



HAL
open science

Exploiting the Reactivity of 1,2-Ketoamides: Enantioselective Syn-thesis of Functionalized Pyrrolidines and Pyrrolo-1,4-benzodiaze-pine-2,5-diones

Paola Acosta, Diana Becerra, Sébastien Gouedranche, Jairo Quiroga, Thierry Constantieux, Damien Bonne, Jean Rodriguez

► To cite this version:

Paola Acosta, Diana Becerra, Sébastien Gouedranche, Jairo Quiroga, Thierry Constantieux, et al.. Exploiting the Reactivity of 1,2-Ketoamides: Enantioselective Syn-thesis of Functionalized Pyrrolidines and Pyrrolo-1,4-benzodiaze-pine-2,5-diones. SYNLETT, 2015, 26, pp.1591-1595. 10.1055/s-0034-1378711 . hal-01219398

HAL Id: hal-01219398

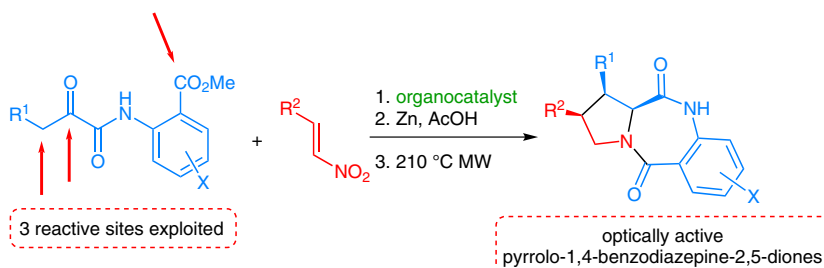
<https://hal.science/hal-01219398>

Submitted on 22 Oct 2015

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Exploiting the Reactivity of 1,2-Ketoamides: Enantioselective Synthesis of Functionalized Pyrrolidines and Pyrrolo-1,4-benzodiazepine-2,5-diones

Paola Acosta^aDiana Becerra^bSébastien Gouedranche^bJairo Quiroga^aThierry Constantieux^bDamien Bonne^{*b}Jean Rodriguez^{*b}

^a Facultad de Ciencias Naturales y Exactas Universidad del Valle
Cali, Colombia

^b Aix Marseille Université, CNRS, Centrale Marseille, iSm2 UMR
7313, 13397 Marseille, France
damien.bonne@univ-amu.fr
jean.rodriguez@univ-amu.fr

Received: 06.03.2015

Accepted after revision: 11.05.2015

Published online: 08.06.2015

DOI: 10.1055/s-0034-1378711; Art ID: st-2015-b0154-l

Abstract A new strategy for the synthesis of optically active pyrrolo[1,4]benzodiazepine-2,5-diones has been developed. The approach is based on an initial Michael addition of functionalized 1,2-ketoamides on nitroalkenes, with a reduction–double cyclization sequence leading to the desired substituted benzodiazepine.

