A Convenient *Trans* Diastereoselective Synthesis of 3-Butadienylazetidinones and Their Diels−Alder Cycloaddition Reactions

Arun K. Sharma, Sujit N. Mazumdar, and Mohinder P. Mahajan*

Department of Chemistry, North-Eastern Hill University, Shillong-793 003, Meghalaya, India

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An efficient *trans* diastereoselective synthesis for azetidinones **3** having 3-dienyl functionalities was developed. The method first involved the [2 + 2] cycloaddition of butadienylketene with various imines **1**. The 3-dienyl functionality of the resulting azetidinones **3** was then exploited in Diels−Alder cycloaddition reactions with dienophiles, *viz*. dimethyl acetylenedicarboxylate (DMAD), maleic anhydride (MA), *N*-phenylmaleimide (NPM), and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). The reactions of **3** with DMAD and PTAD resulted in the diastereoselective synthesis of the corresponding Diels−Alder adducts **5a,b** and **6**. However, the reactions with MA and NPM yielded a mixture (2:1) of diastereoisomers **7/7′** and **8/8′**.

The importance and structural diversity of biologically active β-lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidin-2-ones with attendent control of functional groups and stereochemistry.[1] In recent years several natural monocyclic β-lactams were shown to exhibit high activity against Gram negative organisms,[1a,c] suggesting that a suitably substituted monocyclic β-lactam ring might perhaps be the minimum requirement for biological activity.[2] In view of the reported importance of 3-alkyl/3-acetyl β-lactams[3] and 4-vinyl β-lactams[4] as intermediates in the synthesis of β-lactam antibiotics, efforts to devise/improve synthesis of suitably substituted β-lactams is an ongoing challenge and continues to attract the attention of the synthetic community.

Ketene−imine cycloadditions are a well-documented route to the synthesis of various β-lactam derivatives.[5,6] Although there are numerous reports concerning [2 + 2] cycloadditions of imines to ketenes, extended recently to vinyl- and isopropenylketenes,[3b,7,8] to our knowledge there is no such report involving butadienylketene. During the course of ongoing investigations concerning azadiene−ketene cycloadditions in our laboratory,[9] we have discovered that the use of butadienylketene in such cycloadditions is an efficient route to the synthesis of dienyl-substituted heterocycles. Given the synthetic possibilities offered by functionalized 1,3-butadienes and the biological importance of β-lactams in general and α-substituted β-lactams in particular, we were prompted to initiate a study of reactions of Schiff bases with butadienylketene. As an entry into this area we describe here the diastereoselective synthesis of α-butadienyl β-lactams which served as versatile synthetic intermediates for further elaboration to a variety of targeted α-substituted β-lactam derivatives.

It was reported that reactions of various Schiff bases with vinyl/isopropenylketenes resulted in *trans*, *cis*, or a mixture of *trans* and *cis* β-lactams.[3b,7,8] We observed that reactions of Schiff bases **1** with butadienylketene, generated *in situ* from sorbyl chloride (**2**) in the presence of triethylamine in methylene chloride at room temperature, resulted in stereoselective formation of previously unknown 3-butadienyl β-lactams **3** in good yields (48−63%) (Scheme 1). The products were assigned the azetidinone structure **3** on the basis of analytical and spectral data. Their IR spectra exhibited a strong absorption around 1735 cm^{-1} characteristic of the β-lactam ring. Their ^1H NMR spectra showed, in addition to aromatic protons, the presence of two methine protons and olefinic protons. The assignment of *trans* stereochemistry to the β-lactams **3** was based on the observed coupling constant of about 2.4 Hz for methine protons H-3 and H-4.[8,10]

In order to establish the synthetic potential of the α-dienylazetidinones **3**, we initiated Diels−Alder cycloaddition reactions of **3** with dienophiles, *viz*. dimethylacetylene dicarboxylate (DMAD), maleic anhydride (MA), *N*-phenylmaleimide (NPM), and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). All these reactions resulted in very good yields (92−97%) of the corresponding adducts

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(1) For reviews on β-lactam antibiotics, see: (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982−1983; Vols. 1−3. (b) *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry: Burlington House; London, 1984. (c) *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood: New York, 1980; Vols. 3−4. (d) Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1985; Vol. 47, pp 1−106. (e) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Sheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (f) Koppel, G. A. In *Small Ring Heterocycles*; Hassner, A. Ed.; John Wiley: New York, 1983; Part 2, pp 248−301. Brown, A. G. *Pure Appl. Chem.* **1987**, *59*, 475.

