Pergamon

Tetrahedron 54 (1998) 6957–6976

TETRAHEDRON

Acyclic Stereocontrol in [3+2]-Cycloadditions of Amino Acid-Derived Isomünchnone Dipoles‡

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Received 8 September 1997; revised 23 October 1997; accepted 27 February 1998

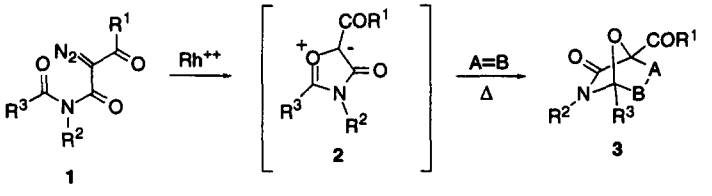
Abstract: α-Diazoimides derived from chiral amines undergo Rh(II)-catalyzed cyclization to give the corresponding chiral isomünchnone dipoles which were trapped with a variety of dipolarophiles. The extent and sense of diastereoselectivity in the [3+2]-cycloaddition is a function of the substitution pattern on the chiral amine. *Exo*-cycloadducts were formed in high yield, but the π-facial selectivity is low with dipoles derived from 1-phenylethyl amine and 1-(1-naphthalenyl)ethyl amine. However, very high facial discrimination was observed when amino acid esters were used as the chiral amine component. The best results (≥ 95 : 5) were obtained using chiral dipoles derived from phenylalanine methyl ester with a variety of dipolarophiles. The observed *syn* preference can be rationalized in terms of a stereoelectronic effect of the ester functional group in the preferred conformation in the transition state of the cycloaddition. Another possibility involves interaction of the ester carbonyl with the rhodium metal thereby causing the attack of the amido group to occur in a stereodefined manner. Effective shielding of one of the π faces by π-stacking with the aromatic ring explains the high level of π-facial selectivity of the phenylalanine derivatives. The present study introduces a new method for efficient acyclic stereocontrol in isomünchnone cycloaddition reactions.

The development of stereocontrolled methods for the construction of acyclic and cyclic structures containing multiple asymmetric centers has received much attention as a consequence of its importance in the synthesis of highly functionalized, biologically active molecules.[1] Cycloadditions are especially versatile for the preparation of polycycles with stereogenic centers because the reactions usually proceed in a concerted manner.[2] High regiospecificity and stereoselectivity along with simultaneous creation of multiple chiral centers makes the 1,3-dipolar cycloaddition reaction a particularly important process for heterocyclic synthesis.[3] Recently, asymmetric catalysis has emerged as an efficient way of controlling relative and absolute stereochemistry for a limited number of cycloadditions.[4-9] The great majority of examples both in the classical Diels-Alder reaction[10-12] and in 1,3-dipolar cycloadditions,[13-16] however, use chiral 2π or 4π-components in substrate-controlled processes. A characteristic common to many asymmetric cycloadditions that occur with high enantio- or diastereoselectivity is the ability of the reactants to form highly ordered rigid transition-state geometries that exhibit a large bias for reaction at one of the diastereotopic faces of the substrate.[17] Steric effects are generally responsible for the reaction bias at one of the diastereotopic faces of the substrate and these effects minimize the number of possible transition states for the stereoselection.

‡. *Dedicated with affection to Madeleine Joullié on the occasion of her 70th birthday*

0040-4020/98/$19.00
PII: S0040-4020(98)00339-1

The realization of a high degree of stereoselectivity with conformationally flexible molecules poses a special challenge to the synthetic organic chemist. For efficient selectivity, it is necessary to control the conformation in the transition state[18] and the substituent groups on the acyclic stereogenic center must lead to a high degree of π-facial discrimination through specific steric or stereoelectronic effects.[19-21] Previous work from this group has established the Rh(II)-catalyzed decomposition of α-diazoimides as an efficient entry into the isomünchnone class of dipoles.[22-24] Starting from simple amides, a variety of substituted mesoionic systems were prepared which underwent cycloadditions with both electron-rich and electron-deficient dipolarophiles.[23] We were able to show that the dipolar-cycloaddition of isomünchnones with alkenes also occurred intramolecularly and that the overall reaction represents an efficient way to synthesize complex poly-heterocyclic ring systems.[24]



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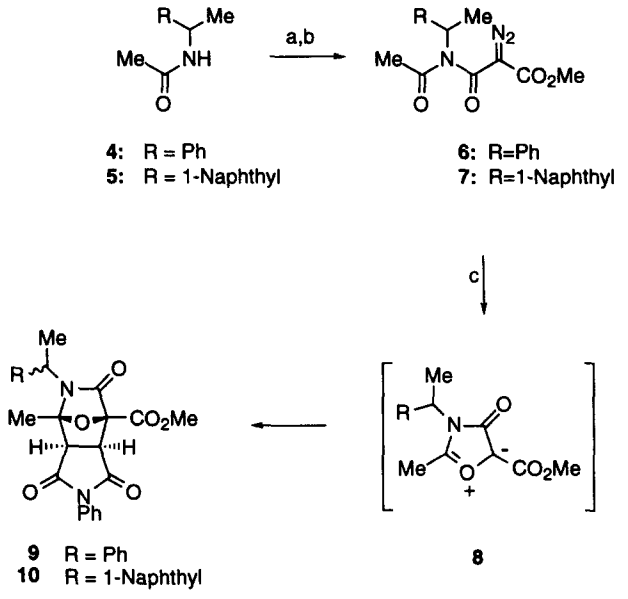
Recently, we have studied the π-facial diastereoselection of the conformationally rigid proline derived bicyclic isomünchnone system toward dipolar cycloaddition.[25] The use of amino acid derivatives as chiral controllers in asymmetric synthesis is of current interest.[26] In the present paper, we have extended our earlier studies to open-chain α-chiral amides. To the best of our knowledge, this work represents the first report on acyclic stereocontrol in the [3+2]-cycloaddition of mesoionic betaines.[27] Our studies reveal that a strategically placed stereogenic center can effect high *syn*-selectivity in these cycloaddition reactions.

Results and Discussion

Construction of the prerequisite diazoimides necessary for dipole generation was accomplished by malonation[28] of the chiral amides **4** and **5** followed by standard diazo transfer.[29] Both of these diazoimides were decomposed by heating in benzene in the presence of an appropriate dipolarophile and a catalytic quantity of rhodium(II) perfluorobutyroamidate ($Rh_2(pfm)_4$). This choice of catalyst and solvent was found to be superior for the tandem cyclization-cycloaddition reaction as it gave a nearly quantitative yield of cycloadduct (≥90%). Cycloadducts **9** and **10**, derived from *N*-phenylmaleimide, were assigned the *exo*-stereochemistry on the basis of their NMR spectra and the characteristic vicinal coupling constant (J = 6.6 Hz) for the two protons at the ring fusion.[30] The corresponding *endo*-isomers were formed in trace quantities (<2%) and could not be

Scheme I



Reagents: (a) MeO_2CH_2COCl, Δ; (b) MsN_3, NEt_3; (c) $Rh_2(pfm)_4$, *N*-phenylmaleimide

isolated from any of the systems used in the present study. For each substrate, two diastereomers were formed in roughly equal amounts and consequently, the relative stereochemistry was not assigned in view of thepoor overall selectivity. The methyl group at C_2 of the isomünchnone dipole appears to control the preferred conformation of the stereogenic unit in the transition state by allylic 1,3-strain.[19] In order to minimize nonbonding interactions, the hydrogen atom would be expected to occupy the sterically most congested inside position and π-facial selectivity should, therefore be a function of the steric interactions between the groups at the stereogenic center with the incoming dipolarophile (Figure 1). The lack of π-facial selectivity in these

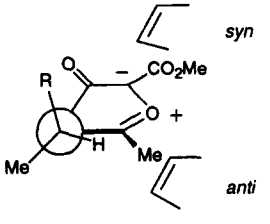
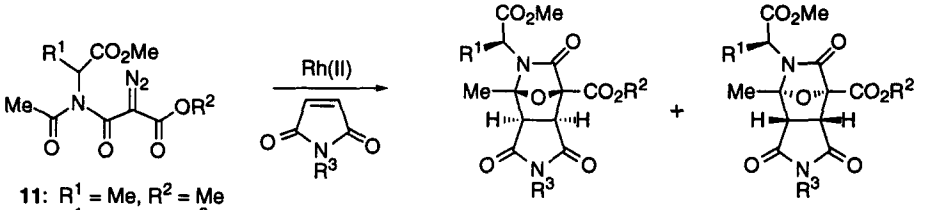


Fig. 1: Weak Steric Interactions for R = Ph, 1-Naphthyl

cycloadditions is presumably a consequence of insufficient discrimination by the steric interactions in the extended and relatively loose *exo*-transition state.