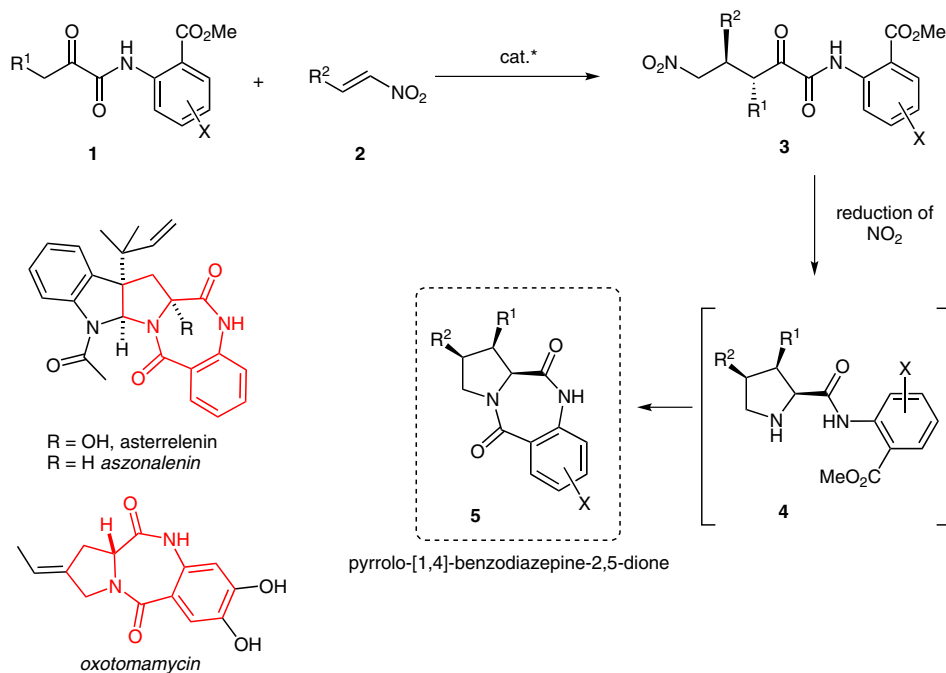
Key words enantioselective Michael addition, benzodiazepine, 1,2-ketoamides

Dicarbonyl compounds are privileged substrates for the development of new multiple bond-forming transformations (MBFTs) because of their high number of adjacent reactive sites that can participate in the successive creation of several bonds.¹ The chemistry associated with 1,3-dicarbonyl compounds is now well understood, and many cascade reactions exploiting their reactivity have been described.² Although underexploited in comparison to their 1,3-dicarbonyl isomers, 1,2-dicarbonyl compounds also possess significant synthetic potential.³ As part of our sustained interest in MBFTs, we reported a few years ago the use of 1,2-ketoamides and 1,2-ketoesters as pronucleophiles in enantioselective Michael addition using hydrogen-bonding organocatalysis.⁴ These methodologies may represent the first step in the design of efficient and original MBFTs by using 1,2-dicarbonyl compounds as substrates.⁵ Indeed the Michael adduct obtained in optically active form can be seen as a synthetic platform for many types of carbo- and heterocycles.

We reasoned that a suitably functionalized ketoamide **1** could be exploited by using our previous methodology to provide enantioselective access to pyrrolidines **4** as precursors

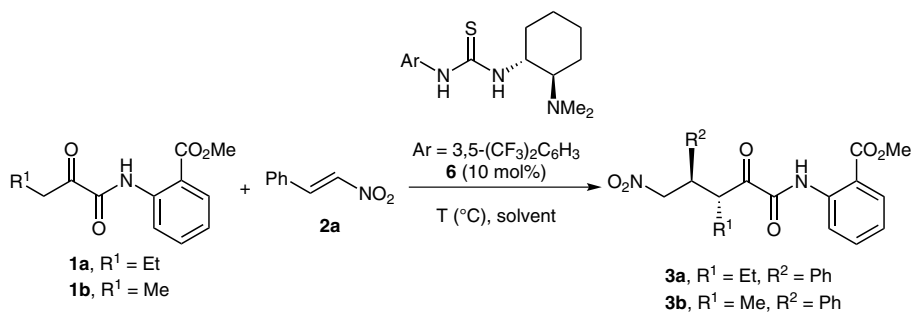
of pyrrolo-1,4-benzodiazepine-2,5-diones **5** (Scheme 1).⁶ The pyrrolo-1,4-benzodiazepine-2,5-dione structural subunit can be found in several natural products such as asterrelenin, azonalenin, and oxotomamycin.⁷ These compounds as well as their analogues or derivatives have shown antitumor,⁸ antibiotic,⁹ anxiolytic,¹⁰ and antithrombic activities.¹¹ Moreover, their structural motifs and physico-chemical properties have led to the benzodiazepine scaffold being considered as a novel non-peptide peptidomimetic, acting as a mimic of peptide secondary structures such as γ - and β -turns.¹² Considering these biological properties, rapid and easy access to this scaffold would be of high interest. The novel strategy we designed constitutes an original route for the synthesis of this molecular scaffold. We anticipated that the reduction of the nitro group could trigger an original domino reductive amination–lactamization sequence giving the desired benzodiazepinone derivative in only two simple synthetic operations from two simple achiral and acyclic starting materials.