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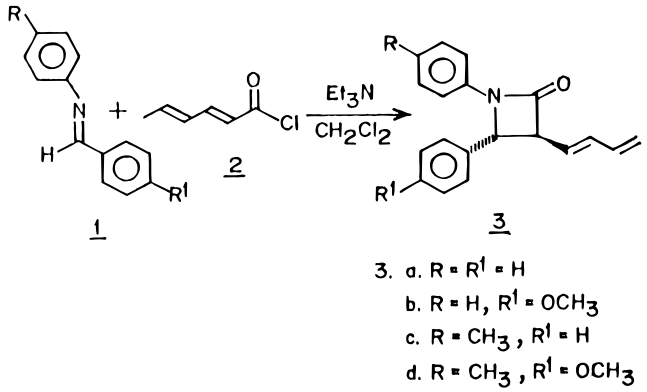
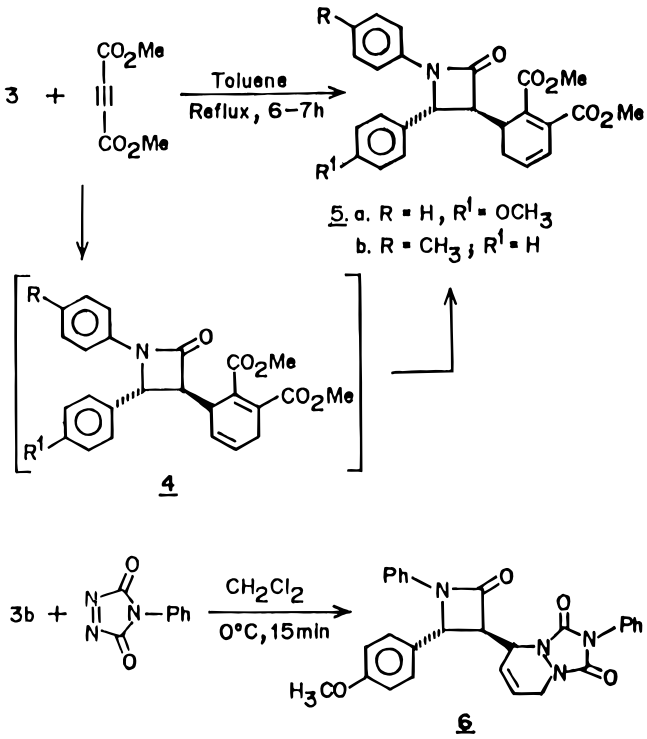
S0022-3263(95)02249-3 CCC: $12.00

Scheme 1



Scheme 2



which were well characterized (elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data). The reactions of **3** with DMAD in refluxing toluene resulted in the exclusive isolation of the conjugated cyclohexadienyl adducts **5** (Scheme 2). The products could be assigned either structure **4** and **5** on the basis of IR, mass spectra, and ^{13}C and simple ^{1}H NMR spectra. However, the products were assigned structure **5** on the basis of a $\{^1H\}-\{^1H\}$ NMR homonuclear spin correlation spectrum (Figure 1) which indicated that both methylene protons were coupled to 1′H, which in turn was coupled with only one of the olefinic protons. Further, the coupling constants observed in the 300 MHZ ^{1}H NMR spectrum between the 1′H and the two methylene protons were *ca.* 7.0 and 5.0 Hz. Values such as these are only possible when 1′H is adjacant to the methylene protons; such large coupling constants between the two cannot be anticipated on the basis of structure **4**. The adducts **5** presumably arise from the rearrangement of the initially formed nonconjugated 2′,5′-cyclohexadienyl Diels−Alder adducts **4**. The reaction of **3b** with PTAD, in methylene chloride at 0 °C, also resulted in the diastereoselective synthesis of the corresponding Diels−Alder adduct **6** (Scheme 2). However, the reactions of **3a** with MA and NPM in refluxing toluene yielded a mixture (2:1), as evidenced by ^{1}H and ^{13}C NMR spectra, of diastereoisomers **7/7′** and **8/8′**, respectively (Scheme 3). Several attempts at chromatographic separations of the two diastereoisomers **7/7′** and **8/8′** failed because of the similar R_f values. The assignment of stereochemistry of these adducts by NMR is complicated. Although **7/7′** and **8/8′** displayed spectroscopic parameters fully compatible with the gross structural features, NOE experiments were inconclusive and their specific relative stereochemistry was not assigned.