The above results suggest that acyclic stereocontrol in isomünchnone cycloadditions should be based on stereoelectronic rather than steric effects in the *exo*-transition state of the reaction. Some recent studies in our laboratory uncovered a *syn*-directing effect of ester functional groups at an asymmetric carbon adjacent to the nitrogen atom of fused bicyclic isomünchnones.[25] Consequently, we examined several π-amino esters as chiral controllers for these mesoionic cycloadditions. Gratifyingly, we discovered that the π-facial diastereoselectivity was significantly increased when diazoimides **11-14** were used. The reaction of these diazoimides with $Rh_2(pfm)_4$ and *N*-phenyl or *N*-methylmaleimide in refluxing benzene resulted in the formation of cycloadducts **15-20** with nearly complete *exo/endo* selectivity as well as high π-facial selectivity. Product distributions and yields are summarized in Table 1.



11: R^1 = Me, R^2 = Me
12: R^1 = CH_2iPr, R^2 = Me
13: R^1 = CH_2Ph, R^2 = Me
14: R^1 = CH_2Ph, R^2 = Et

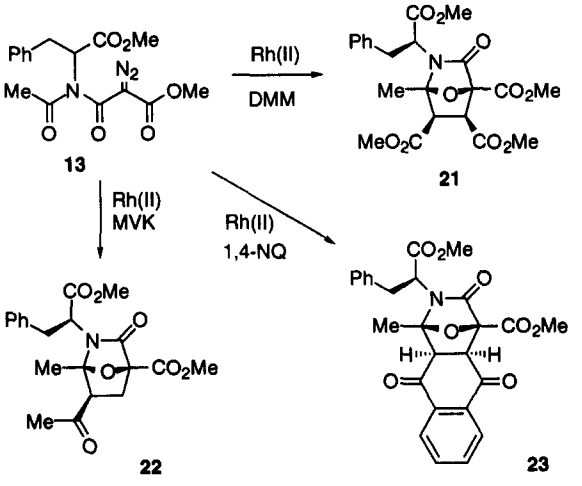
15: R^1 = Me, R^2 = Me, R^3 = Ph
16: R^1 = Me, R^2 = Me, R^3 = Me
17: R^1 = CH_2iPr, R^2 = Me, R^3 = Ph
18: R^1 = CH_2Ph, R^2 = Me, R^3 = Ph
19: R^1 = CH_2Ph, R^2 = Et, R^3 = Ph
20: R^1 = CH_2Ph, R^2 = Et, R^3 = Me

The *syn*-stereochemistry of the major diastereomer was assigned on the basis of its NMR data. For example, the phenylalanine-derived cycloadducts **18** - **23** show an unusual upfield shift for the bridgehead methyl group (δ 0.77 - 0.99 ppm) compared to cycloadducts **15-17** (δ 1.83 - 1.88 ppm). This difference in chemical shift stems from the methyl group being located in the shielding cone of the aromatic ring in the phenylalanine-derived cycloadducts. AM1 semiempirical calculations provides good support for the suggestion that the methyl group lies over the face of the aromatic ring in the preferred conformation of the *syn*-cycloadduct **18**. For the *anti*-adduct, such a conformational arrangement does not correspond to an energy minimum. The *syn*-stereochemistry for the major diastereomer was unambiguously established by an X-ray analysis of cycloadduct **19**.[31]

Table 1: Product Distribution in the Cyclization-Cycloaddition Sequence of Diazoimides

Substrate	Dipolarophile[a]	Product	yield[b]	*syn* : *anti* [c]
4	NPM	**9**	92	55 : 45
5	NPM	**10**	95	60 : 40
11	NPM	**15**	89	88 : 12
11	NMM	**16**	89	83 : 17
12	NPM	**17**	92	82 : 18
13	NPM	**18**	89	≥ 95 : 5
14	NPM	**19**	88	≥ 95 : 5
14	NMM	**20**	84	≥ 95 : 5
13	DMM	**21**	79	≥ 95 : 5
13	MVK	**22**	90	≥ 95 : 5
13	1,4-NQ	**23**	88	≥ 95 : 5
24	NPM	**26**	80	82 : 18
24	NMM	**27**	84	80 : 20
25	NPM	**28**	94	80 : 20

a) NPM = *N*-phenylmaleimide, NMM = *N*-methylmaleimide, DMM = dimethyl maleate, MVK = methyl vinyl ketone, 1,4-NQ = 1,4-naphthoquinone; b) yield of isolated product; c) determined by NMR analysis of the crude reaction mixtures.



The stereoelectronic effect on the ester functionality in the preferred isomünchnone conformation (see Figure 2) favors *syn* attack by the electrophilic dipolarophile, perhaps by enhancing the overall electron density at the *syn*-face.[21] It should be pointed out, however, that other rationalizations to account for the stereoselectivity are also conceivable. For example, one alternative explanation invokes dipolar alignment of the carboxylate carbonyl with the isomünchnone dipole which provides both steric and electronic inhibition of *anti* attack. There is also the distinct possibility that the rhodium metal is still associated with the isomünchnone

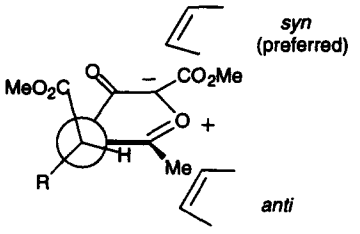


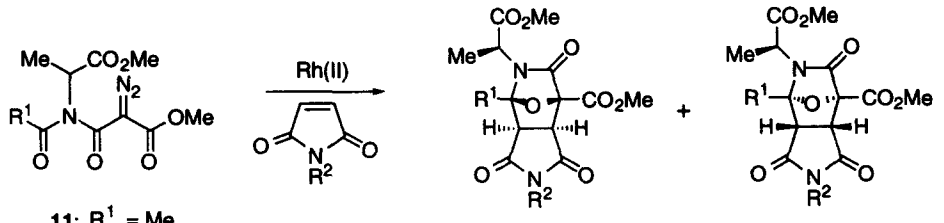
Fig. 2: Stereoelectronic Effects in Ester-Substituted Systems

dipole. Indeed, earlier work in our laboratory showed that Rh(II) catalyst dependent changes occurred in the regiochemistry of intramolecular cycloaddition following carbonyl ylide formation.[32] This result strongly suggests that the metal plays an important role in the 3+2-cycloaddition step. More recently, Hodgson and coworkers have reported the first example of catalytic enantioselective tandem carbonyl-ylide formation-cycloaddition.[33] The asymmetric induction (*ca* 50% ee) encountered in his system clearly implies that the metal is coordinated with the dipole in the crucial cycloaddition step. In an earlier study, Davies and coworkers found that esters of chiral alcohols such as (S)-methyl lactate and (R)-pantolactone are excellent chiral auxiliaries for asymmetric cyclopropanation by vinylcarbenoids.[34] The high stereoselectivity was proposed to be due to an interaction between the carbonyl group of the auxiliary and the rhodium carbenoid. Therefore, on the basis of the above observations, an alternate mechanism that can be invoked to rationalize the asymmetric induction with the isomünchnones is that the ester carbonyl interacts with the carbenoid, causing the attack of the amide carbonyl to occur in a stereo defined manner.[35] The resulting isomünchnone, still bonded to the rhodium, is now set for the 3+2-cycloaddition from the face opposite to the rhodium.[36]

It should be noted that the steric bulk of the R-substituent in the amino acid precursor shows a negligible effect on diastereoselectivity as can be seen from a comparison of the alanine-derived system **11** (R=Me) with the leucine-derived substrate **12** ($R=CH_2iPr$). The significantly enhanced stereocontrol with diazoimides **13** and **14** ($R=CH_2Ph$) may be related to π-stacking[37] between the phenyl group of the amino acid and the isomünchnone dipole which efficiently shields the *anti* face of the reactive dipole thereby resulting in the exclusive formation of the *syn*-cycloadducts. In this case, the *syn*-directing effect of the ester functionality and the π-stacking effect act in a synergistic manner.