We selected 1,2-ketoamides **1a** and **1b**, bearing an ester moiety on the phenyl ring of the amide, as model ketoamides, and β -nitrostyrene (**2a**) as the electrophilic partner (Table 1). Takemoto thiourea catalyst **6**¹³ was selected to promote this reaction because it gave us excellent results in previous studies.⁴ Preliminary optimization of the reaction conditions led us to the conclusions that dichloromethane (CH_2Cl_2) was a better solvent than ethyl acetate, because the former solvent allowed a higher enantioselectivity to be achieved (entries 1 and 3). Moreover, conducting the reaction in CH_2Cl_2 was possible at room temperature, affording the desired Michael adduct in good yield and excellent stereoselectivities (entries 3 and 5). The diastereoselectivity, which favored the *trans* adduct **3a** or **3b**, was excellent in all cases.



Scheme 1 Strategy for the synthesis of optically active benzodiazepine-2,5-diones

Table 1 Reaction Optimization^a



Entry	1	Solvent	Temp. (°C)	3	Yield (%) ^b	dr ^c	ee (%) ^d
1	1a	EtOAc	r.t.	3a	67	>20:1	85
2	1a	EtOAc	0	3a	65	>20:1	92
3	1a	CH ₂ Cl ₂	r.t.	3a	61	>20:1	95
4	1b	EtOAc	0	3b	63	>20:1	80
5	1b	CH ₂ Cl ₂	r.t.	3b	61	>20:1	89

^a 1,2-Ketoamide **1** (0.2 mmol), *trans*- β -nitrostyrene (**2a**; 0.24 mmol) and catalyst **6** (0.02 mmol) were successively added in a sealed tube and dissolved in CH₂Cl₂ (0.5 mL). The reaction was stirred at r.t. until consumption of starting ketoamide **1** (usually 48 h, reaction monitored by TLC).

^b Isolated yield after flash chromatography.

^c Determined by ¹H NMR spectroscopic analysis of the crude reaction product.

^d Determined by chiral HPLC analysis.

Having identified the best conditions for this reaction, we studied its scope (Scheme 2) and found that various aryl nitroalkenes with electron-donating or electron-withdrawing substituents can be used for this transformation with

