N-(2-Propenyl)-N-(methyl-2-diazo-3-oxopropanoyl)-benzamide (26). To a flask containing 27 g (190 mmol) of benzoyl chloride in 250 mL CH_2Cl_2 was added 250 mL of 0.5 M KOH and 10 g (175 mmol) of allyl amine at 0°C. After stirring at rt for 2 h, the solution was washed with 10% HCl, dried over $MgSO_4$, and concentrated under reduced pressure to give 25 g (87%) of N-(2-propenyl)-benzamide as a pale yellow oil; IR (neat) 1603 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.08 (t, 2H, J=5.7 Hz), 5.15-5.28 (m, 2H), 5.86-5.99 (m, 1H), 6.35 (s, 1H), and 7.25-7.86 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 42.4, 116.6, 126.9, 128.5, 131.5, 134.1, 134.5, and 167.3.

A solution containing 5.0 g (31 mmol) of the above amide and 6.7 mL (62 mmol) of methyl malonylchloride in 75 mL of benzene was heated at reflux for 1 h. The crude reaction mixture was concentrated under reduced pressure and chromatographed on silica gel to give 7.3 g (91%) of N-(2-propenyl)-N-(methyl 3-oxopropanoyl)-benzamide as a yellow oil; IR (neat) 1746, 1601, and 849 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 3.82 (s, 2H), 4.32 (d, 2H, J=5.0 Hz), 5.03-5.15 (m, 2H), 5.72-5.85 (m, 1H), and 7.41-7.59 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 44.5, 48.6, 52.0, 117.0, 127.9, 128.5, 132.0, 132.5, 134.5, 167.5, 168.3, and 174.0.

To a solution containing 2.0 g (7.7 mmol) of the above imide and 1.4 g (12 mmol) of mesyl azide in 10 mL of THF was added 3.5 mL (25 mmol) of Et_3N under N_2 at 0°C. After warming to rt over 12 h, the crude reaction mixture was concentrated under reduced pressure and chromatographed on silica gel to give 1.8 g (83%) of N-(2-propenyl)-N-(methyl 2-diazo-3-oxopropanoyl)-benzamide (**26**) as a bright yellow oil; IR (neat) 2138, 1642, 1602, and 1582 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.52 (s, 3H), 4.34 (d, 2H, J=5.0 Hz), 5.05-5.18 (m, 2H), 5.77-5.86 (m, 1H), and 7.28-7.54 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 49.2, 52.3, 65.7, 117.8, 128.2, 128.7, 132.1, 132.6, 135.2, 160.7, 165.8, and 172.3.

Rhodium (II) Catalyzed Reaction of N-(2-Propenyl)-N-(methyl-2-diazo-3-oxopropanoyl)-benzamide (26). To a refluxing solution containing 2 mg of the Rh(II) catalyst and 0.09 g (0.5 mmol) of N-phenylmaleimide in benzene was slowly added 0.14 g (0.5 mmol) of α-diazo ketone **26**. The mixture was stirred under N_2 for 3 h and the solvent was removed under reduced pressure. The crude product mixture was chromatographed on silica gel. The major fraction was identified as hexahydro-7-carbomethoxy-4,7-epoxy-5-(2-propenyl)-1,3,6-trioxo-2,4-diphenyl-1H-pyrrolo[3,4-c]pyridine (**29**) (60%) as a white crystalline solid; mp 237-238°C; IR (neat) 1765 and 1718 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.41 (dd, 1H, J=15.5 and 7.4 Hz), 3.87 (d, 1H, J=6.5 Hz), 3.93 (ddd, 1H, J=15.5, 5.0 and 1.0 Hz), 4.02 (s, 3H), 4.05 (d, 1H, J=6.5 Hz), 5.02 (dd, 1H, J=17.3 and 1.0 Hz), 5.09 (d, 1H, J=10.3 Hz), 5.44-5.57 (m, 1H), and 7.08-7.82 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 42.8, 49.2, 53.3, 53.7, 61.3, 99.5, 119.6, 126.2, 127.9, 128.3, 128.4, 128.5, 128.9, 129.0, 130.7, 130.9, 162.7, 166.3, 170.1, and 170.9; Anal. Calcd. for $C_{24}H_{20}N_2O_6$: C, 66.66; H, 4.66; N, 6.48. Found: C, 66.62; H, 4.69; N, 6.47.

The second fraction was identified as methyl 3-benzoyl-2-oxo-3-azabicyclo-[3.1.0]hexane-1-carboxylate (**27**) (20%) as a clear liquid; IR (neat) 1752, 1740, and 1674 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.49 (dd, 1H, J=5.1 and 5.0), 2.13 (dd, 1H, J=7.8 and 5.1 Hz), 2.59 (ddd, 1H, J=7.8, 5.5 and 5.0 Hz), 3.74 (s, 3H), 3.85 (d, 1H, J=12.0 Hz), 4.09 (dd, 1H, J=12.0 and 5.5 Hz), and 7.23-7.46 (m, 5H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 21.9, 23.3, 32.7, 45.5, 52.7, 127.8, 128.3, 131.8, 134.0, 167.6, 168.6, and 170.2; HRMS Calcd. for $C_{14}H_{13}NO_4$: 259.0845. Found: 259.0851.

The minor fraction isolated from the column was assigned as methyl 1-benzoyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**28**) (17%); mp 109-110°C; IR (neat) 1759, 1741, and 1672 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 2.42 (s, 3H), 3.80 (s, 3H), 4.52 (s, 2H), and 7.34-7.60 (m, 5H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 15.9, 52.0, 52.9, 124.0, 127.8, 128.8, 131.9, 133.9, 162.1, 164.8, 168.5, 169.2; Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.07; N, 5.38.

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