The scope and generality of the *syn*-directing effect of the ester group was established from a study of diazoimides **24** and **25** derived from the corresponding alanine methyl esters. By varying the nature of the acyl group on nitrogen, the extent of steric strain in the isomünchnone dipole can be adjusted. If conformational control in the transition state were the limiting factor for π-facial discrimination, then an effect on the degree of

diastereoselectivity should be observed. The product ratio obtained in the cycloaddition of **24** and **25** with *N*-phenyl and *N*-methylmaleimides was, however, nearly identical regardless of the substituent R^1 at the C_2-position of the mesoionic dipole. This observation suggests that the methyl group in **11** exerts sufficient allylic 1,3-strain in the transition state of the [3+2]-cycloaddition for efficient conformational control. Thus, the observed π-facial selectivity is an inherent function of the substituents at the stereogenic center and a diastereoselectivity of *ca* 85 : 15 is the upper limit in reactions of alanine derived diazoimides.



11; R^1 = Me
24; R^1 = Ph
25; R^1 = iPr

	syn (major)		*anti* (minor)
15; R^1 = Me, R^2 = Ph	88	:	12
26; R^1 = Ph, R^2 = Ph	82	:	18
27; R^1 = Ph, R^2 = Me	80	:	20
28; R^1 = iPr, R^2 = Ph	80	:	20

In conclusion, we have demonstrated that a strategically placed stereogenic center can effect high *syn*-selectivity in 1,3-dipolar cycloadditions of isomünchnone dipoles. Conformational control through allylic 1,3-strain coupled with the stereoelectronic effects of ester and aryl substituents provides for efficient acyclic stereocontrol. The present study also shows that α-amino acid derivatives can act successfully as asymmetric controllers in [3+2]-cycloadditions of mesoionic dipoles. Experiments to exploit the methodology in the stereocontrolled synthesis of azapolycyclic systems are presently underway in our laboratories.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70eV. Unless otherwise noted, all reactions were performed under an atmosphere of dry argon in flame-dried glassware. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-hexane mixture as the eluent unless specified otherwise. Due to a very long relaxation time, the resonance for the carbon atom next to the diazo functional group was usually not detected for the diazo compounds prepared in this study.

General Procedure for the Preparation of α–Diazoimides. A solution of the appropriate chiral amide (5.5 mmol) and methyl malonyl chloride (1.5 equiv) in benzene (30 mL) at reflux for 5-8 h. Evaporation of the solvent afforded the crude malonate as a colorless oil, which was purified by silica gel column chromatography.

To a solution of the above malonate (2.0 mmol) in dichloromethane (25 mL) was added either methylsulfonyl azide or *p*-nitrobenzenesulfonyl azide (1.1 to 1.5 equiv) and triethylamine (1 to 2 equiv) at - 10 °C. The mixure was stored at - 20 °C overnight and the insoluble precipitate that had formed in the reaction was removed by filtration. The solvent was removed under reduced pressure to give the diazo compound, which was purified by silica gel column chromatography.

General Procedure for the Rhodium(II)-Catalyzed Reaction of α–Diazoimides. To a solution of the α–diazoimide (600 μmol) in benzene (10 mL) was added the appropriate dipolarophile (1 to 2 equiv) and the mixture was placed into an oil bath preheated to 90 °C. Rhodium perfluorobutyroamidate [$Rh_2(pfm)_4$, 1 mg] was added and the mixture was heated at reflux until the starting material was completely consumed. The solvent was removed under reduced pressure and the crude cycloadduct was purified by flash silica gel chromatography.

3-[Acetyl-(1-phenylethyl)-amino]-3-oxo-propionic Acid Methyl Ester. A mixture of *N*-(1-phenylethyl)acetamide (**4**) (1.12 g, 6.9 mmol) and methyl malonyl chloride (1.03 g, 7.6 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 1.29 g (72 %) of the desired imide as a colorless oil: IR (neat) 1744, 1698, 1388, 1263, and 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.79 (d, 3H, *J* = 7.2 Hz), 2.13 (s, 3H), 3.72 (s, 3H), 3.79 (s, 2H), 5.88 (q, 1H, *J* = 7.2 Hz), and 7.26-7.38 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 17.4, 26.0, 46.2, 52.2, 52.5, 125.7, 127.1, 128.6, 140.3, 167.8, 168.8, and 174.4; HRMS Calcd. for $C_{14}H_{18}NO_4$ $(M+H)^+$: 264.1236. Found: 264.1235.

3-[Acetyl-(1-phenylethyl)amino]-2-diazo-3-oxo-propionic Acid Methyl Ester (6). A mixture of the above imide (880 mg, 3.34 mmol), mesyl azide (445 mg, 3.68 mmol) and triethylamine (372 mg, 3.68 mmol) was allowed to react according to the general procdure. Flash silica gel chromatography gave 623 mg (64 %) of diazoimide **6** as yellow powder, mp 87-88 °C; IR (KBr) 2140, 1766, 1744, 1154, and 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.69 (d, 3H, *J* = 7.2 Hz), 2.15 (s, 3H), 3.78 (s, 3H), 5.50 (q, 1H, *J* = 7.2 Hz), and 7.22-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.9, 24.1, 52.4, 55.9, 126.9, 127.3,128.3, 140.4, 160.6, 168.8, and 171.8; Anal Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.17; H, 5.31; N, 14.25.

3-[Acetyl-(1-naphthalen-1-yl-ethyl)amino]-3-oxo-propionic Acid Methyl Ester. A sample of *N*-(1-naphthalen-1-yl-ethyl)acetamide (**5**)[38] (3.97 g, 18.6 mmol) and methyl malonyl chloride (2.79 g, 20.5 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 3.12 g (54 %) of the desired imide as a colorless oil: IR (neat) 1747, 1695, 1511, 1380, 1228, and 1116 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.88 (d, 3H, *J* = 6.9 Hz), 1.98 (s, 3H), 3.65 (d, 1H, *J* = 16.2 Hz), 3.67 (s, 3H), 3.79 (d, 1H, *J* = 16.2 Hz), 3.55 (q, 1H, *J* = 6.9 Hz), 7.44-7.53 (m, 3H), 7.63 (d, 1H, *J* = 7.2 Hz), 7.75 (d, 1H, *J* = 7.5 Hz), and 7.77-7.85 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.0, 26.4, 45.9, 50.6, 52.2, 123.1, 124.8, 125.7, 126.0, 126.9, 128.9, 129.1, 130.8, 133.8, 134.8, 167.7, 169.1, and 174.6; HRMS Calcd. for $C_{18}H_{20}NO_4$ $(M+H)^+$: 314.1392. Found: 314.1393.

3-[Acetyl-(1-naphthalen-1-yl-ethyl)amino]-2-diazo-3-oxo-propionic Acid Methyl Ester (7). A mixture of the above imide (500 mg, 1.60 mmol), *p*-nitrobenzenesulfonyl azide (437 mg, 1.9 mmol) and triethylamine (252 mg, 2.5 mmol) was allowed to react according to the general procedure to give 360 mg (66 %) of diazoimide **7** as yellow oil: IR (neat) 2144, 1728, 1694, 1645, 1235, and 1127 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.80 (d, 3H, *J* = 7.2 Hz), 2.14 (s, 3H), 3.60 (s, 3H), 6.36 (q, 1H, *J* = 7.2 Hz), 7.41-7.53 (m, 3H), 7.72-7.80 (m, 3H), and 8.08 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 19.2, 23.9, 52.3, 52.4, 123.1, 125.1,125.5, 125.9,.126.4, 128.5, 128.7, 130.7, 133.5, 135.0, 160.2, 166.4, and 171.0; HRMS Calcd. for $C_{18}H_{18}N_3O_4$ $(M+H)^+$: 340.1297. Found: 340.1295.

7-Methyl-3,5,9-trioxo-4-phenyl-8-(1-phenylethyl)-10-oxa-4,8-diazatricyclo[5.2.1.0^{2,6}]-decane-1-carboxylic Acid Methyl Ester (9). Diazoimide **6** (195 mg, 674 μmol) and *N*-phenyl-maleimide (117 mg, 674 μmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture showed the formation of two diastereomeric cycloadducts **9** (90 %, *d.r.* 55 : 45) which were separated by flash silica gel chromatography.