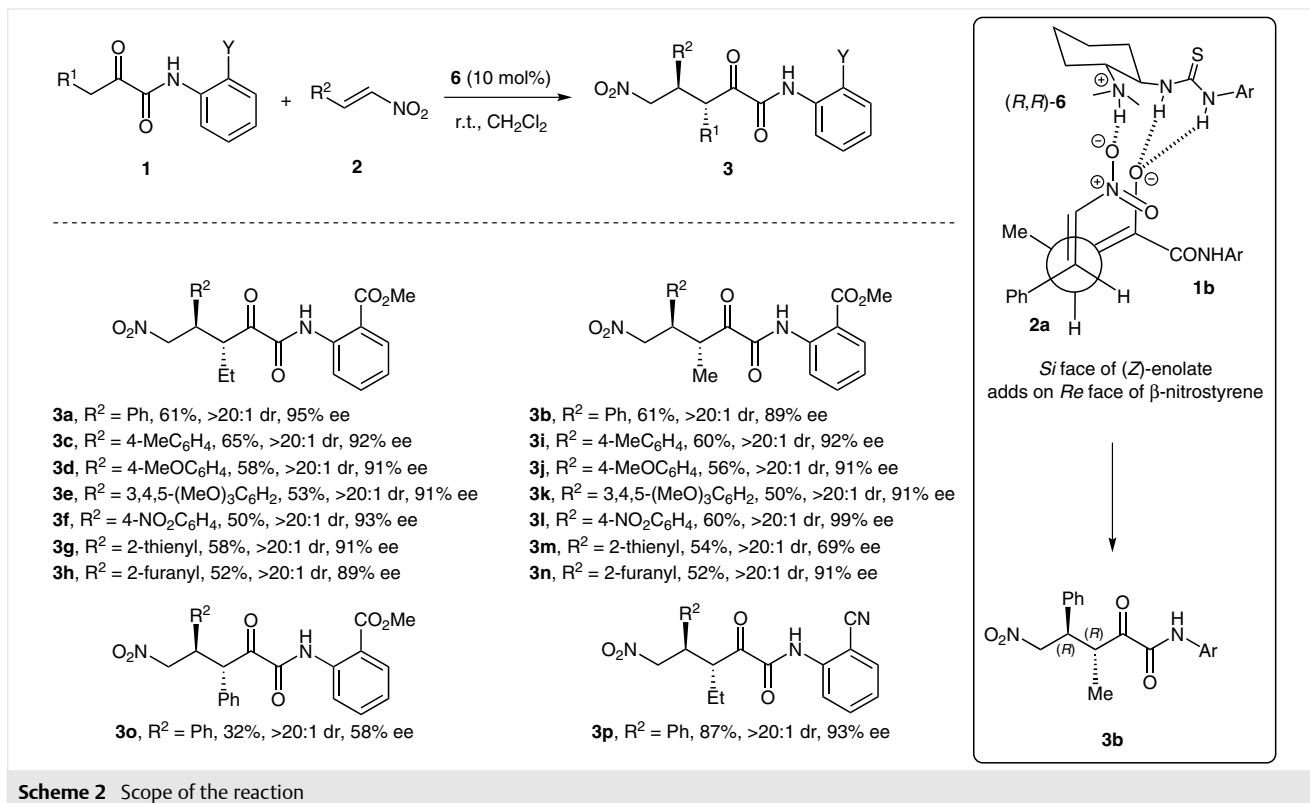
yields ranging from 50 to 65% and, in all cases, excellent enantioselectivities (91–99% ee). We always observed incomplete conversion of the starting nitroalkene. No perceptible evolution was found after 48 h, possibly due to inhibition of

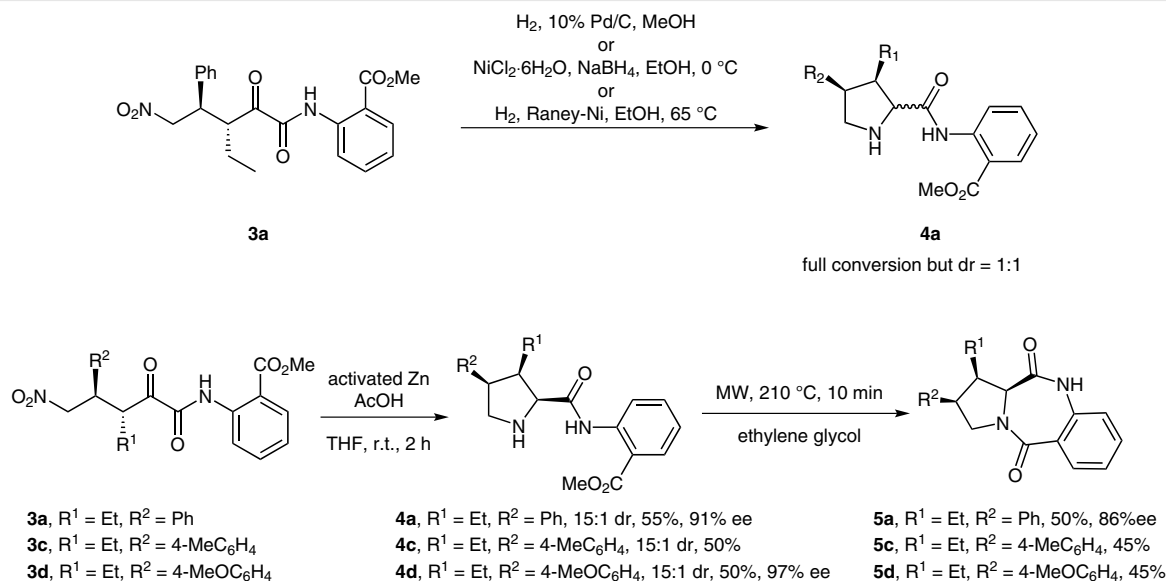
the catalyst by hydrogen bonding with the product of the reaction. In addition, heteroaryl-substituted nitroolefins were found to be suitable substrates, affording the desired Michael adduct with similar efficiency (**3g**, **3h**, **3m**, and **3n**). Surprisingly, the use of ketoamide **1c** ($R^1 = \text{Ph}$, $Y = \text{CO}_2\text{Me}$) gave the product **3o** in moderate yield (32%) and enantioselectivity (58%). In contrast, the reaction was found to be very efficient for ketoamide **1d** ($R^1 = \text{Et}$, $Y = \text{CN}$) incorporating a cyano moiety instead of the ester function (**3p**; 87% yield, >20:1 dr, 93% ee). The relative and absolute stereochemistry can be justified by the transition state proposed in preliminary studies. Hence, the thiourea moiety of the catalyst activates the (*Z*)-enolate of ketoamide¹⁴ while the ammonium ion activates the nitroalkene through H-bonding interaction. Therefore, a preferential approach of the *Si* face of the enolate on the *Re* face of **2a** could account for the observed stereochemistry.

