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β-Aryl-α-nitro-α,β-enals as Heterodienes and Dienophiles

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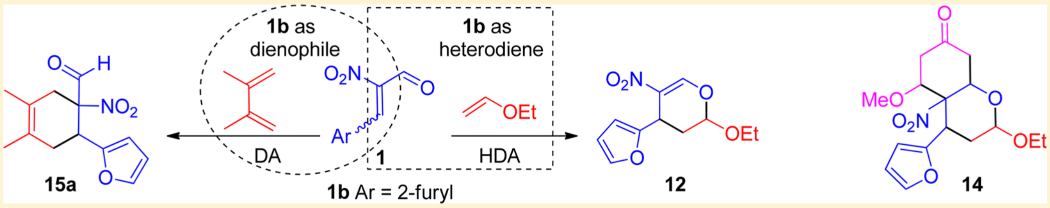
S *Supporting Information*

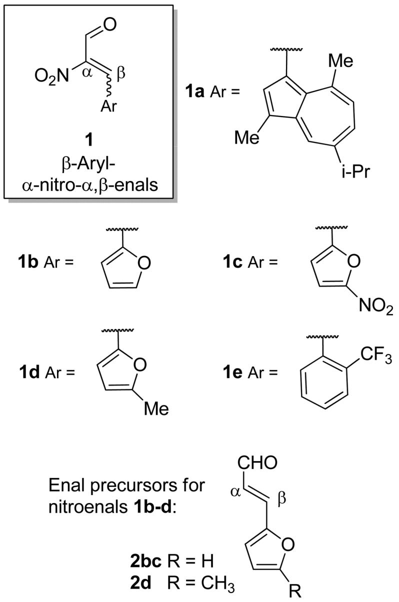


ABSTRACT: As demonstrated with the β-(2-furyl)-substituted analogue **1b**, β-aryl-α-nitro-α,β-enals (**1**) behave as heterodienes against enamines and enol ethers using their enal unit (e.g., **1b** → **12**). α-Nitro-α,β-enals can act as well as highly reactive dienophiles to render adducts endowed with nitrogenated quaternary centers (e.g., **1b** → **15a**). A hetero-Diels–Alder (HDA)/Diels–Alder (DA) sequence from **1b** also proved feasible on serial treatment with ethyl vinyl ether and Danishefsky's diene (**1b** → **14**).

INTRODUCTION

β-Aryl-α-nitro-α,β-enals (**1**) were first described in 1961 by Kirby and Reid, who prepared **1a** in 36% yield by condensation of guaiazulene (5-isopropyl-3,8-dimethylazulene) with nitromalondialdehyde in the presence of perchloric acid.[1] Three β-furyl analogs (**1b**, **1c**, and **1d**)[2] were reported in the 1970s by Fridman and co-workers. Preparation of **1b**, **1c**, and **1d** involved N_2O_4-promoted nitration of the corresponding β-furyl-α,β-enal precursors: 3-(2-furyl)-propenal (**2bc**) for both **1b** and **1c**, and 3-(5-methyl-2-furyl)-propenal (**2d**) for **1d**. Nitration of **2bc** took place at the formyl α-position to give **1b** in 17% yield[2a] and concurrently, to some extent, in the furane ring, thus also giving dinitrocompound **1c**.[2b] Blockade of the furyl-ring most-activated C5 position with a methyl group, as in **2d**, allowed the nitration to be more selective, rendering **1d** in 53% yield.[2c] The last nitroenal of type **1** known before our work in the area was **1e**, included by Goldmann and Bechem in a 1994 patent.[3]

We recently reported a general method for the synthesis of a variety of α-nitroenals **1** by condensation of aromatic aldehydes with 2-nitroethanol followed by IBX-oxidation.[4] In the same article, we described some properties of **1**, in particular those related with their appearance (yellow, orange, or red solids), their stability (which is higher when the aromatic group at the β-position is furyl rather than phenyl), and their structure (the aryl, vinyl, formyl, and nitro groups are all in a planar arrangement; the C=C and the C=O double bonds are exclusively in their s_{1-2}-*cis* oriented most stable conformation), as well as their (solvent-dependent, thermal-promoted, and photopromoted) easy *E*–*Z* interconversion.[4]



We also reported the first synthetic use of α-nitroenals **1**: their formal [3 + 3] annulation with enamines **4**, derived from 2,2-dimethyl-1,3-dioxan-5-one (**3**) and secondary amines (e.g., pyrrolidine) to render nitrogen-bearing polyoxygenated cyclohexanes of type **5**, a procedure where five stereocenters are created in a most stereoselective manner (Scheme 1).[5,6] The annulation could also be carried out using chiral pyrrolidines as the secondary-amine promoters to obtain **5** in an enantiomerically enriched form.[7] On the preparative side, use of the nitroenal annulation procedure as one of the main key steps allowed the development of a formal synthesis of (±)-tetrodotoxin[8] and a total synthesis of (+)-pancratistatin,[7] as well

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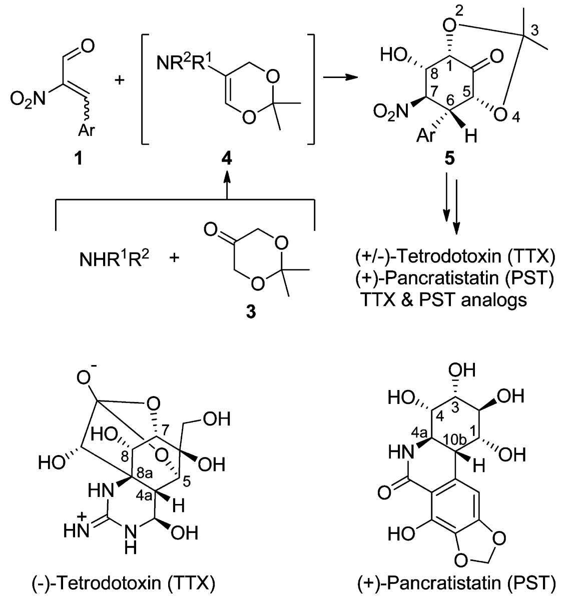
Scheme 1. Annulation of Nitroenals 1 with Enamines 4 Derived from Dioxanone 3: Convergent Synthesis of Nitrogen-Bearing Polyoxygenated Cyclohexanes 5, and Tetrodotoxins and Pancratistatins Therefrom



as the preparation of some *epi*- and deoxy-analogues of pancratistatin[9,10] and a convergent approach to the dioxaadamantane core of (±)-tetrodotoxin and its 6-*epi*-analogue.[11]

Herein we report additional data on the reactivity of α-nitroenals **1**. In particular, we further looked at the reaction of nitroenal **1b** (**1**, Ar = 2-furyl) with morpholine-derived enamine **4b** (*vide infra*), with implications for the mechanistic rationale, and studied the behavior of **1b** with ethyl vinyl ether and with conjugated dienes.[12]

■ RESULTS AND DISCUSSION

Insights into the Annulation of Nitroenals 1 with Dioxanone Enamines 4. As indicated above, the annulation of nitroenals of type **1** with enamines **4** gave protected nitrocyclitols **5**. Most conveniently for our synthetic purposes, the relative stereochemistry at positions 1, 5, 6, 7, and 8 in **5** perfectly matched those at C7, C5, C4a, C8a, and C8 in tetrodotoxin and those at C3, C1, C10b, C4a, and C4 in pancratistatin (Scheme 1).