The major diastereomer **9a** (137 mg, 47 %) exhibited the following spectral properties, mp 178-179 °C; IR (KBr) 1756, 1717, 1499, 1387, and 1208 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 1.87 (d, 3H, *J* = 7.2 Hz), 2.93 (d, 1H, *J* = 6.9 Hz), 3.46 (d, 1H, *J* = 6.9 Hz), 3.96 (s, 3H), 4.80 (q, 1H, *J* = 7.2 Hz), 7.13-7.16 (m, 2H), and 7.30-7.42 (m, 8 H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.2, 19.9, 48.4, 53.1, 53.4, 54.4, 86.7, 97.0, 126.1, 126.7, 128.3, 128.8, 129.0, 129.1, 130.9, 140.2, 162.7, 167.3, 171.1, and 171.2; Anal Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.23; H, 5.13; N, 6.35.

The minor diastereomer **9b** (131 mg, 45 %) exhibited the following spectral properties, mp 191-192 °C; IR (KBr) 1781, 1713, 1398, 1342, and 1205 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.76 (d, 3H, *J* = 7.2 Hz), 1.87 (s, 3H), 2.96 (d, 1H, *J* = 6.9 Hz), 3.66 (d, 1H, *J* = 6.9 Hz), 3.96 (s, 3H), 5.09 (q, 1H, *J* = 7.2 Hz), 7.13-7.18 (m, 2H), and 7.29-7.41 (m, 8 H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.7, 18.6, 48.8, 52.1, 53.2, 54.1, 86.5, 97.3, 126.1, 126.8, 128.4, 128.9, 129.0, 129.1, 131.0, 138.9, 162.8, 167.2, 171.2, and 171.3; Anal Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.41; H, 5.01; N, 6.33.

7-Methyl-3,5,9-trioxo-4-phenyl-8-(1-naphthalen-1-yl-ethyl)-10-oxa-4,8-diazatricyclo-[5.2.1.0^{2,6}]decane-1-carboxylic Acid Methyl Ester (10). Diazoimide **7** (134 mg, 395 μmol) and *N*-phenylmaleimide (69 mg, 395 μmol) were allowed to react according to general procedure. Proton NMR analysis of the crude product mixture showed formation of the two diastereomeric cycloadducts identified as **10** (90 %, *d.r.* 60 : 40) which were separated by flash silica gel chromatography.

The major diastereomer **10a** (110 mg, 58 %) exhibited the following spectral properties, mp 256-257 °C; IR (KBr) 1754, 1721, 1500, 1207, 1143, and 1097 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 3H), 1.92 (d, 3H, *J* = 7.2 Hz), 2.05 (d, 1H, *J* = 6.9 Hz), 3.39 (d, 1H, *J* = 6.9 Hz), 4.02 (s, 3H), 6.11 (q, 1H, *J* = 7.2 Hz), 7.05 (d, 2H, *J* = 8.1 Hz), 7.32-7.39 (m, 3H), 7.52-7.63 (m, 3H), 7.75 (d, 1H, *J* = 7.2 Hz), and 7.89-7.94 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.4, 19.6, 47.0, 48.9, 53.4, 54.1, 86.3, 97.4, 122.0, 125.3, 125.8, 126.1, 126.9, 127.6, 128.9, 129.0, 129.6, 129.8, 130.9, 131.4, 132.2, 133.6, 162.9, 166.9,

170.9, and 171.0; Anal Calcd. for $C_{28}H_{24}N_2O_6$: C, 69.41; H, 4.99; N, 5.78. Found: C, 69.39; H, 5.04; N, 5.71.

The minor diastereomer **10b** (71 mg, 37 %) exhibited the following spectral properties, mp 248-249 °C; IR (KBr) 1750, 1718, 1210, 1154, and 1103 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 1.97 (d, 3H, J = 7.2 Hz), 3.21 (d, 1H, J = 6.9 Hz), 3.76 (d, 1H, J = 6.9 Hz), 4.02 (s, 3H), 5.84 (q, 1H, *J* = 7.2 Hz), 7.14 (d, 2H, *J* = 7.5 Hz), 7.32-7.66 (m, 7H), 7.84-7.91 (m, 2H), and 8.00 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.7, 18.9, 48.5, 49.1, 53.4, 55.0, 86.6, 97.4, 122.2, 124.7, 125.1, 126.2, 127.3, 129.0, 129.1, 129.3, 130.9, 133.8, 135.1, 162.8, 167.5, 171.0, and 171.2; Anal Calcd. for $C_{28}H_{24}N_2O_6$: C, 69.41; H, 4.99; N, 5.78. Found: C, 69.33; H, 5.02; N, 5.73.

2-(Acetyl-methoxycarbonylacetylamino)propionic Acid Methyl Ester. A mixture of *N*-acetyl-alanine methyl ester[39] (1.9 g, 13.1 mmol) and methyl malonyl chloride (1.96 g, 14.4 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 1.96 g (66 %) of the desired imide as a colorless oil: IR (neat) 1745, 1702, 1439, 1261, and 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, 3H, *J* = 6.9 Hz), 2.27 (s, 3H), 3.61 (d, 1H, *J* = 15.5 Hz), 3.62 (s, 3H), 3.63 (s, 3H), 3.78 (d, 1H, *J* = 15.5 Hz), and 4.47 (q, 1H, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.8, 25.1, 45.6, 52.1, 52.3, 54.5, 167.2, 167.9, 170.0, and 172.4; HRMS Calcd. for $C_{10}H_{15}NO_6Li$ $(M+Li)^+$: 252.1059. Found: 252.1059.

2-[Acetyl-(diazomethoxycarbonylacetyl)amino]-propionic Acid Methyl Ester (11). A mixture of the above imide (1.15 g, 4.7 mmol), *p*-nitrobenzenesulfonyl azide (1.07 g, 4.7 mmol) and triethylamine (475 mg, 4.7 mmol) were allowed to react according to the general procedure to give 980 mg (77 %) of diazoimide **11** as yellow oil: IR (neat) 2143, 1745, 1645, 1439, and 1126 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.51 (d, 3H, *J* = 6.9 Hz), 2.28 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 4.85 (q, 1H, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.2, 24.2, 52.5, 52.6, 54.7, 160.6, 165.6, 170.9, and 171.6; HRMS Calcd. for $C_{10}H_{13}N_3O_6Li$ $(M+Li)^+$: 278.0964. Found: 278.0966.

2-(Acetyl-methoxycarbonylacetylamino)-4-methyl-pentanoic Acid Methyl Ester. A sample of *N*-acetylleucine methyl ester[40] (1.56 g, 8.3 mmol) and methyl malonyl chloride (1.37 g, 10 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 1.70 g (71 %) of the desired imide as a colorless oil: IR (neat) 1754, 1710, 1695, 1228, and 1154 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, 6H, *J* = 6.3 Hz), 1.63-1.77 (m, 2H), 2.07-2.16 (m, 1H), 2.31 (s, 3H), 3.67 (d, 1H, *J* = 16.2 Hz), 3.69 (s, 6H), 3.84 (d, 1H, *J* = 16.2 Hz), and 4.56 (dd, 1H, *J* = 7.5 Hz, 6.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.2, 22.8, 25.1, 25.3, 38.5, 45.9, 52.2, 52.6, 56.9, 167.3, 168.3, 170.4, and 173.0; Anal Calcd. for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.27; H, 7.31; N, 4.72.