We then attempted to validate our strategy by converting Michael adducts **3** into the functionalized diazepinones **5** (Scheme 3). First, the reaction conditions used to convert nitroalkane **3a** into the substituted pyrrolidine **4a** were screened. The use of various reductive conditions such as H_2 in combination with Pd on charcoal or Raney-Ni, or sodium borohydride in the presence of nickel(II) salt, gave the desired product **4a** in good yields, but invariably with no diastereoselectivity. However, we observed that the use of activated zinc and acetic acid in THF led to the formation of the

desired pyrrolidine in moderate yield (**4a**; 55%) and very good diastereoselectivity (dr = 15:1). At this stage, subsequent formation of the 1,4-benzodiazepin-2,5-dione was studied. Optimized reaction conditions consisted of heating **4a** at 210 °C in ethylene glycol for 10 min under microwave irradiation, and afforded **5a** in 50% yield. The desired benzodiazepinone **5a** was isolated with 86% ee starting from pyrrolidine **4a** (91% ee). To increase the synthetic efficiency of the cyclization, a two-step sequence for conversion of pyrrolidine **4a** into **5a** was then conducted. The ester function of **4a** was first saponified to give the corresponding carboxylic acid in quantitative yield. Unfortunately, intramolecular amide coupling only afforded the desired benzodiazepinone **5a** in poor yields with significant loss of enantiomeric purity (70% ee).¹⁵ With this synthetic procedure in hand, microwave-assisted lactamization was finally chosen and applied for two other examples; benzodiazepinones **5c** and **5d** were both obtained with modest yields (45%).

In conclusion, we have developed a new strategy for the synthesis of optically active pyrrolo[1,4]benzodiazepine-2,5-diones.¹⁶ The approach is based on an initial Michael addition of functionalized 1,2-ketoamides on nitroalkenes, with the adduct then being converted into the desired substituted benzodiazepine by following a reduction-double cyclization sequence.





Scheme 3 Synthesis of pyrrolo[1,4]benzodiazepine-2,5-diones **5**

Acknowledgment

Financial support from the Agence Nationale pour la Recherche (ANR-11-BS07-0014), the Centre National de la Recherche Scientifique (CNRS), Aix-Marseille Université, Departamento Administrativo de Ciencia, Tecnología e Innovación (COLCIENCIAS), and Universidad del Valle is gratefully acknowledged. We also thank Dr. N. Vanthuyne and M. Jean (ee measurements).

Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1378711>.