However, the relative stereochemistry at positions 5 and 6 of **5** was surprising because it was contrary to that previously described at the corresponding carbons 4 and 1′, respectively, both for **7**, the major diastereomer (98:2) obtained in the reaction of enamine **4b**[13] with the electron-deficient imine **6**,[14] and for **9**, the adduct we obtained when **4b** was treated with β-nitrostyrene (**8**, Scheme 2).[15,16]

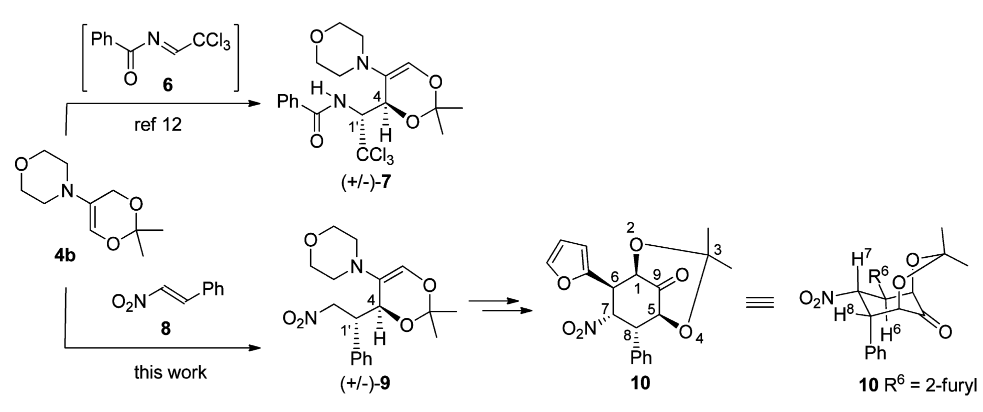
To clarify this stereochemical discrepancy, we looked for intermediates of the annulation process of α-nitroenals **1** with enamines **4** to nitrocyclitols **5**. In the event, treatment of **1b**[4] with **4b**[14] in acetonitrile at 0 °C resulted in the quick formation of a precipitate, which was identified as compound **11** (Scheme 3). The relative stereochemistry of **11**, determined by X-ray crystallography,[17] revealed that the spatial arrangement of its furyl substituent at C6 with respect to the contiguous bridgehead hydrogen at C5 is analogous to that observed between the trichloromethyl group of **7** or the phenyl substituent of **9** and their corresponding contiguous hydrogens at C4; i.e., regarding stereochemistry, nitroenal **1b** behaves against enamines of type **4** in the same way as other acceptors (e.g., the imine **6** and the nitroolefin **8**) do.

Whereas the yield of **11** isolated by filtration of the reaction mixture was just 36%, its formation was actually considerably more efficient and on the order of 78%, as deduced by NMR monitorization of the reaction using 1,4-dichlorobenzene as the internal standard. The quick and efficient formation of **11** and the fact that treatment of isolated **11** under conditions used to generate protected nitrocyclitols **5** (e.g., with PPTS or silica in CH$_3$CN) gave **5b**[5] pointed to **11** as a plausible intermediate for the annulation process (**1** + **4** → **5**).

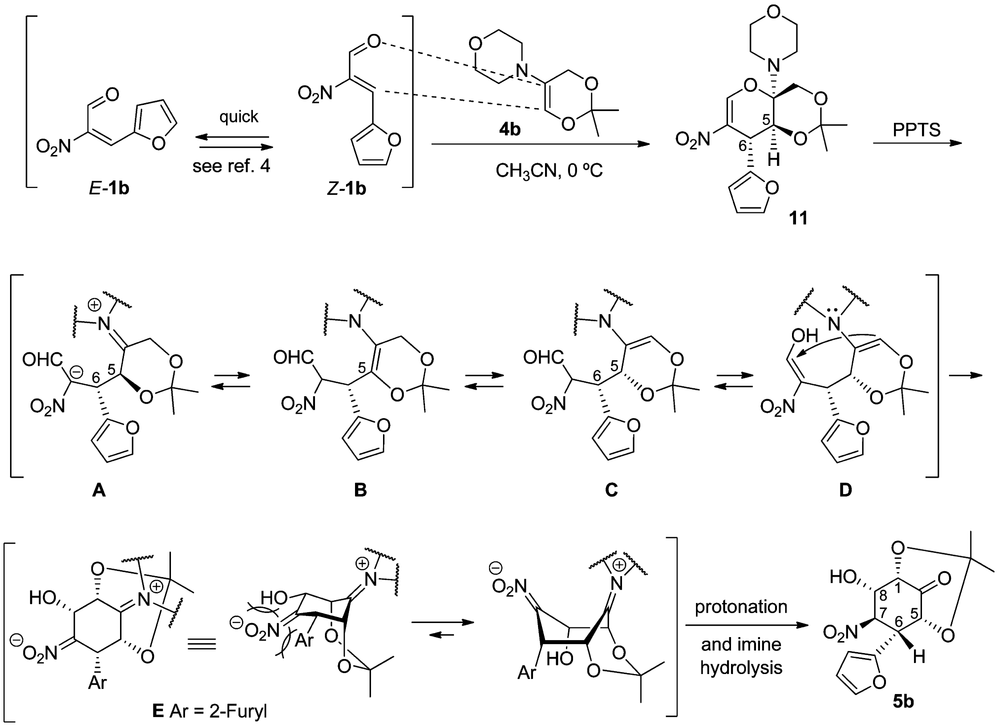
A mechanistic rationale for the transformation **1b** + **4b** → **5b** through **11** is outlined in Scheme 3. Compound **11** could have been formed by a concerted hetero-Diels−Alder addition of *Z*-**1b** and enamine **4b** through an endo TS. This reaction outcome would be in agreement with the good complementarity of electronic density of the dienophile (the electron-rich double bond of **4b**) and the heterodiene (the electron-deficient and highly polarized enal moiety in **1b**), and with the rapid *E*−*Z* equilibration of **1b** in acetonitrile and the pronounced prevalence of the *cis* conformation for the enal moiety in nitroenals **1**.[4]