2-[Acetyl-(diazomethoxycarbonylacetyl)amino]-4-methyl-pentanoic Acid Methyl Ester (12). A mixture of the above imide (1.60 g, 5.6 mmol), *p*-nitrobenzenesulfonyl azide (1.27 g, 5.6 mmol) and triethylamine (1.13 g, 11.1 mmol) was allowed to react according to the general procedure to give 1.49 g (85 %) of diazoimide **12** as yellow oil: IR (neat) 2140, 1752, 1709, 1405, 1346, and 1135 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.71 (d, 3H, *J* = 6.3 Hz), 0.72 (d, 3H, *J* = 7.2 Hz), 1.33-1.40 (m, 1H), 1.62-1.75 (m, 2H), 2.11

(s, 3H), 3.50 (s, 3H), 3.63 (s, 3H), and 4.75 (dd, 1H, J = 9.0 Hz and 5.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.8, 22.7, 23.8, 24.2, 37.0, 51.9, 52.1, 56.7, 73.2, 160.1, 164.8, 170.5, and 171.8; Anal Calcd. for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.11; N, 13.41. Found: C, 50.23; H, 5.10; N, 13.70

2-(Acetyl-methoxycarbonylacetylamino)-3-phenyl-propionic Acid Methyl Ester. A sample of *N*-acetyl-phenylalanine methyl ester[41] (1.03 g, 4.7 mmol) and methyl malonyl chloride (700 mg, 5.1 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 1.19 g (80 %) of the desired imide as colorless oil: IR (neat) 1752, 1710, 1667, 1275, and 1154 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.83 (s, 3H), 3.27 (dd, 1H, J = 14.1 Hz and 10.5 Hz), 3.54 (dd, 1H, J = 14.1 Hz and 3.6 Hz), 3.73 (s, 2H), 3.75 (s, 6H), 4.44 (dd, 1H, J = 10.5 Hz and 3.6 Hz), and 7.17-7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.7, 34.9, 46.1, 52.2, 52.6, 61.5, 127.1, 128.8, 129.4, 137.3, 167.1, 168.4, 169.2, and 172.8; HRMS Calcd. for $C_{16}H_{19}NO_6Li$ $(M+Li)^+$: 328.1372. Found: 328.1376.

2-[Acetyl-(diazomethoxycarbonylacetyl)amino]-3-phenyl-propionic Acid Methyl Ester (13). A mixture of the above imide (2.01 g, 6.2 mmol), *p*-nitrobenzenesulfonyl azide (1.42 g, 6.2 mmol) and triethylamine (1.25 g, 12.4 mmol) was allowed to react according to the general procedure to give 1.67 g (77 %) of diazoimide **13** as yellow oil: IR (neat) 2140, 1738, 1645, 1139, and 1218 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.97 (s, 3H), 3.21 (dd, 1H, J = 15.1 Hz and 10.8 Hz), 3.43 (dd, 1H, J = 15.1 Hz and 5.1 Hz), 3.60 (s, 3H), 3.68 (s, 3H), 5.10 (dd, 1H, J = 10.8 Hz and 5.1 Hz), and 7.10-7.20 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.7, 35.2, 52.2, 52.3, 60.2, 73.8, 126.5, 128.,1, 129.0, 136.6, 160.0, 164.9, 169.8, and 172.0; Anal Calcd. for $C_{16}H_{17}N_3O_6$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.27; H, 4.79; N, 11.97.

2-[Acetyl-(diazoethoxycarbonylacetyl)amino]-2-phenyl-propionic Acid Methyl Ester (14). To a solution of *N*-acetyl phenylalanine methyl ester (1.27 g, 5.7 mmol) in THF (25 mL) was added lithium *bis*(trimethylsilyl)amide (1.0 equiv, 1.0 M in hexane) at -78°C and the mixture was stirred at -78°C for 15 min. Ethyl diazo malonyl chloride[42] (1.0 g, 5.7 mmol) was added *via* syringe and the mixture was allowed to warm to rt. Evaporation of the solvent afforded the crude diazoimide as orange oil which was purified by silica gel column chromatography to give 1.06 g (51 %) of **14** as a yellow oil: IR (neat) 2947, 2143, 1716, 1645, and 1368 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, J = 7.2 Hz), 2.05 (s, 3H), 3.29 (dd, 1H, J = 14.4 Hz and 10.5 Hz), 3.51 (dd, 1H, J = 14.4 Hz and 5.1 Hz), 3.77 (s, 3H), 4.10-4.17 (m, 2H), 5.20 (dd, 1H, J = 10.5 Hz and 5.1 Hz), and 7.19-7.28 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.1, 24.1, 35.5, 52.6, 60.5, 61.9, 126.8, 128.3, 129.3, 136.9, 159.9, 165.3, 170.1, and 172.2; Anal Calcd. for $C_{17}H_{19}N_3O_6$: C, 56.51; H, 5.30; N, 11.63. Found: C, 56.39; H, 5.34; N, 11.52.

8-(1-Methoxycarbonylethyl)-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-4,8-diazatricyclo-[5.2.1.0^{2,6}]decane-1-carboxylic Acid Methyl Ester (15). Diazoimide **11** (215 mg, 792 μmol) and *N*-phenylmaleimide (137 mg, 792 μmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture showed formation of two cycloadducts identified as *syn*-**15a** and *anti*-**15b** (90 %, *d.r.* 88 : 12). Flash silica gel chromatography gave 295 mg (89 %) of an inseparable mixture

of the two diastereomers as a white powder, mp 199-200 °C; IR (KBr) 1766, 1738, 1709, 1410, 1382, and 1197 cm^{-1}; Anal Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.55; H, 4.79; N, 6.61.

Cycloadduct *syn*-**15a** (major isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.67 (d, 3H, *J* = 7.2 Hz), 1.92 (s, 3H), 3.78 (s, 3H), 3.81 (d, 1H, *J* = 6.8 Hz), 3.88 (d, 1H, *J* = 6.8 Hz), 3.98 (s, 3H), 4.00 (q, 1H, *J* = 7.2 Hz), 7.23-7.26 (m, 2H), and 7.40-7.48 (m 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.5, 16.7, 48.8, 51.0, 53.0, 53.3, 53.4, 86.4, 97.0, 126.2, 129.0, 129.1, 131.1, 162.6, 167.0, 169.9, 171.4, and 171.9.

Cycloadduct *anti*-**15b** (minor isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.60 (d, 3H, *J* = 7.6 Hz), 1.97 (s, 3H), 3.75 (d, 1H, *J* = 6.8 Hz), 3.80 (s, 3H), 3.99 (s, 3H), 4.12 (d, 1H, *J* = 6.8 Hz), 4.82 (q, 1H, *J* = 7.6 Hz), 7.23-7.25 (m, 2H), and 7.40-7.48 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.9, 48.5, 50.4, 52.9, 53.3, 54.8, 86.2, 97.5, 126.2, 129.0, 129.1, 131.1, 162.6, 167.0, 170.5, 171.6, and 171.8.

8-(1-Methoxycarbonylethyl)-4,7-dimethyl-3,5,9-trioxo-10-oxa-4,8-diazatricyclo[5.2.1.0^{2,6}]-decane-1-carboxylic Acid Methyl Ester (16). Diazoimide **11** (280 mg, 1.03 mmol) and *N*-methylmaleimide (115 mg, 1.03 mmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture showed formation of two cycloadducts identified as *syn*-**16a** and *anti*-**16b** (90 %, *d.r.* 83 : 17). Flash silica gel chromatography gave 323 mg (89 %) of an inseparable mixture of the two diastereomers as a white powder, mp 195-196°C; IR (KBr) 1766, 1745, 1702, 1439, 1218, and 1154 cm^{-1}; Anal Calcd. for $C_{15}H_{18}N_2O_8$: C, 50.85; H, 5.12; N, 7.91. Found: C, 50.78; H, 5.18; N, 7.83.

Cycloadduct *syn*-**16a** (major isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.62 (d, 3H, *J* = 7.2 Hz), 1.83 (s, 3H), 2.94 (s, 3H), 3.63 (d, 1H, *J* = 6.8 Hz), 3.69 (d, 1H, *J* = 6.8 Hz), 3.73 (s, 3H), 3.96 (s, 3H), and 3.98 (q, 1H, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.4, 16.6, 25.4, 48.8, 50.9, 53.0, 53.8, 53.9, 86.0, 96.7, 162.7, 166.9, 169.9, 172.2, and 172.8.

Cycloadduct *anti*-**16b** (minor isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.54 (d, 3H, *J* = 7.2 Hz), 1.88 (s, 3H), 2.94 (s, 3H), 3.58 (d, 1H, *J* = 6.8 Hz) 3.75 (s, 3H), 3.90 (d, 1H, *J* = 6.8 Hz), and 4.73 (q, 1H, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.4, 17.0, 25.4, 48.5, 50.3, 52.9, 53.3, 54.8, 85.8, 97.2, 162.6, 167.0, 170.5, 172.2, and 172.6.