In summary, the use of butadienylketene resulted in a convenient method for the synthesis of 3-butadienyl β-lactams and various α-substituted β-lactams. The cycloadditions of butadienylketene with various imines and heterodienes could, in fact, prove to be a general method for the synthesis of various 1,3-butadiene-substituted heterocyclic systems. The scope and utility of these reactions are under active investigation in our laboratories, and results will be reported in due course.

Experimental Section

All melting points are uncorrected. ^{1}H NMR (300 MHz) and proton-decoupled ^{13}C NMR (75.4 MHz) spectra were recorded in $CDCl_3$ solutions using TMS as internal standard. Mass spectra were obtained by electron impact at 70 eV.

Preparation of Sorbyl Chloride (2). Equivalent amounts of sorbic acid (45 mmol, 5.0 g) and thionyl chloride (45 mmol, 5.3 g, 3.3 mL) were refluxed in dry toluene (20 mL) for 2.5−3 h. The solvent was removed under reduced pressure, and the sorbyl chloride thus obtained was further purified by distillation under reduced pressure: yield 4.90 g (84%); bp (observed 75 °C, 20 mm; lit.[11] 75 °C, 20 mm).

General Procedure for Azetidinones 3. A solution of sorbyl chloride (**2**) (3 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a solution of Schiff base **1** (2 mmol) and triethylamine (6 mmol) in CH_2Cl_2 under stirring at rt. After the addition was complete (*ca.* 1.5 h), the solution was stirred for an additional 15 min, washed with water (5 × 50 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the crude product thus obtained was further purified by column chromatography (silica gel) using a solution of ethyl acetate and hexane (1:9) as eluent.

***trans*-3-(1′,3′-Butadienyl)-1,4-diphenylazetidin-2-one (3a):** yield 59%; mp 118−119 °C; IR (KBr) ν 1734, 1596, 1496 cm^{-1}; ^{1}H NMR δ 3.77 (dd, J = 8.1 and 2.5 Hz, 1H), 4.80 (d, J = 2.5 Hz, 1H), 5.14 (d, J = 9.8 Hz, with fine splitting, 1H), 5.24 (d, J = 16.2 Hz, with fine splitting, 1H), 5.88 (dd, J = 14.3 and 8.1 Hz, with fine splitting, 1H), 6.30−6.39 (m, 2H), 7.02−7.07 (m, 1H), and 7.21−7.38 (m, 9H); ^{13}C NMR δ 61.7, 63.3, 117.1, 118.5, 124.0, 125.5, 125.8, 128.6, 129.1, 129.2, 135.5, 135.9, 137.2, 137.5, and 165.4; ms *m/z* 275 (M^+), 156 (M^+ − Ph−N=C=O). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.08. Found: C, 82.83; H, 6.25; N, 5.15.

***trans*-3-(1′,3′-Butadienyl)-4-(*p*-methoxyphenyl)-1-phenylazetidin-2-one (3b):** yield 63%; mp 104−105 °C; IR (CCl_4) ν 1726, 1591, 1492 cm^{-1}; ^{1}H NMR δ 3.71 (dd, J = 8.0 and 1.7 Hz, 1H), 3.78 (s, 3H), 4.75 (d, J = 1.7 Hz, 1H), 5.12 (d, J = 9.5 Hz, with fine splitting, 1H), 5.22 (d, J = 16.0 Hz, with fine splitting, 1H), 5.86 (dd, J = 14.0 and 8.0 Hz, with fine splitting, 1H), 6.25−6.41 (m, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.00−7.05 (m, 1H), 7.17−7.35 (m, 6H); ^{13}C NMR (one C missing) δ 55.3, 61.3, 63.4, 114.5, 117.0, 118.4, 123.9, 125.6, 127.1, 129.0, 135.4, 135.9, 137.5, 159.7, 165.5; ms *m/z* 305 (M^+), 186 (M^+ − Ph−N=C=O). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.72; H, 6.23; N, 4.49.