Conversion of **11** into the annulated product **5b** should have next required the opening of **11** to zwitterion **A**, followed by isomerization to enamine **B** and subsequent tautomerization of **B** to **C** with net inversion at C5 (from **A**, thus providing the required change in the relative stereochemistry between C5 and

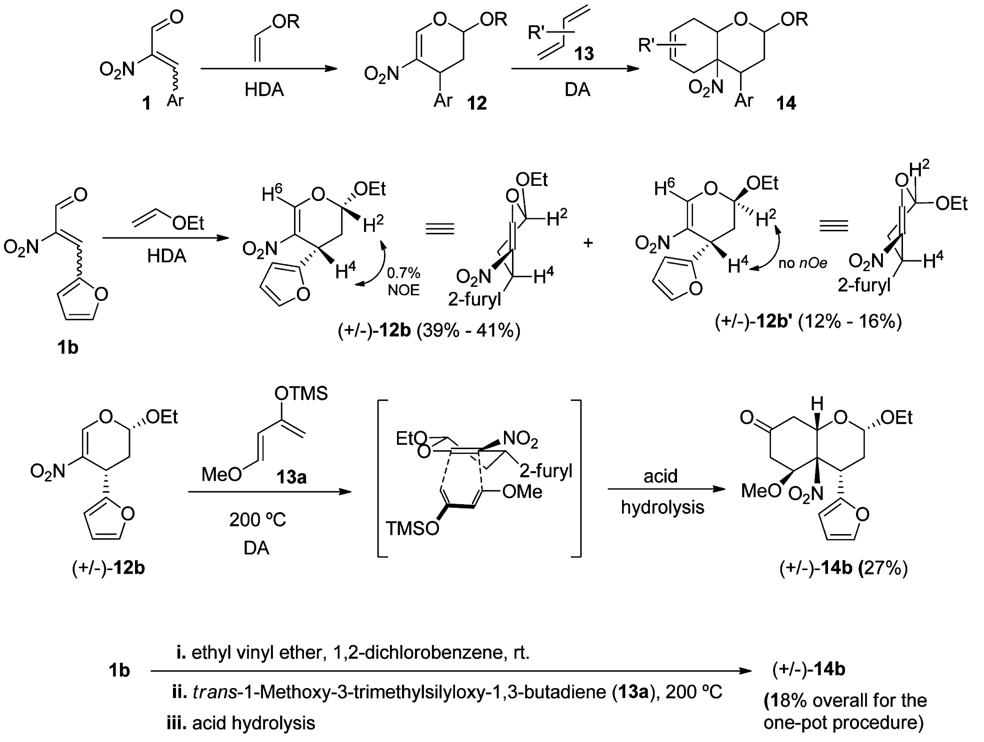
Scheme 2. Reaction of Enamine 4b with Activated Imine 6 and β-Nitrostyrene (8)



Scheme 3. Mechanistic Rationale for the Annulation of α-Nitroenal 1b with Enamine 4b



Scheme 4. α-Nitroenals 1 as Heterodienes with Enol Ethers; HDA − DA Sequence



C6 of **11** to match that of the protected nitrocyclitol **5b**).[18]Cyclization of **C** to **E**, most likely through an intramolecular Michael type addition of enol **D**, followed by protonation of the most stable conformer of **E** from its least crowded face and imine hydrolysis would have given **5b**.

Nitroenals 1 as Heterodienes: Hetero-Diels–Alder (HDA) of 1b with Ethyl Vinyl Ether; HDA + DA Sequence. The ease and efficiency with which nitroenal **1b** reacted with enamine **4b** to generate the corresponding hetero-Diels−Alder adduct **11** suggested that nitroenals of type **1** could similarly react with other electron-rich olefins. In particular, we decided to explore the behavior of **1b** with enol ethers. Should the cycloaddition take place to give the expected cycloadducts **12** [a special type of nitroolefins (conjugated, cyclic, and β-oxygenated), Scheme 4], we were curious to evaluate the reactivity of **12** as dienophiles against dienes because the corresponding final products **14** would have a highly functionalized cyclohexane ring endowed with a nitrogenated quaternary carbon (an important type of substructure found in a number of biologically relevant natural products, e.g., in the already cited sodium channel-blocker tetrodotoxin or in the immunosuppressive agent FR901483).[19]

In practice, treatment of **1b** with ethyl vinyl ether at rt resulted in the formation of adducts (±)-**12b** and (±)-**12b′**, isolated with yields of about 40% and 14%, respectively. Their most diagnostic NMR signals included those of protons H2 [acetalic, at 5.29 ppm (t, J = 2.8 Hz) and 5.17 (dd, J = 9 and 2.3 Hz), respectively], H4 [α to the furan ring, at 4.38 ppm (dd, J = 7 and 2.8 Hz) and 4.43 (dd, J = 5.9 and 3.2 Hz), respectively], and H6 (vinylic, α to the oxygen atom of the dihydropyran ring and β to the nitro group at 8.25 and 8.23 ppm, respectively).

The relative configuration of carbons C2 and C4 was determined by NOE studies, which revealed the existence of an Overhauser effect between H2 and H4 in compound **12b** (in which both protons enjoy a proximal pseudo-1,3-diaxial arrangement in the half-chair conformation shown in Scheme 4), but not in **12b′**.

Formation of **12b** and **12b′** indicated that nitroenal **1b** reacts with ethyl vinyl ether in much the same way as it does with enamine **4b**: (a) it prefers to employ its enal function instead of their nitroolefin subunit as the heterodiene, and (b) it shows preference for an endo approximation to *Z*-**1b**; i.e., the ethoxy group of the enol ether is oriented toward the central carbons of the enal function, thus resulting in the major formation of (±)-**12b**.

With cycloadduct **12b** in hand, and in accordance with the plan previously mentioned, we looked at its transformation into compounds of type **14**. To that end, we evaluated its behavior against a series of dienes **13**, either cyclic (furan and cyclopentadiene) or acyclic [2-methyl-1,3-butadiene, 1,3-dimethyl-1,3-butadiene, 2,3-dimethyl-1,3-butadiene, and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene, **13a**)].