8-(1-Methoxycarbonyl-3-methyl-butyl)-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-4,8-diaza-tricyclo[5.2.1.0^{2,6}]decane-1-carboxylic Acid Methyl Ester (17). Diazoimide **12** (170 mg, 546 μmol) and *N*-phenylmaleimide (95 mg, 546 μmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture showed formation of two cycloadducts identified as *syn*-**17a** and *anti*-**17b** (90 %, *d.r.* 82 : 18) which were separated by flash silica gel chromatography.

Cycloadduct *anti*-**17a** (39 mg, 16 %), mp 191-192 °C; IR (KBr) 1766, 1730, 1716, 1382, and 1197 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, 3H, *J* = 6.4 Hz), 0.95 (d, 3H, *J* = 6.4 Hz), 1.57-1.64 (m, 1H), 1.79-1.86 (m, 1H), 1.89-1.95 (m, 1H), 1.96 (s, 3H), 3.73 (d, 1H, *J* = 6.8 Hz), 3.78 (s, 3H), 3.99 (s, 3H), 4.19 (d, 1H, *J* = 6.8 Hz), 4.90 (dd, 1H, *J* = 10.8 Hz and 5.2 Hz), 7.22-7.26 (m, 2H), and 7.37-7.48 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 16.3, 21.2, 22.9, 24.7, 40.0, 48.5, 52.8, 53.4, 53.6, 54.9, 86.4, 98.0,

126.3, 129.1, 129.2, 131.1, 162.9, 167.6, 171.0, 171.5, and 171.7; Anal Calcd. for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.33; H, 5.72; N, 6.02.

Cycloadduct *syn*-**17b** (189 mg, 76 %), mp 128-129 °C; IR (KBr) 1759, 1730, 1713, 1382, and 1197 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, 6H, *J* = 6.4 Hz), 1.62-1.75 (m, 1H), 1.86 (ddd, 1H, *J* = 14.0 Hz, 10.0 Hz, and 4.4 Hz), 1.87 (s, 3H), 2.23 (ddd, 1H, *J* = 14.0 Hz, 10.4 Hz, and 3.6 Hz), 3.75 (s, 3H), 3.85 (d, 1H, *J* = 6.8 Hz), 3.87 (d, 1H, *J* = 6.8 Hz), 3.93 (dd, 1H, *J* = 10.4 Hz and 4.4 Hz), 3.97 (s, 3H), 7.18-7.20 (m, 2H), and 7.32-7.44 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.8, 21.2, 23.0, 24.6, 38.5, 48.9, 53.0, 53.3, 53.9, 54.5, 86.5, 97.2, 126.2, 129.0, 129.1, 131.1, 162.7, 167.4, 170.2, 171.5, and 172.1; Anal Calcd. for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.29; H, 5.77; N, 6.07.

8-(1-Methoxycarbonyl-2-phenylethyl)-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-4,8-diaza-tricyclo[5.2.1.0^{2,6}]decane-1-carboxylic Acid Methyl Ester (18). Diazoimide **13** (180 mg, 518 μmol) and *N*-phenylmaleimide (108 mg, 622 μmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture indicated predominant formation of cycloadduct *syn*-**18** (90 %, *d.r.* ≥ 95 : 5) which was isolated by flash silica gel chromatography (227 mg, 89 %); mp 109-110 °C; IR (KBr) 1758, 1718, 1500, 1382, and 1147 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.01 (s, 3H), 3.35 (dd, 1H, *J* = 13.8 Hz and 11.4 Hz), 3.44 (dd, 1H, *J* = 13.8 Hz and 4.2 Hz), 3.76 (d, 1H, *J* = 6.9 Hz), 3.81 (s, 3H), 3.82 (d, 1H, *J* = 6.9 Hz), 3.95 (dd, 1H, *J* = 11.4 Hz and 4.2 Hz), 3.98 (s, 3H), and 7.14-7.45 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 35.2, 48.9, 53.0, 53.1, 53.5, 58.2, 86.0, 96.9, 126.1, 127.1, 128.6, 128.8, 128.9, 129.3, 131.0, 133.9, 136.8, 162.6, 167.3, 138.8, 171.4, and 171.7; Anal Calcd. for $C_{26}H_{24}N_2O_8$: C, 63.41; H, 4.91; N, 5.69. Found: C, 63.60; H, 5.15; N, 5.57.

8-(1-Methoxycarbonyl-2-phenylethyl)-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-4,8-diaza-tricyclo[5.2.1.0^{2,6}]decane-1-carboxylic Acid Ethyl Ester (19). Diazoimide **14** (134 mg, 371 μmol) and *N*-phenylmaleimide (64 mg, 371 μmol) were allowed to react according to the general procedure to give cycloadduct *syn*-**19** (90 %, d.r. ≥ 95 : 5). Flash silica gel chromatography of the crude product mixture afforded 168 mg (88 %) of *syn*-**19**, mp 117-118 °C; IR (KBr) 1759, 1709, 1496, 1190, and 748 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 3H), 1.39 (t, 3H, *J* = 7.2 Hz), 3.38 (dd, 1H, *J* = 13.8 Hz and 11.2 Hz), 3.46 (dd, 1H, *J* = 13.8 Hz and 4.2 Hz), 3.75 (d, 1H, *J* = 6.6 Hz), 3.80 (s, 3H), 3.81 (d, 1H, *J* = 6.6 Hz), 3.94 (dd, 1H, *J* = 11.2 Hz and 4.2 Hz), 4.92-4.98 (m, 2H), and 7.10-7.42 (m, 10 H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 35.3, 48.8, 53.0, 53.7, 58.3, 62.7, 86.0, 96.8, 126.2, 127.1, 128.7, 128.8, 129.0, 129.3, 131.0, 136.7, 162.1, 167.5, 169.0, 171.3, and 171.8; Anal Calcd. for $C_{27}H_{26}N_2O_8$: C, 64.03; H, 5.17; N, 5.53. Found: C, 64.18; H, 5.37; N, 5.23.

8-(1-Methoxycarbonyl-2-phenylethyl)-4,7-dimethyl-3,5,9-trioxo-10-oxa-4,8-diaza-tricyclo-[5.2.1.0^{2,6}]decane-1-carboxylic Acid Ethyl Ester (20). Diazoimide **14** (330 mg, 914 μmol) and *N*-methylmaleimide (120 mg, 914 μmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture showed the predominant formation of cycloadduct *syn*-**20** (90 %, *d.r.* ≥ 95 : 5). Flash silica gel chromatography afforded 338 mg (84 %) of *syn*-**20**, mp 178-179 °C; IR (KBr) 1745,

1701, 1431, 1346, 1275, and 1133 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3H), 1.38 (t, 3 H, *J* = 7.2 Hz), 2.84 (s, 3H), 3.28 (dd, 1H, *J* = 13.6 Hz and 11.2 Hz), 3.38 (dd,1H, *J* = 13.6 Hz and 4.0 Hz), 3.52 (d, 1H, *J* = 6.8 Hz), 3.58 (d, 1H, *J* = 6.8 Hz), 3.75 (s, 3H), 3.85 (dd, 1H, *J* = 11.2 Hz and 4.0 Hz), 4.34-4.49 (m, 2H), 7.07-7.09 (m, 2H), and 7.15-7.26 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.3, 25.2, 35.3, 48.8, 53.1, 53.8, 58.3, 62.7, 85.7, 96.6, 127.2, 128.7, 129.3, 136.9, 162.2, 167.6, 169.0, 172.1, and 172.7; Anal Calcd. for $C_{22}H_{24}N_2O_8$: C, 59.46; H, 5.44; N, 6.30. Found: C, 59.36; H, 5.41; N, 6.31.