References and Notes

- (1) (a) *Stereoselective Multiple Bond-Forming Transformations in Organic Synthesis*; Rodriguez, J.; Bonne, D., Eds.; John Wiley & Sons, Inc: Hoboken, NJ, **2015**. (b) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2013**, *19*, 2218. (c) Green, N. J.; Sherburn, M. S. *Aust. J. Chem.* **2013**, *66*, 267. (d) Menéndez, J. C. *Curr. Org. Chem.* **2013**, *18*, 1919; and reviews included in this special issue. (e) Coquerel, Y.; Boddaert, T.; Presset, M.; Mailhol, D.; Rodriguez, J. In *Ideas in Chemistry and Molecular Sciences: Advances in Synthetic Chemistry*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, Germany, **2010**, Chap. 9, pp. 187-202.
- (2) (a) Bugaut, X.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. In *Multicomponent Reactions in Organic Synthesis*; Zhu, J.; Wang, Q.; Wang, M.-X., Eds.; Wiley-VCH: Weinheim, **2014**, Chap. 5, pp. 109-158. (b) Bugaut, X.; Bonne, D.; Coquerel, Y.; Rodriguez, J.; Constantieux, T. *Curr. Org. Chem.* **2013**, 1920. (c) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085.
- (3) (a) Raimondi, W.; Bonne, D.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 40. (b) Raimondi, W.; Bonne, D.; Rodriguez, J. *Chem. Commun.* **2012**, 48, 6763.
- (4) (a) Baslé, O.; Raimondi, W.; Sanchez Duque, M. M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246. (b) Raimondi, W.; Baslé, O.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Adv. Synth. Catal.* **2012**, *354*, 563.
- (5) For the use of α -ketoamides in organocatalyzed transformations, see: (a) Gouedranche, S.; Pierrot, D.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Chem. Commun.* **2014**, *50*, 15605. (b) Sanchez Duque, M. M.; Gouedranche, S.; Quintard, A.; Constantieux, T.; Bugaut, X.; Bonne, D.; Rodriguez, J. *Synthesis* **2013**, 45, 1659. (c) Joie, C.; Deckers, K.; Enders, D. *Synthesis* **2014**, 46, 799. (d) Joie, C.; Deckers, K.; Raabe, G.; Enders, D. *Synthesis* **2014**, 46, 1539. (e) Lefranc, A.; Guénee, L.; Goncalves-Contal, S.; Alexakis, A. *Synlett* **2014**, 25, 2947.
- (6) MacQuarrie-Hunter, S.; Carlier, P. R. *Org. Lett.* **2005**, *7*, 5305.
- (7) (a) Kariyone, K.; Yazawa, H.; Kohsaka, M. *Chem. Pharm. Bull.* **1971**, *19*, 2289. (b) Li, G.-Y.; Li, B.-G.; Yang, T.; Yin, J.-H.; Qi, H.-Y.; Liu, G.-Y.; Zhang, G.-L. *J. Nat. Prod.* **2005**, *68*, 1243. (c) Capon, R. J.; Skene, C.; Stewart, M.; Ford, J.; O'Hair, R. A. J.; Williams, L.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *Org. Biomol. Chem.* **2003**, *1*, 1856. (d) Rank, C.; Phipps, R. K.; Harris, P.; Frisvad, J. C.; Gotfredsen, C. H.; Larsen, T. O. *Tetrahedron Lett.* **2006**, *47*, 6099.
- (8) (a) Deck, P.; Pendzialek, D.; Biel, M.; Wagner, M.; Popkirova, B.; Ludolph, B.; Kragol, G.; Kuhlmann, J.; Giannis, A.; Waldmann, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 4975. (b) He, J.; Wijeratne, E. M. K.; Bashyal, B. P.; Zhan, J.; Seliga, C. J.; Liu, M. X.; Pierson, E. E.; Pierson, L. S.; VanEtten, H. D.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2004**, *67*, 1985. (c) Kamal, A.; Shankaraiah, N.; Prabhakar, S.; Reddy, C. R.; Markandeya, N.; Reddy, K. L.; Devaiah, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2434.
- (9) Bouhlal, D.; Godé, P.; Goethals, G.; Massoui, M.; Villa, P.; Martin, P. *Heterocycles* **2001**, *55*, 303.
- (10) Wright, W. B.; Brabander, H. J.; Greenbatt, E. N.; Day, I. P.; Hardy, R. A. *J. Med. Chem.* **1978**, *21*, 1087.
- (11) (a) McDowell, R. S.; Blackburn, B. K.; Gadek, T. R.; McGee, L. R.; Rawson, T.; Reynolds, M. E.; Robarge, K. D.; Somers, T. C.; Thorsett, E. D.; Tischler, M.; Webb, R. R.; Venuti, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 1234.