***trans*-3-(1′,3′-Butadienyl)-1-(*p*-methylphenyl)-4-phenylazetidin-2-one (3c):** yield 59%; viscous oil; IR (KBr)

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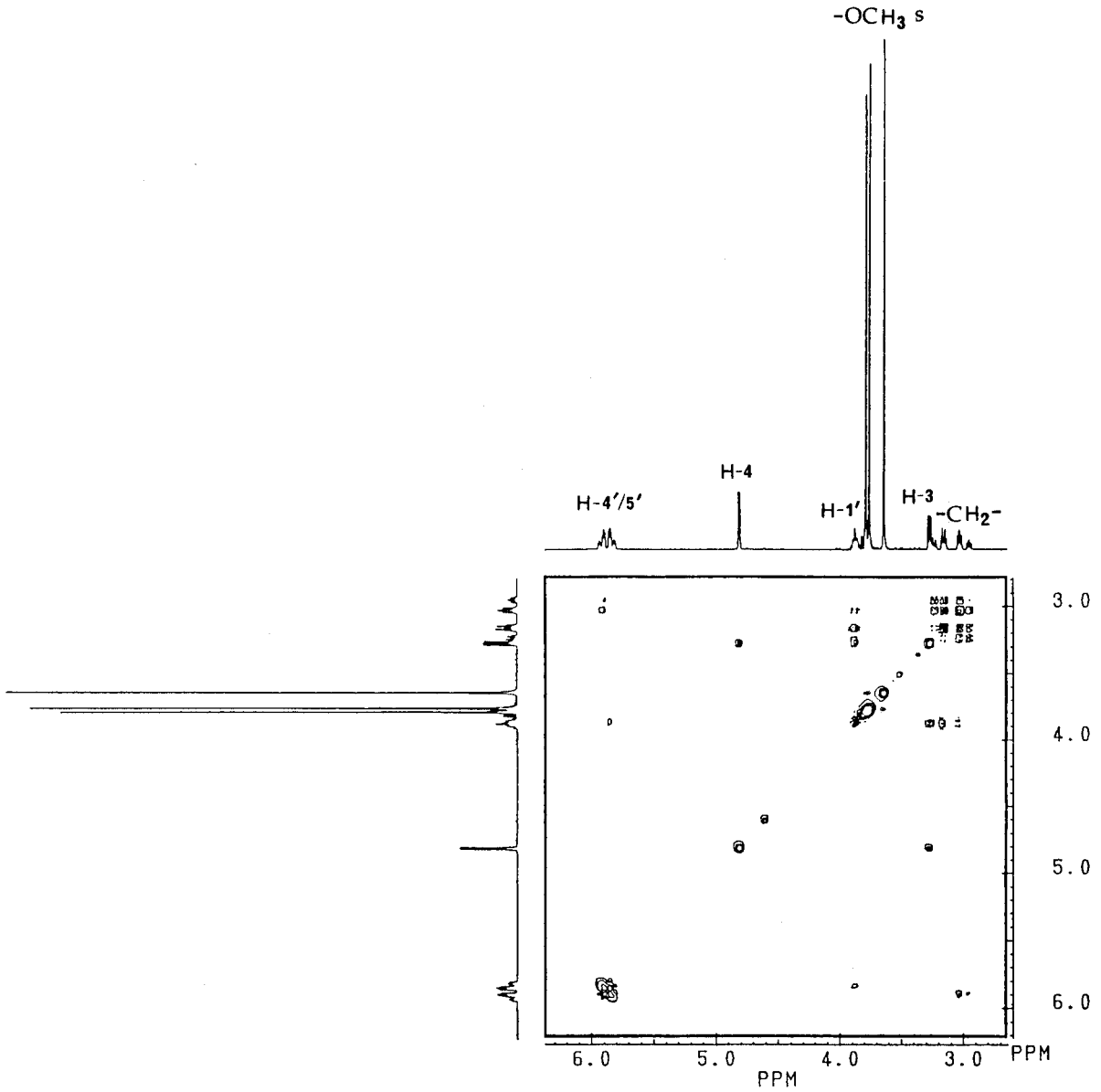
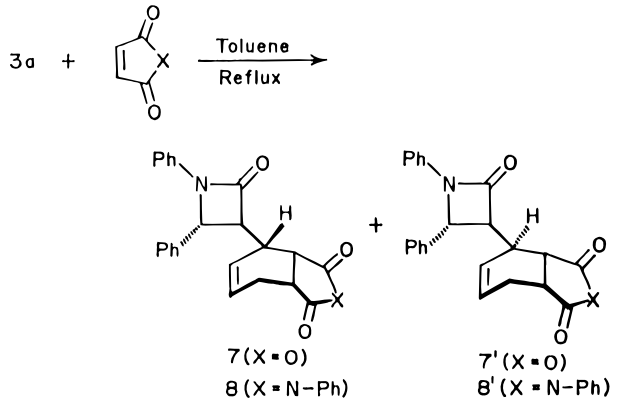


Figure 1. 300 MHz {^{1}H}−{^{1}H} NMR homonuclear spin correlation (COSY) spectrum for **5a** in $CDCl_3$.