It was only with the latter with which we were able to obtain the desired cycloadduct **14b**, which was isolated in 27% yield by heating **12b** with **13a** at 200 °C in 1,2-dichlorobenzene, followed by acid hydrolysis of the enol ether intermediate (Scheme 4).[20]

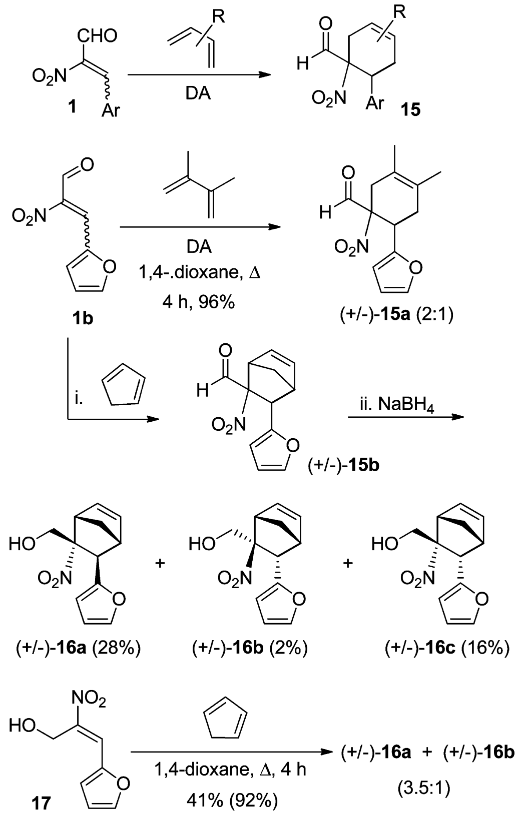
Cyclohexanone **14b** (the relative stereochemistry was assigned on the basis of NOE data)[16] would have been the result of an endo approximation of diene **13a** to the face of **12b** carrying the pseudoequatorially disposed furyl substituent, so that the vicinal 2-furyl and nitro groups further separate along the reaction coordinate until their final 1,2-*trans*-relationship.

We found that nitroenal **1b** could be transformed into **14b** with no isolation of **12b** by sequentially performing the two cycloaddition processes in the same reaction flask. Thus, treatment of a solution of **1b** in dichlorobenzene, first with ethyl vinyl ether at rt for 14 h, and then with diene **13a** at 200 °C, led, after final hydrolysis, to ketone **14b** in 18% overall yield (Scheme 4).[20]

Nitroenals 1 as Dienophiles: DA Cycloadditions of 1b with 2,3-Dimethyl-1,3-butadiene and Cyclopentadiene.

We finally decided to explore the behavior of α-nitro-α,β-enals **1** as dienophiles in Diels−Alder cycloadditions. In particular, we wondered if nitroenals **1** could be useful to prepare cyclic adducts of type **15** (endowed with a nitrogenated quaternary carbon, Scheme 5) and if such adducts would be stable under the reaction conditions.

Scheme 5. α-Nitroenals 1 as Dienophiles; DA of 1b with 2,3-Dimethyl-1,3-butadiene and Cyclopentadiene



We were also curious to estimate the relative reactivity of nitroenals **1** as dienophiles, i.e., to evaluate the influence that the extra formyl group present in nitroenals **1** (in comparison with simpler nitroolefins) has in their reactivity against dienes in DA cycloadditions.

To address the first issue, we treated nitroenal **1b** with 2,3-dimethyl-1,3-butadiene in refluxing 1,4-dioxane for 4 h. Evaporation of the solvent led indeed to the Diels−Alder cycloadduct (±)-**15a** as the only reaction product in 96% yield (Scheme 5). Similarly, the reaction of **1b** with cyclopentadiene yielded the desired norbornene **15b** in 60% yield. Attempts to purify the DA cycloadducts **15a,b** by chromatography on silica gel resulted in deformylation. Fortunately, the integrity of the desired quaternary center in the cycloadduct could be preserved by reduction of its formyl group before chromatography. Thus, sequential treatment of **1b** with cyclopentadiene and $NaBH_4$ led to norbornene **16** as a mixture of three diastereoisomers **16a−c**. The alternative formation of two of them, **16a** and **16b**, by DA of the (*E*)-nitropropenol **17**[4,5,8,21] with cyclopentadiene allowed the *cis* arrangement of their hydroxymethyl and furyl groups to be unveiled. Accordingly, a *trans* arrangement between these two groups was assigned to the third stereoisomer **16c**. Moreover, a distal relationship between their nitro groups and their methylene bridges, i.e., the stereochemical result of preferred endotype cycloadditions, was assigned as most likely for **16a** (the most abundant of the two (hydroxymethyl-furyl)-*cis* stereoisomers **16a,b**) as well as for **16c** (the single isolated cycloadduct with a (hydroxymethyl-furyl)-*trans* relationship).

Regarding the reactivity issue, we found that α-nitroenal **1b** is much more reactive as a dienophile than its corresponding nitroolefin analogue lacking the formyl group, i.e., *E*-2-(2-nitrovinyl)furan (**18**). In the event, equimolar quantities of nitroenal **1b** (mix *E*/*Z* 2.78:1) and **18** were treated with freshly distilled cyclopentadiene in 1,4-dioxane at rt. As monitored by NMR, the reaction led only to the formation of norbornene **15b**, the cycloadduct between **1b** and cyclopentadiene, while nitroolefin **18** remained unaltered.[16]

■ CONCLUSION

In summary, α-nitroenals **1** react with enamines of 2,2-dimethyl-1,3-dioxan-5-one using their enal function as a heterodiene to form endo HDA cycloadducts, as demonstrated with the isolation of **11** starting from the morpholine-derived enamine **4b**. This transformation, in which the stereochemistry is analogous to that observed for reactions of **4b** with other electron-poor acceptors, is suggested as the first step in the mechanistic rationale herein proposed for the annulation reaction of **1** with **4** to give protected nitrocyclitols **5**.

α-Nitroenals **1** also reacted as heterodienes with enol ethers, a process that preferentially took place through an endo path and could be combined with a subsequent DA reaction to form adducts endowed with nitrogenated quaternary centers. In addition, nitroenals **1** can participate as highly reactive dienophiles in intermolecular DA reactions, allowing adducts that can be elaborated at their quaternary center before deformylation.