2-(1-Methoxycarbonyl-2-phenylethyl)-1-methyl-3-oxo-7-oxa-2-azabicyclo[2.2.1]heptane-4,5,6-tricarboxylic Acid Trimethyl Ester (21). Diazoimide **13** (280 mg, 806 μmol) and dimethyl maleate (174 mg, 1.21 mmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture indicated formation of the cycloadduct *syn*-**21** (90 %, *d.r.* ≥ 95 : 5). Flash silica gel chromatography afforded 297 mg (79 %) of *syn*-**21**, mp 217-218°C; IR (KBr) 1766, 1730, 1716, 1282, 1239, and 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 3H), 3.31 (dd, 1H, *J* = 14.0 Hz and 11.6 Hz), 3.43 (dd, 1H, *J* = 14.0 Hz and 4.0 Hz), 3.61 (s, 3H), 3.64 (s, 3H), 3.70 (d, 1H, *J* = 9.2 Hz), 3.78 (d, 1H, *J* = 9.2 Hz), 3.82 (dd, 1H, *J* = 11.6 Hz and 4.0 Hz), 3.84 (s, 3H), 3.94 (s, 3H), 7.13-7.15 (m, 2H), and 7.24-7.33 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.5, 35.5, 49.7, 52.2, 52.5, 52.9, 53.1, 55.4, 58.3, 86.1, 96.7, 127.1, 128.7, 129.4, 137.0, 164.0, 165.6, 168.5, 168.6, and 168.8; Anal Calcd. for $C_{22}H_{25}NO_{10}$: C, 57.02; H, 5.44; N, 3.02. Found: C, 56.73; H, 5.49; N, 2.97.

6-Acetyl-2-(1-methoxycarbonyl-2-phenylethyl)-1-methyl-3-oxo-7-oxa-2-azabicyclo[2.2.1]-heptane-4-carboxylic Acid Methyl Ester (22). Diazoimide **13** (360 mg, 1.0 mmol) and methyl vinyl ketone (145 mg, 2.1 mmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture indicated formation of the *syn*-**22** cycloadduct (90 %, *d.r.* ≥ 95 : 5). Flash silica gel chromatography gave 363 mg (90 %) of pure *syn*-**22**, mp 119-120°C; IR (KBr) 1752, 1709, 1405, 1346, 1261, and 1135 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 3H), 2.13 (s, 3H), 2.42 (dd, 1H, *J* = 12.8 Hz and 8.0 Hz), 2.49 (dd, 1H, *J* = 12.8 Hz and 4.0 Hz), 3.35 (dd, 1H, *J* = 13.6 Hz and 11.2 Hz), 3.38 (dd, 1H, *J* = 8.0Hz and 4.0 Hz), 3.44 (dd, 1H, *J* = 13.6 Hz and 4.0 Hz), 3.82 (s, 3H), 3.84 (dd, 1H, *J* = 11.2 Hz and 4.0 Hz), 3.95 (s, 3H), 7.16-7.18 (m, 2H), and 7.24-7.34 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.0, 29.5, 32.6, 35.5, 52.9, 53.0, 57.9, 58.2, 84.9, 97.3, 127.0, 128.6, 129.3, 137.2, 165.2, 169.1, 169.7, and 205.6; Anal Calcd. for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.75; H, 5.96; N, 3.52.

1,4-Epoxy-1,2,3,4,4a,10a-hexahydro-2-(1-methoxycarbonyl-2-phenylethyl)-1-methyl-3,5,10-trioxobenzo[g]isoquinoline-4-carboxylic Acid Methyl Ester (23). Diazoimide **13** (280 mg, 806 μmol) and 1,4-naphthoquinone (127 mg, 806 μmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture indicated formation of cycloadduct *syn*-**23** (90 %, *d.r.* ≥ 95 : 5). Flash silica gel chromatography gave 337 mg (88 %) of *syn*-**23**, mp 114-115°C; IR (KBr) 1747, 1681, 1588, 1410, 1254, and 1147 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.77 (s, 3H), 3.33 (dd, 1H, *J* = 13.6 Hz and 11.6 Hz), 3.46 (dd, 1H, *J* = 13.6 Hz and 3.6 Hz), 3.82 (d, 1H, *J* = 8.0 Hz), 3.83 (s, 3H), 3.87 (d, 1H, *J* = 8.0 Hz), 3.94 (dd, 1H, *J* = 11.6 Hz and 3.6 Hz), 3.99 (s, 3H), 7.13-7.28 (m, 5H), 7.69-7.74 (m,

2H), and 7.89-7.95 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.5, 35.6, 52.7, 53.2, 53.3, 57.4, 58.4, 88.1, 97.8, 126.7, 127.1, 127.2, 128.8, 129.4, 134.8, 134.9, 135.0, 136.0, 137.1, 163.4, 167.2, 169.0, 192.1, and 192.3; Anal Calcd. for $C_{26}H_{23}NO_8$: C, 65.40; H, 4.86; N, 2.93. Found: C, 65.13; H, 5.11; N, 2.96.

2-(Benzoyl-methoxycarbonylacetylamino)propionic Acid Methyl Ester. A sample of *N*-benzoyl-alanine methyl ester[43] (1.94 g, 9.4 mmol) and methyl malonyl chloride (1.4 g, 10.3 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 1.83 g (63 %) of the desired imide as a colorless oil: IR (neat) 1745, 1695, 1666, 1275, and 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, 3H, *J* = 6.9 Hz), 3.50 (d, 1H, *J* = 16.5 Hz), 3.62 (d, 1H, *J* = 16.5 Hz), 3.66 (s, 3H), 3.73 (s, 3H), 4.71 (q, 1H, *J* = 6.9 Hz), 7.45-7.50 (m, 2H), 7.55-7.60 (m, 1H), and 7.71-7.74 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.9, 44.7, 52.3, 52.5, 55.9, 128.3, 129.0, 132.8, 134.5, 167.0, 168.2, 170.4, and 173.4; HRMS Calcd. for $C_{15}H_{17}NO_6Li$ $(M+Li)^+$: 314.1216. Found: 314.1226.

2-[Benzoyl-(diazomethoxycarbonylacetyl)amino]propionic Acid Methyl Ester (24). A mixture of the above imide (1.50 g, 4.9 mmol), *p*-nitro-benzenesulfonyl azide (1.11 g, 4.9 mmol) and triethylamine (494 mg, 4.9 mmol) was allowed to react according to the general procedure to give 1.42 g (82 %) of diazoimide **24** as a yellow oil: IR (neat) 2136, 1745, 1645, 1439, and 1126 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.61 (d, 3H, *J* = 6.9 Hz), 3.63 (s, 3H), 3.75 (s, 3H), 5.15 (q, 1H, *J* = 6.9 Hz), 7.38-7.43 (m, 2H), 7.49-7.52 (m, 1H), and 7.60-7.66 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.9, 52.4, 52.5, 54.9, 128.3, 128.7, 132.3, 135.4, 160.5, 165.4, 171.0, and 171.6; HRMS Calcd. for $C_{15}H_{15}N_3O_6Li$ $(M+Li)^+$: 340.1118. Found: 340.1121.

2-(Isobutyryl-methoxycarbonylacety-amino)-propionic Acid Methyl Ester. A sample of *N*-isobutyrylalanine methyl ester[44] (2.39 g, 13.8 mmol) and methyl malonyl chloride (2.64 g, 19.3 mmol) was allowed to react according to the general procedure. Flash silica gel chromatography gave 2.58 g (68 %) of the desired imide as a colorless oil: IR (neat) 1744, 1695, 1431, 1218, and 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, 3H, *J* = 6.8 Hz), 1.21 (d, 3H, *J* = 6.8 Hz), 1.58 (d, 3H, *J* = 6.8 Hz), 2.86 (sept, 1H, *J* = 6.8 Hz), 3.71 (d, 1H, *J* = 16.4 Hz), 3.72 (s, 3H), 3.73 (s, 3H), 3.85 (d, 1H, *J* = 16.4 Hz), and 4.67 (q, 1H, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.5, 19.2, 19.5, 34.6, 45.7, 52.3, 52.6, 56.6, 167.5, 168.5, 170.5, and 180.0; Anal Calcd. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.49; H, 6.93; N, 4.97.

2-[Isobutyryl-(diazomethoxycarbonylacetyl)amino]-propionic Acid Methyl Ester (25). A mixture of the above imide (1.40 g, 5.12 mmol), *p*-nitrobenzenesulfonyl azide (1.75 g, 7.7 mmol) and triethylamine (1.03 g, 10.2 mmol) was allowed to react according to the general procedure to give 1.42 g (92 %) of diazoimide **25** as yellow oil: IR (neat) 2143, 1752, 1723, 1638, 1325, and 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.12 (d, 3H, *J* = 6.8 Hz), 1.13 (d, 3H, *J* = 6.8 Hz), 1.48 (d, 3H, *J* = 6.8 Hz), 2.97 (sept, 1H, *J* = 6.8 Hz), 3.69 (s, 3H), 3.80 (s, 3H), and 4.89 (q, 1H, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.1, 18.9, 19.7, 35.3, 52.3, 52.6, 54.5, 160.5, 165.7, 171.1, and 179.1; Anal Calcd. for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.26; H, 5.69; N, 13.93.