Scheme 3



ν 1739, 1493, 1498 cm^{-1}; ^{1}H NMR δ 2.25 (s, 3H), 3.72 (dd, J = 8.1 and 2.4 Hz, 1H), 4.76 (d, J = 2.4 Hz, 1H), 5.11 (d, J = 10.0 Hz, with fine splitting, 1H), 5.22 (d, J = 16.3 Hz, with fine splitting, 1H), 5.84 (dd, J = 14.2 and 8.1 Hz, with fine splitting, 1H), 6.23−6.39 (m, 2H), 7.01 (d, J = 8.2 Hz, with fine splitting, 2H), 7.19 (d, J = 8.2 Hz, with fine splitting, 2H), 7.27−7.39 (m, 5H); ^{13}C NMR δ 20.9, 61.6, 63.2, 117.0, 118.5, 125.8, 126.9, 128.8, 129.3, 129.7, 133.6, 135.0, 135.5, 135.9, 137.2, 165.2; ms m/z 289 (M^+), 170 (M^+ − Ph−N=C=O). Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.12; H, 6.61; N, 4.76.

***trans*-3-(1′,3′-Butadienyl)-4-(*p*-methoxyphenyl)-1-(*p*-methylphenyl)azetidin-2-one (3d):** yield 48%; viscous oil; IR (CCl_4) ν 1751, 1583, 1511 cm^{-1}; ^{1}H NMR δ 2.22 (s, 3H), 3.70 (dd, J = 8.2 and 2.4 Hz, 1H), 3.74 (s, 3H), 4.71 (d, J = 2.4 Hz, 1H), 5.10 (d, J = 9.3 Hz, with fine splitting, 1H), 5.20 (d, J = 16.4 Hz, with fine splitting, 1H), 5.84 (dd, J = 14.1 and 8.2 Hz, with fine splitting, 1H), 6.23−6.40 (m, 2H), 6.87 (d, J = 8.7 Hz, with fine splitting, 2H), 7.01 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, with fine splitting, 2H), 7.24 (d, J = 8.7 Hz, with fine splitting, 2H); ^{13}C NMR δ 20.8, 55.2, 61.2, 63.3, 114.5, 117.0, 118.3, 124.2, 125.8, 127.1, 128.2, 129.1, 129.4, 129.6, 133.4, 135.2, 135.8, 135.9, 136.1, 159.7, 165.2; ms m/z 319 (M^+), 200 (M^+ − Ph−N=C=O). Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.93; H, 6.59; N, 4.31.

General Procedure for Diels−Alder Adducts 5. Equivalent amounts of β-lactam **3** and DMAD were refluxed in dry toluene for 6−7 h. The solvent was removed under reduced pressure, and the crude product was purified by recrystallization from a benzene:hexane (3:1) mixture.

***trans*-3-[2′,3′-Bis(methoxycarbonyl)-2′,4′-cyclohexadienyl]-4-(*p*-methoxyphenyl)-1-phenylazetidin-2-one (5a):** yield 95%; mp 178−179 °C; IR (KBr) ν 1733, 1715, 1597, 1497

cm^{-1}; ^{1}H NMR δ 2.98 (ddd, J = 23.3, 4.9, and 4.9 Hz, 1H), 3.19 (dddd, J = 23.3, 6.9, 4.6, and 2.2 Hz, 1H), 3.26 (dd, J = 4.7 and 2.6 Hz, 1H), 3.63 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.87 (m, 1H), 4.81 (d, J = 2.3 Hz, 1H), 5.82 (m, 1H), 5.91 (m, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.98−7.03 (m, 1H), 7.18−7.26 (m, 6H); ^{13}C NMR δ 27.8, 36.4, 52.3, 52.4, 55.2, 57.6, 63.6, 114.5, 117.0, 123.8, 124.3, 125.1, 127.3, 128.9, 129.4, 134.2, 134.7, 137.4, 159.7, 164.9, 167.4, 168.2; ms m/z 447 (M^+), 328 (M^+ − Ph−N═C═O). Anal. Calcd for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13. Found: C, 69.65; H, 5.64; N, 3.19.