■ EXPERIMENTAL SECTION

4-((*S)-2,2-Dimethyl-4-((*R**)-2-nitro-1-phenylethyl)-4*H*-1,3-dioxin-5-yl)morpholine (±)-9.** β-Nitrostyrene (441 mg, 2.96 mmol) was added to a solution of enamine **4b** (583 mg, 2.93 mmol) in dry CH_3CN (1.5 mL) under argon at −20 °C. After stirring for 12 h at rt, the reaction mixture was diluted with Et_2O and washed with H_2O. After drying and solvent removal, chromatography (EtOAc−hexane, 10:90) afforded **9** (796 mg, 78%) as an oil. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.39−7.35 (m, 2H), 7.25−7.22 (m, 3H), 5.76 (s, 1H), 4.94 (dd, J = 13.5 Hz, J = 8.5 Hz, 1H), 4.67 (dd, J = 13.5 Hz, J = 6.9 Hz, 1H), 4.66 (d, J = 2.2 Hz, 1H), 3.99 (ddd, J = 8.5 Hz, J = 6.9 Hz, J = 2.2 Hz, 1H), 3.72−3.68 (m, 4H), 2.75−2.67 (m, 2H), 2.23−2.15 (m, 2H), 1.47 (s, 3H), 1.44 (s, 3H). ^{13}C NMR and DEPT ($CDCl_3$, 62.83 MHz) δ 135.8, 129.6, 127.7, 127.5, and 126.6 (8C, Ar and C=C), 98.1, 76.8, 67.7, 66.8 (2C), 50.5 (2C), 45.1, 27.7 (CH_3), 20.3 (CH_3). ^1H NMR [$(CD_3)_2CO$, 250 MHz] δ 7.37−7.33 (m, 2H), 7.16−7.07 (m, 3H), 5.68 (s, 1H), 4.92 (dd, J = 13.5 Hz, J = 6.6 Hz, 1H), 4.81 (dd, J = 13.5 Hz, J = 4.1 Hz, 1H), 4.73 (d, J = 2.8 Hz, 1H), 3.95 (m, 1H), 3.58−3.55 (m, 4H), 2.74−2.64 (m, 2H), 2.10−2.02 (m, 2H), 1.33 (s, 3H), 1.30 (s, 3H). ^{13}C NMR and DEPT (62.83 MHz) δ 138.2, 131.8, 130.9, 129.2, 128.9, 128.8 (8C), 99.5, 79.3, 70.2, 68.2 (2C), 52.4 (2C), 47.1, 29.0, 21.6. LRMS (EI) m/z (%): 348 (M^+, 1), 244 (16), 230 (18), 156 (100), 126 (60), 115 (28), 91 (27), 77 (15). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}N_2NaO_5$ 371.1577; found 371.1581.

(1*S,5*R**,6*R**,7*S**,8*R**)-6-(Furan-2-yl)-3,3-dimethyl-7-nitro-8-phenyl-2,4-dioxabicyclo[3.3.1]nonan-9-one (10).** Furfural (12 μL, 0.14 mmol) and TBAF·$3H_2O$ (54 mg, 0.17 mmol) were added to a solution of **9** (44 mg, 0.13 mmol) in dry CH_2Cl_2 (0.3 mL) under argon at −78 °C. After 7 h, Ac_2O (15 μL, 0.15 mmol) and DMAP (5 mg, 0.04 mmol) were added. After the mixture stirred for 2.5 h at −78 °C and 15 h at rt, SiO_2 (44 mg) was added and the mixture refluxed for 6 h. Solvent removal and column chromatography (EtOAc−hexane 10:90) gave **10** (6 mg, 13%, oil) together with unreacted **9** (13 mg, 30%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (s, 1H), 7.32−7.28 (m, 3H), 7.11−7.09 (m, 2H), 6.35 (s, 2H), 6.06 (dd, J = 11.9 Hz, J = 7.2 Hz, 1H), 4.58−4.57 (m, 1H), 4.49 (dd, J = 7.2 Hz, J = 3.3 Hz, 1H), 4.41−4.39 (m, 2H), 1.60 (s, 3H), 1.49 (s, 3H). ^{13}C NMR and DEPT (62.83 MHz) δ 207.5, 149.6, 142.2, 131.8, 128.9 (2C), 128.84 (2C), 128.8, 110.7, 107.6, 100.3, 82.5, 78.8, 77.5, 54.9, 46.0, 28.9, 25.7. IR (KBr): 1755, 1553 cm^{-1}. LRMS (EI) m/z (%): 357 (M^+, 0.2), 253 (22), 223 (22), 196 (53), 186 (69), 161 (100), 115 (68), 91 (67), 81 (70). HRMS (EI-TOF) m/z: M^+ calcd for $C_{19}H_{19}NO_6^+$ 357.1207; found 357.1212.

Cicloadduct (±)-11. Nitroenal **1b** (300 mg, 1.79 mmol) was added to a solution of enamine **4b** (393 mg, 1.97 mmol) in CH_3CN (9 mL, 0.2 M) kept at 0 °C under argon. After 45 min, **11** was filtered and washed with cold CH_3CN [238 mg, 36%, R_f = 0.2 (30% EtOAc/hexane), mp = 125−130 °C (CH_3CN, decomposition)]. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (s, 1H), 7.30 (s, 1H), 6.29 (s, 1H), 5.99 (s, 1H), 4.83 (s, 1H), 4.22 (s, 1H), 4.05 (d, J = 12.6 Hz, 1H), 3.92 (d, J = 12.6 Hz, 1H), 3.36−3.10 (m, 4H), 2.65 (bs, 2H), 2.17 (bs, 2H), 1.51 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 150.4, 141.4, 129.8, 110.9, 106.9, 99.2, 87.2, 66.3, 64.8, 59.6 (2C), 45.9 (2C), 33.9, 28.2, 19.1. IR (KBr): 1555 cm^{-1}. LRMS (IE) m/z (%): 366 (M^+, 3), 308 (2), 262 (24), 220 (68), 156 (100), 128 (17), 58 (10). HRMS (EI-TOF) m/z: M^+ calcd for $C_{17}H_{22}N_2O_7^+$ 366.1422; found 366.14217.