8-(1-Methoxycarbonylethyl)-3,5,9-trioxo-10-oxa-4,7-diphenyl-4,8-diazatricyclo[5.2.1.$0^{2,6}$]-decane-1-carboxylic Acid Methyl Ester (26). Diazoimide **24** (185 mg, 555 μmol) and *N*-phenylmaleimide (96 mg, 555 μmol) were allowed to react according to general procedure. Proton NMR analysis of the crude product mixture showed formation of two cycloadducts identified as *syn*-**26a** and *anti*-**26b** (90%, *d.r.* 82 : 18). Flash silica gel chromatography gave 212 mg (80 %) of an inseparable mixture of the two diastereomers, mp 213-215 °C; IR (KBr) 1780, 1752, 1716, 1496, 1389, and 1211 cm^{-1}; Anal Calcd. for $C_{25}H_{22}N_2O_8$: C, 62.76; H, 4.63; N, 5.85. Found: C, 62.64; H, 4.76; N, 5.65.

Cycloadduct *syn*-**26a** (major isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 3H, *J* = 7.2 Hz), 3.68 (q, 1H, *J* = 7.2 Hz), 3.77 (s, 3H), 3.97 (d, 1H, *J* = 6.8 Hz), 4.03 (s, 3H), 4.54 (d, 1H, *J* = 6.8 Hz), 7.13-7.16 (m, 2H), 7.32 -7.39 (m, 3H), 7.47-7.52 (m, 3H), and 7.84-7.86 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.9, 49.1, 50.9, 52.5, 52.9, 53.2, 86.4, 100.0, 126.2, 127.9, 128.2, 128.3, 128.6, 128.7, 128.9, 131.1, 162.6, 165.9, 170.3, 170.5, and 171.2.

Cycloadduct *anti*-**26b** (minor isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, 3H, *J* = 7.6 Hz), 3.72 (s, 3H), 3.92 (d, 1H, *J* = 6.8 Hz), 4.04 (s, 3H), 4.66 (q, 1H, *J* = 7.6 Hz), 4.84 (d, 1H, *J* = 6.8 Hz), 7.11-7.16 (m, 2H), 7.36-7.40 (m, 3H), 7.45-7.50 (m, 3H), and 7.79-7.82 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.7, 48.8, 50.2, 52.5, 52.7, 53.8, 86.2, 99.6, 126.2, 127.9, 128.2, 128.3, 128.7, 128.8, 130.0, 131.1, 162.7, 166.2, 170.3, 170.6, and 171.3.

8-(1-Methoxycarbonylethyl)-4-methyl-3,5,9-trioxo-7-phenyl-10-oxa-4,8-diazatricyclo-[5.2.1.$0^{2,6}$]decane-1-carboxylic Acid Methyl Ester (27). Diazoimide **24** (360 mg, 1.08 mmol) and *N*-methylmaleimide (120 mg, 1.08 mmol) were allowed to react according to the general procedure. Proton NMR analysis of the crude product mixture showed formation of two cycloadducts identified as *syn*-**27a** and *anti*-**27b** (90 %, *d.r.* 80 : 20). Flash silica gel chromatography gave 379 mg (84 %) of an inseparable mixture of the two diastereomers, mp 209-210 °C; IR (KBr) 1766, 1748, 1695, 1382, 1211, and 1133 cm^{-1}; Anal Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.83; H, 4.86; N, 6.78.

Cycloadduct *syn*-**27a** (major isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3H, *J* = 7.6 Hz, 2.88 (s, 3H), 3.62 (q, 1H, *J* = 7.6 Hz), 3.74 (s, 3H), 3.81 (d, 1H, *J* = 6.8 Hz), 4.03 (s, 3H), 4.38 (d, 1H, *J* = 6.8 Hz), 7.46-7.54 (m, 3 H), and 7.80-7.82 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 16.0, 25.5, 49.1, 50.9, 52.6, 53.0, 53.3, 86.1, 99.8, 128.0, 128.5, 128.7, 131.2, 162.7, 166.0, 170.4, 171.1, and 172.0.

Cycloadduct *anti*-**27b** (minor isomer): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, 3H, *J* = 7.6 Hz), 2.87 (s, 3H), 3.70 (s, 3H), 3.77 (d, 1H, *J* = 6.8 Hz), 4.04 (s, 3H), 4.60 (d, 1H, *J* = 7.6 Hz), 4.67 (d, 1H, *J* = 6.8 Hz), 7.46-7.54 (m, 3H), and 7.76-7.81 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.9, 25.4, 48.7, 50.2, 52.7, 53.0, 53.9, 85.8, 99.1, 128.0, 128.2, 128.8, 131.1, 162.8, 166.0, 170.4, 171.6, and 171.9.

8-(1-Methoxycarbonylethyl)-7-isopropyl-3,5,9-trioxo-4-phenyl-10-oxa-4,8-diazatricyclo-[5.2.1.$0^{2,6}$]decane-1-carboxylic Acid Methyl Ester (28). Diazoimide **25** (171 mg, 546 μmol) and *N*-phenylmaleimide (95 mg, 546 μmol) were allowed to react according to the general procedure. Proton NMR

analysis of the crude product mixture showed formation of two cycloadducts identified as the *syn*-**28a** and *anti*-**28b** diastereomers (90 %, *d.r.* 80 : 20) which was separated by flash silica gel chromatography.

Cycloadduct *anti*-**28a** (91 mg, 20 %), mp 247-248 °C; IR (KBr) 1766, 1745, 1713, 1389, 1211, and 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 3H, *J* = 7.2 Hz), 1.44 (d, 3H, *J* = 7.2 Hz), 1.49 (d, 3H, *J* = 7.2 Hz), 2.54 (sept, 1 H, *J* = 7.2 Hz), 3.71 (d, 1H, *J* = 6.8 Hz), 3.74 (d, 1H, *J* = 6.8 Hz), 3.75 (s, 3H), 3.93 (s, 3H), 4.37 (q, 1H, *J* = 7.2 Hz), 7.18-7.22 (m, 2H), and 7.36-7.46 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.6, 16.4, 17.4, 30.3, 49.1, 51.3, 52.9, 53.2, 54.0, 85.8, 102.2, 126.2, 129.1, 129.2, 131.0, 162.5, 167.3, 169.2, 171.0, and 171.2; Anal Calcd. for $C_{22}H_{24}N_2O_8$: C, 59.46; H, 5.44; N, 6.30. Found: C, 59.39; H, 5.43; N, 6.36.

Cycloadduct *syn*-**28b** (340 mg, 74 %), mp 177-178 °C; IR (KBr) 1770, 1716, 1595, 1375, 1254, and 1197 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, 3H, *J* = 7.2 Hz), 1.44 (d, 3H, *J* = 7.2 Hz), 1.74 (d, 3H, *J* = 7.2 Hz), 2.51 (sept, 1H, *J* = 7.2 Hz), 3.77 (s, 3H), 3.84 (d, 1H, *J* = 7.2 Hz), 3.96 (s, 3H), 4.15 (d, 1H, *J* = 7.2 Hz), 4.22 (q, 1H, *J* = 7.2 Hz), 7.12-7.22 (m, 2H), and 7.36-7.46 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 16.3, 17.3, 18.3, 30.1, 49.6, 52.4, 53.0, 53.1, 53.2, 86.0, 102.7, 126.3, 129.0, 129.1, 131.2, 162.8, 168.7, 170.4, 171.4, and 171.8; Anal Calcd. for $C_{22}H_{24}N_2O_8$: C, 59.46; H, 5.44; N, 6.30. Found: C, 59.40; H, 5.45; N, 6.29.

Acknowledgement: We gratefully acknowledge the National Cancer Institute (CA-26751) for generous support of this work. M. P. wishes to acknowledge the NATO for a postdoctoral fellowship through the Deutscher Akademischer Austauschdienst (DAAD). Use of high-field NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

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