***trans*-3-[2′,3′-Bis(methoxycarbonyl)-2′,4′-cyclohexadienyl]-1-(*p*-methylphenyl)-4-phenylazetidin-2-one (5b):** yield 97%; mp 182−182.5 °C; IR (KBr) ν 1719, 1506, 1431, 1383, 1253 cm^{-1}; ^{1}H NMR δ 2.25 (s, 3H), 2.98 (ddd, J = 23.3, 5.3, and 4.6 Hz, 1H), 3.21 (dddd, J = 23.3, 7.0, 5.0, and 2.5 Hz, 1H), 3.27 (dd, J = 4.6 and 2.6 Hz, 1H), 3.64 (s, 3H), 3.76 (s, 3H), 3.85−3.91 (m, 1H), 4.83 (d, J = 2.3 Hz, 1H), 5.81 (m, 1H), 5.91 (m, 1H), 7.02 (d, J = 8.3, 2H), 7.20 (d, J = 8.4, with fine splitting, 2H), 7.25−7.36 (m, 5H); ^{13}C NMR (two C missing) δ 20.8, 27.8, 36.4, 52.3, 52.4, 57.8, 63.5, 116.9, 124.3, 125.2, 126.0, 128.4, 129.0, 129.5, 133.4, 134.9, 137.6, 164.5; ms m/z 431 (M^+), 312 (M^+ − Ph−N═C═O). Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.38; H, 5.84, N, 3.25. Found: C, 72.30, H, 5.91; N, 3.29.

***trans*-4-(*p*-Methoxyphenyl)-1-phenyl-7′,9′-dioxo-3-[8′-phenyl-1′,6′,8′-triaza[4.3.0]bicyclonon-3′-en-yl]azetidin-2-one (6).** To a stirred solution of PTAD (0.58 g, 3.3 mmol) in methylene chloride (25 mL) at 0 °C was added **3b** (1 g, 3.3 mmol) in portions over a period of 5 min. The solution was stirred at 0 °C for an additional 10 min. The crude product obtained after removal of the solvent was purified by column chromatography (silica gel, 60−120 mesh) using a solution of ethyl acetate and hexane (1:3) to yield 1.46 g (92%) of adduct **6**: mp 200−202 °C; IR (KBr) ν 1744, 1708, 1595, 1493 cm^{-1}; ^{1}H NMR δ 3.47 (dd, J = 10.3 and 2.3 Hz, 1H), 3.76 (s, 3H), 3.97 (dq, J = 16.7 and 2.4 Hz, 1H), 4.30 (dddd, J = 16.7, 4.2, 1.9, and 0.8 Hz, 1H) 5.11 (m, 1H), 5.46 (d, J = 2.3 Hz, 1H), 6.04 (dddd, J = 10.3, 4.0, 2.0, and 2.0 Hz, 1H), 6.42 (dddd, J = 10.3, 4.8, 2.4, and 2.4 Hz, 1H), 6.74 (d, J = 8.7 Hz, with fine splitting, 2H), 7.00−7.06 (m, 1H), 7.18−7.31 (m, 8H), 7.39−7.52 (m, 3H); ^{13}C NMR δ 44.5, 52.9, 55.3, 58.7, 63.7, 114.5, 117.2, 121.7, 123.6, 124.2, 125.9, 127.6, 128.5, 129.1, 129.2, 130.7, 137.1, 151.6, 153.6, 159.8, 163.2; ms m/z 480 (M^+), 361 (M^+ − Ph−N═C═O). Anal. Calcd for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.11; H, 5.09; N, 11.59.