(2*S,4*S**)-2-Ethoxy-4-(furan-2-yl)-5-nitro-3,4-dihydro-2*H*-pyran (±)-12b and (2*R**,4*S**)-2-Ethoxy-4-(furan-2-yl)-5-nitro-3,4-dihydro-2*H*-pyran (±)-12b′.** (i) *In THF (analogous results were obtained in DMF, CH₃CN, and toluene).* A solution of nitroenal **1b** (1.5 g, 9 mmol, *E*/*Z* = 5.27:1) and ethyl vinyl ether (1.55 mL, 16.2 mmol) in THF (45 mL) was stirred for 16 h at rt. Solvent removal and chromatography (eluents: hexane and EtOAc/hexane 5:95) afforded (±)-**12b** (0.84 g, 39%) and (±)-**12b′** (0.34 g, 16%) as yellowish oils. (ii) *Using ethyl vinyl ether as the solvent and the reagent.* A solution of nitroenal **1b** (0.5 g, 3 mmol) in ethyl vinyl ether (1.2 mL, 12.5 mmol) was stirred for 15 h at rt. Solvent removal and chromatography (as before) afforded (±)-**12b** (0.295 g, 41%) and (±)-**12b′** (0.088 g, 12%). (±)-**12b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.25 (s, 1H), 7.27 (br s, 1H), 6.25 (dd, J = 3.2 Hz, J = 1.8 Hz, 1H), 5.96 (d, J = 3.2 Hz, 1H), 5.29 (t, J = 2.8 Hz, 1H), 4.38 (dd, J = 7.0 Hz, J = 2.8 Hz, 1H), 3.77 (dq, J = 9.3 Hz, J = 7.0 Hz, 1H), 3.50 (dq, J = 9.3 Hz, J = 7.0 Hz, 1H), 2.54 (dt, J = 14.3 Hz, J = 2.8 Hz, 1H), 2.11 (ddd, J = 14.3 Hz, J = 7.0 Hz, J = 2.8 Hz, 1H), 1.05 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 152.5, 140.6, 131.7, 110.3, 105.3, 98.5, 64.8, 30.7, 28.3, 14.6. HRMS (EI-TOF) m/z: M^+ calcd for $C_{11}H_{13}NO_5^+$ 239.0788; found 239.0790. (±)-**12b′**: ^1H NMR ($CDCl_3$, 250 MHz) δ 8.23 (s, 1H), 7.33 (d, J = 1.8 Hz, 1H), 6.31 (dd, J = 3.2 Hz, J = 1.8 Hz, 1H), 6.12 (d, J = 3.2 Hz, 1H), 5.17 (dd, J = 9.0 Hz, J = 2.3 Hz, 1H), 4.43 (dd, J = 5.9 Hz, J = 3.2 Hz, 1H), 4.01 (dq, J = 9.3 Hz, J = 7.1 Hz, 1H), 3.66 (dq, J = 9.3 Hz, J = 7.1 Hz, 1H), 2.32 (m, 1H), 2.11 (ddd, J = 14.0 Hz, J = 9.0 Hz, J = 5.9 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 153.1, 142.0, 130.8, 110.5, 106.8, 100.2, 65.9, 31.7, 30.3, 15.0. HRMS (EI-TOF) m/z: M^+ calcd for $C_{11}H_{13}NO_5^+$ 239.0788; found 239.0786.

(2*S,4*S**,4a*S**,5*S**,8a*S**)-2-Ethoxy-4-(furan-2-yl)-5-methoxy-4a-nitrohexahydro-2*H*-chromen-7(3*H*)-one (±)-14b.** (i) *Through a DA Cycloaddition from* ***12b***. A solution of **12b** (238 mg, 1 mmol) and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**13a**, 779 μL, 4 mmol) in 1,2-dichlorobenzene (8 mL) was heated in a closed glass tube at 200 °C for 24 h. After cooling to rt, 0.01 M aqueous HCl (10 mL) was added and the solvent was removed. Chromatography (EtOAc/hexane, 5:95−25:75) afforded (±)-**14b** (90 mg, 27%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 1.8, 0.8 Hz, 1H), 6.28 (dd, J = 3.3, 1.8 Hz, 1H), 6.09 (dd, J = 3.3, 0.8 Hz, 1H), 4.78 (dd, J = 9.7, 2.8 Hz, 1H), 4.37 (dd, J = 14, 4.5 Hz, 1H), 4.31 (t, J = 3.2 Hz, 1H), 4.14 (dd, J = 10, 6.6 Hz, 1H), 3.93 (dq, J = 10, 7.1 Hz, 1H), 3.56 (dq, J = 10, 7.1 Hz, 1H), 3.13 (dd, J = 15.5, 10.0 Hz, 1H), 3.04 (s, 3H), 2.95 (dd, J = 15.5, 6.6 Hz, 1H), 2.57 (d, J = 3.2 Hz, 2H), 2.35 (ddd, J = 14.0, 4.5, 2.8 Hz, 1H), 2.18 (dt, J = 14, 14, 9.7 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 151.7, 141.9, 110.1, 106.2, 101.5, 91.3, 76.0, 73.6, 65.1, 57.9, 42.5, 42.1, 39.7, 31.6, 15.0; HRMS (ESI-TOF) m/z: $(M + Na)^+$ calcd for $C_{16}H_{21}NNaO_7^+$ 362.1210; found 362.1223. (ii) *Through an HDA-DA sequence from* ***1b***. A solution of **1b** (500 mg, 2.99 mmol, *E*/*Z* = 5.27:1) and ethyl vinyl ether (1.2 mL, 12.53 mmol) in 1,2-dichlorobenzene (15 mL) was stirred for 14 h at rt. *trans*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (1.75 mL, 9.16 mmol) was then added, and the mixture was heated at

200 °C in a closed glass container for 12 h. Addition of 0.01 M aqueous HCl (10 mL) followed by solvent removal and chromatography afforded (±)-**14b** (0.18 g, 18%).

(1*R,6*R**)- and (1*R**,6*S**)-6-(Furan-2-yl)-3,4-dimethyl-1-nitrocyclohex-3-enecarbaldehyde (±)-15a.** A solution of **1b** (80 mg, 0.48 mmol, *E*/*Z* = 9:1) and commercial 2,3-dimethyl-1,3-butadiene (181 μL, 1.6 mmol) in 1,4-dioxane (1.60 mL) was refluxed in a closed glass tube for 4 h. Solvent removal afforded (±)-**15a** as a 2:1 diastereoisomeric mixture (114 mg, 96%, oil). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.71 (s, $1H_{min}$), 9.64 (s, $1H_{maj}$), 7.33 (dd, *J* = 0.7 Hz, *J* = 1.8 Hz, $1H_{maj}$), 7.30 (dd, *J* = 0.7 Hz, *J* = 1.7 Hz, $1H_{min}$), 6.33−6.30 (m, $1H_{maj} + 1H_{min}$), 6.19 (d, *J* = 3.3 Hz, $1H_{maj}$), 6.13 (d, *J* = 3.3 Hz, $1H_{min}$), 4.08 (t, *J* = 7.4 Hz, $1H_{maj}$), 3.89 (t, *J* = 6.8 Hz, $1H_{min}$), 2.85−2.82 (m, $4H_{min}$), 2.54−2.39 (m, $4H_{maj}$), 1.71−1.65 (m, $6H_{min} + 6H_{maj}$). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 192.5, 190.8, 151.8, 151.0, 142.4, 142.0, 124.3, 123.6, 121.5, 120.8, 110.6, 110.6, 108.7, 107.8, 96.0, 95.0, 38.5, 38.4, 34.7, 34.5, 33.1, 32.9, 18.7 (2C), 18.5 (2C). LRMS (CI) *m*/*z* (%): 250.1 ($(M + 1)^+$, 37), 220.1 (20), 203.1 (100), 175.1 (89), 107.1 (62). HRMS (CI-TOF) *m*/*z*: $(M+1)^+$ calcd for $C_{13}H_{16}NO_4^+$ 250.1074; found 250.1076.

3-(Furan-2-yl)-2-nitrobicyclo[2.2.1]hept-5-en-2-yl)methanols (±)-16a−c. (i) *Norbornenes **16a−c** from nitroenal **1b** through a DA cycloaddition followed by reduction.* A solution of nitroenal **1b** (99 mg, 0.59 mmol, *E*/*Z* = 1:1) and cyclopentadiene (130 μL, 1.55 mmol) in 1,4-dioxane (2 mL) was stirred for 70 min at 16 °C. After adding $NaBH_4$ (41 mg, 1.062 mmol) and stirring for 40 min, the mixture was washed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (3 × 10 mL). Chromatography (EtOAc/hexane, 15:85 a 20:80) afforded one chromatographic fraction containing a mixture of (±)-**16a** and (±)-**16b** (42 mg, 30%, **16a**/**16b** = 13:1, oil) and another chromatographic fraction consisting of pure (±)-**16c** (23 mg, 16%, oil). A small sample of essentially pure **16a** (oil) could be obtained from the mixture of **16a** and **16b** by careful rechromatography. (±)-**16a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (dd, *J* = 0.5 Hz, *J* = 1.9 Hz, 1H), 6.52 (dd, *J* = 3.2 Hz, *J* = 5.6 Hz, 1H), 6.38 (dd, *J* = 1.9 Hz, *J* = 3.2 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 6.17 (dd, *J* = 3.2 Hz, *J* = 5.6 Hz, 1H), 3.84 (m, 2H), 3.74 (d, *J* = 2.6 Hz, 1H), 3.51 (bs, 1H), 3.09 (bs, 1H), 2.19 (d, *J* = 9.7 Hz, 1H), 1.97 (bs, 1H), 1.79 (ddd, *J* = 1.7 Hz, *J* = 4.4 Hz, *J* = 9.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.4, 142.5, 140.3, 135.5, 110.6, 108.5, 101.9, 67.3, 48.6, 47.2, 46.6, 45.3. HRMS (CI-TOF) *m*/*z*: $(M + 1)^+$ calcd for $C_{12}H_{14}NO_4^+$ 236.0917; found 236.0913. Mixture of (±)-**16a** and (±)-**16b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J* = 1.9 Hz, $1H_{16a}$), 7.32 (d, *J* = 1.9 Hz, $1H_{16b}$), 6.55 (dd, *J* = 2.9, 5.6 Hz, $1H_{16b}$), 6.51 (dd, *J* = 3.2, 5.6 Hz, $1H_{16a}$), 6.38 (dd, *J* = 1.9, 3.2 Hz, $1H_{16a}$), 6.31 (m, $1H_{16a} + 2H_{16b}$), 6.17 (m, $1H_{16a} + 1H_{16b}$), 4.24 (t, *J* = 2.7 Hz, $1H_{16b}$), 3.9−3.6 (m, $3H_{16a} + 2H_{16b}$), 3.51 (bs, $1H_{16a}$), 3.42 (m, $1H_{16b}$), 3.19 (bs, $1H_{16b}$), 3.08 (bs, $1H_{16a}$), 2.19 (m, $1H_{16a} + 1H_{16b}$), 2.06 (bs, $1H_{16a} + 1H_{16b}$), 1,80 (m, $1H_{16a} + 1H_{16b}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.4_{16a}, 151.8_{16b}, 142.4_{16a}, 142.0_{16b}, 140.3_{16a}, 139.4_{16b}, 135.5_{16a}, 133.0_{16b}, 110.5_{16a}, 110.3_{16b}, 108.5_{16a}, 108.4_{16b}, 102.5_{16b}, 101.9_{16a}, 67.3_{16a}, 65.9_{16b}, 50.6_{16b}, 48.5_{16a}, 48.3_{16b}, 47.2_{16a}, 46.7_{16b}, 46.7_{16b}, 46.6_{16a}, 45.4_{16a}. HRMS (CI-TOF) *m*/*z*: $(M + 1)^+$ calcd for $C_{12}H_{14}NO_4^+$ 236.0917; found 236.0921. (±)-**16c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (dd, *J* = 0.8 Hz, *J* = 1.8 Hz, 1H), 6.53 (dd, *J* = 3.0 Hz, *J* = 5.5 Hz, 1H), 6.42 (dd, *J* = 3.0 Hz, *J* = 5.5 Hz, 1H), 6.24 (dd, *J* = 1.8 Hz, *J* = 3.1 Hz, 1H), 6.00 (d, *J* = 3.1 Hz, 1H), 4.34 (d, *J* = 12.2 Hz, 1H), 4.01 (d, *J* = 12.2 Hz, 1H), 3.57 (d, *J* = 3.0 Hz, 1H), 3.47 (bs, 1H), 3.07 (bs, 1H), 2.60 (bs,1H), 1.74 (dt, *J* = 1.7 Hz, *J* = 9.2 Hz, 1H), 1.66 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 141.6, 137.0, 135.9, 110.3, 107.6, 103.4, 69.5, 47.8, 47.6, 47.5, 47.0. HRMS (CI-TOF) *m*/*z*: $(M + 1)^+$ calcd for $C_{12}H_{14}NO_4^+$ 236.0917; found 236.0919. (ii) *Norbornenes **16a** and **16b** from nitropropenol **17** through a DA cycloaddition.* A solution of (*E*)-3-(furan-2-il)-2-nitroprop-2-en-1-ol **17** (82 mg, 0.48 mmol) and freshly distilled cyclopentadiene (146 mg, 2.21 mmol) in 1,4-dioxane (1.6 mL) was refluxed for 7 h. Solvent removal and chromatography [EtOAc/hexane (10:90 until 25:75)] afforded a mixture of (±)-**16a** and (±)-**16b** (47 mg, 41%, **16a**/**16b** = 3.5:1) as a yellow oil together with unreacted starting **17** (42 mg, 51%).