Diels−Alder Adduct of 3a and Maleic Anhydride (7/7′). A solution of **3a** (0.30 g, 1.10 mmol) and maleic anhydride (0.11 g, 1.11 mmol) in toluene (4 mL) was refluxed for 1 h. The reaction mixture was then purified by chromatography on a 60−120 mesh silica gel column (eluent: mixture of AcOEt/hexane in a 1:4 ratio), affording a colorless solid consisting in a mixture of diastereoisomers in 2:1 ratio (0.38 g, 93%): IR (KBr, mixture of diastereoisomers in 2:1 ratio) ν 1770, 1739, 1596, 1497 cm^{-1}; ^{1}H NMR (mixture of diastereoisomers is 2:1 ratio) δ 2.21−2.30 (m, 2H, both isomers), 2.70−2.90 (m, 4H, both isomers), 3.45−3.57 (m, 3H, two for minor isomer and one for major isomer), 3.84 (dd, J = 11.4 and 2.4 Hz, 1H, minor isomer), 3.92 (dd, J = 12.0 and 2.4 Hz, 1H, major isomer), 4.01 (dd, J = 9.8 and 5.8 Hz, 1H, major isomer), 4.72 (d, J = 2.4 Hz, 1H, major isomer), 4.83 (d, J = 2.4 Hz, 1H, minor isomer), 5.85 (ddd, J = 9.3, 3.2 and 3.2 Hz, 1H, major isomer), 6.03−6.13 (m, 2H, both isomers), 6.29 (ddd, J = 9.4, 3.2, and 3.2 Hz, 1H, minor isomer), 7.01−7.07 (m, 2H, both isomers) 7.22−7.28 (m, 8H, both isomers), 7.34−7.40 (m, 10H, both isomers); ^{13}C NMR (mixture of diastereoisomers in 2:1 ratio) δ 24.2, 35.6, 40.2, 42.7, 59.3, 60.1 (minor isomer); 24.7, 36.4, 40.5, 42.9, 59.1, 61.1 (major isomer); 117.0, 124.1, 124.2, 126.1, 126.2, 128.6, 128.8, 128.9, 129.1, 129.2, 129.4, 129.8, 130.4, 130.6, 136.7, 137.0, 137.2, 137.3, 165.9 (both isomers), 171.1, 173.7 (minor isomers); 171.7, 174.0 (major isomer); ms m/z 373 (M^+), 254 (M^+ − Ph−N═C═O).

Diels−Alder Adduct of 3a and *N*-Phenylmaleimide (8/8′). A solution of **3a** (0.30 g, 1.10 mmol) and *N*-phenylmaleimide (0.19 g, 1.12 mmol) in toluene (4 mL) was refluxed for 2h. The reaction mixture was then purified by chromatography on 60−120 mesh silica gel column (eluent: mixture of AcOEt/hexane in 1:3 ratio), affording a colorless solid consisting in a mixutre of diastereoisomers in a 2:1 ratio (0.45 g, 92%): IR (KBr, mixture of diastereoisomers in a 2:1 ratio) ν 1727, 1702, 1591, 1492, 1379 cm^{-1}; ^{1}H NMR (mixture of diastereoisomers in 2:1 ratio) δ 2.25−2.31 (m, 2H, both isomers); 2.83−2.94 (m, 4H, both isomers); 3.30−3.41 (m, 3H, two for minor isomer and one for major isomer); 3.91 (dd, J = 8.9 and 5.6 Hz, 1H, major isomer); 4.07 (dd, J = 10.9 and 2.1 Hz, 1H, minor isomer); 4.17 (dd, J = 12.1 and 2.1 Hz, 1H, major isomer), 4.72 (d, J = 2.1 Hz, 1H, major isomer); 4.86 (d, J = 2.1 Hz, 1H, minor isomer), 5.85 (ddd, J = 9.1, 3.2, and 3.2 Hz, 1H, major isomer), 6.06−6.12 (m, 2H, both isomers), 6.30 (ddd, J = 9.3, 3.2 and 3.2 Hz, 1H, minor isomer), 7.01−7.05 (m, 2H, both isomers); 7.16 (d, J = 7.3 Hz, with fine splitting, 4H, both isomers), 7.19−7.41 (m, 24H, both isomers); ^{13}C NMR (mixture of diastereoisomers in a 2:1 ratio) δ 24.5, 36.8, 39.8, 42.0, 59.6, 60.6 (minor isomer); 25.1, 37.3, 40.0, 42.0, 59.7, 61.4, (major isomer); 117.0, 124.0, 126.1, 126.3, 126.4, 126.5, 128.6, 128.7, 129.0, 129.1, 129.3, 129.5, 130.0, 130.5, 131.7, 137.4, 137.5 (both isomers); 166.5, 176.0, 178.4 (minor isomer); 166.6, 176.7, 178.6 (major isomer); ms m/z 448 (M^+), 329 (M^+ − Ph−N═C═O).

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