3-(Furan-2-yl)-2-nitrobicyclo[2.2.1]hept-5-ene-2-carbaldehydes (±)-15b. (i) *Aldehydes (±)-**15b** from **1b** and cyclopentadiene.* A solution of nitroenal **1b** (115 mg, 0.69 mmol, *E*/*Z* = 90/10) and freshly distilled cyclopentadiene (168 mg, 2.54 mmol) in 1,4-dioxane (2.3 mL) was stirred at rt for 45 min. Solvent removal afforded **15b** (96 mg, 60%, oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.36 (td, *J* = 1.7, 0.8 Hz, 1H), 6.64 (dd, *J* = 5.5, 3.2 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.27 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.19 (dd, *J* = 5.5, 2.8 Hz, 1H), 3.93 (d, *J* = 2.8 Hz, 1H), 3.67 (br s, 1H), 3.25 (br s, 1H), 2.46 (d, *J* = 9.8 Hz, 1H), 1.92 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.8, 150.1, 142.8, 142.0, 134.7, 110.7, 108.7, 50.2, 48.0, 47.3, 46.8 (the quaternary carbon signal of **15b** is missing in the spectrum, probably because of relaxation problems; in line with this, the corresponding quaternary carbons appear as weak signals after reduction of **15b** to **16a−c**). LRMS (CI) *m*/*z* (%): 187.1 [$(M - NO_2)^+$, 23], 168.0 (100), 131.0 (30), 99.0 (42). HRMS (CI-TOF) *m*/*z*: $(M - NO_2)^+$ calcd for $C_{12}H_{12}O_2^+$ 188.0832; found 188.0836. (ii) *Aldehydes (±)-**15b**: relative reactivity of nitroenal **1b** and E-2-(2-nitrovinyl)furan (**18**) as dienophiles.* A solution of equimolar quantities of nitroenal **1b** (*E*/*Z* ≈ 2.8:1) and nitroolefin **18** in deuterated 1,4-dioxane prepared in an NMR tube was treated with freshly distilled cyclopentadiene at rt. NMR monitorization of the reaction mixture (see the Supporting Information) showed unreacted **18** and conversion of **1b** into **15b**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for **9−12**, **14−16**. X-ray data for **11**. NMR monitorization for the relative reactivity of nitroenal **1b** and *E*-2-(2-nitrovinil)furan (**18**) as heterodienes against cyclopentadiene. NOE data for **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kirby, E. C.; Reid, D. H. *J. Chem. Soc.* **1961**, 3579.

(2) (a) Sitkin, A. I.; Klimenko, V. I.; Fridman, A. L. *Zh. Org. Khim.* **1975**, *11*, 2452. (b) Klimenko, V. I.; Sitkin, A. I.; Fridman, A. L. *Vses. Nauchn. Konf. Khim. Tekhnol. Furanovykh Soedin., [Tezisy Dokl.]*, 3rd; Stradyn, Y. P., Ed.; Riga, USSR, 1978; p 116. (c) Sitkin, A. I.; Klimenko, V. I.; Fridman, A. L. *Khim. Geterotsikl. Soedin.* **1977**, 1604.

(3) Goldmann, S.; Bechem, M. Ger. Offen. (1994), DE 4222770 A1. Neither details nor references, regarding preparation, properties, and use of **1e**, are explicitly given.

(4) Martínez-Bescos, P.; Cagide-Fagín, F.; Roa, L. F.; Ortiz-Lara, J. C.; Kierus, K.; Ozores-Viturro, L.; Fernández-González, M.; Alonso, R. *J. Org. Chem.* **2008**, 73, 3745−3753.

(5) Ortiz, J. C.; Ozores, L.; Cagide-Fagin, F.; Alonso, R. *Chem. Commun.* **2006**, 4239−4241.

(6) For new synthetic applications of nitroenals **1** (their conversion into nitroazetidines and nitrothioethanes), see: (a) Rai, A.; Yadav, L. D. S. *Org. Biomol. Chem.* **2011**, *9*, 8058−8061. (b) Rai, A.; Yadav, L. D. S. *Tetrahedron* **2012**, *68*, 2459−2464.

(7) Cagide-Fagín, F.; Nieto-García, O.; Lago-Santomé, H.; Alonso, R. *J. Org. Chem.* **2012**, *77*, 11377−11382.

(8) Cagide-Fagín, F.; Alonso, R. *Eur. J. Org. Chem.* **2010**, *2010*, 6741−6747.

(9) Nieto-Garcia, O.; Lago-Santome, H.; Cagide-Fagin, F.; Ortiz-Lara, J. C.; Alonso, R. *Org. Biomol. Chem.* **2012**, *10*, 825−834.

(10) Nieto-Garcia, O.; Alonso, R. *Org. Biomol. Chem.* **2013**, *11*, 515−522.

(11) Lago-Santomé, H.; Meana-Paneda, R.; Alonso, R. *J. Org. Chem.* **2014**, *79* (10), 4300−4305.

(12) *β*-Furyl nitroenal **1b**, which annulates with enamines in much the same way as its *β*-aryl substituted analogs (see, for example, refs 5 and 7), was selected for these studies because, comparatively, it is easier to isolate and more stable (see refs 4 and 8).

(13) Miltz, X.; Steglich, W. *Synthesis* **1990**, *9*, 750−751.

(14) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W. *Tetrahedron* **1985**, *41*, 1693−1701.

(15) The relative stereochemistry at positions 4 and 1′ of **9** was determined by NMR after transformation of **9** into **10** (Scheme 2).

(16) For details, see the Supporting Information.

(17) Crystallographic data were deposited at The Cambridge Crystallographic Data Centre with the deposition number CCDC 949754 and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(18) Presumably, the C5-epimer of **C** (formed, either from **A**, by isomerization, or from **B**, by tautomerization with no inversion at C5) would be in equilibrium with **C** in the reaction mixture.

(19) See for example: Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125−1128.

(20) **14b** was the major product and the only compound we could isolate in pure form from the mixture.

(21) (a) Haruo, S.; Haruhiko, H. *Yakugaku Zasshi* **1958**, *78*, 917−20. (b) Rastogi, N.; Namboothiri, I. N. N.; Cojocaru, M. *Tetrahedron Lett.* **2004**, *45*, 4745−4748.