- Chem. Soc.* **1994**, *116*, 5077. (b) Webb, R. R.; Barker, P. L.; Baier, M.; Reynolds, M. E.; Robarge, K. D.; Blackburn, B. K.; Tischler, M. H.; Weese, K. J. *Tetrahedron Lett.* **1994**, *35*, 2113.
- (12) (a) Verdié, P.; Subra, G.; Feliu, L.; Sanchez, P.; Bergé, G.; Garcin, G.; Martinez, J. J. *Comb. Chem.* **2007**, *9*, 254. (b) Cabedo, N.; Pannecoucke, X.; Quirion, J.-C. *Eur. J. Org. Chem.* **2005**, 1590.
- (13) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
- (14) Xu, Y.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 3246.
- (15) It is difficult to give a rational answer to this experimental observation and unfortunately no simple mechanism can be proposed to account for partial epimerization of the final products.
- (16) **Synthesis of Michael Adducts 3; General Procedure:** 1,2-Ketoamide **1** (0.20 mmol, 1.0 equiv), nitroalkene **2** (0.24 mmol, 1.2 equiv) and catalyst **6** (0.02 mmol, 0.1 equiv) were successively added in a sealed tube with a magnetic stir bar and dissolved in CH₂Cl₂ (0.5 mL). The reaction was then stirred at r.t. until consumption of starting ketoamide **1** was observed (48–72 h, reaction monitored by TLC). The crude product was purified directly by flash chromatography on silica gel (EtOAc-petroleum ether (PE), 20:80).
- Methyl 2-[(3R,4R)-3-Ethyl-5-nitro-2-oxo-4-phenylpentanamide]benzoate (3a):** By following the general procedure, the reaction between **1a** (49.8 mg, 0.20 mmol), β-nitrostyrene **2a** (35.8 mg, 0.24 mmol) and catalyst **6** (8.3 mg, 0.02 mmol) afforded **3a** (61%) as a white solid; mp 155–156 °C; *R_f* = 0.3 (PE-EtOAc, 8:2); HPLC (Chiralpak IA; hexane-EtOH, 90:10; flow rate = 1.0 mL/min; λ = 220 nm); *t_R* = 10.12 (major), 10.91 (minor) min; ee = 95%. ¹H NMR (400 MHz, CDCl₃): δ = 12.21 (br s, NH, 1 H), 8.75 (dd, *J* = 8.4, 0.9 Hz, 1 H), 8.15–8.13 (m, 1 H), 7.68–7.64 (m, 1 H), 7.34 (d, *J* = 4.3 Hz, 4 H), 7.28–7.23 (m, 2 H), 4.89–4.81 (m, 2 H), 4.29 (td, *J* = 9.1, 3.9 Hz, 1 H), 4.10–4.06 (m, 1 H), 4.03 (s, 3 H), 1.99–1.86 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 199.6 (C), 168.1 (C), 158.3 (C), 139.5 (C), 137.5 (C), 134.6 (CH), 131.4 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 124.1 (CH), 120.4 (C), 116.7 (C), 77.8 (CH₂), 52.8 (CH₃), 48.0 (CH), 44.5 (CH), 22.2 (CH₂), 11.3 (CH₃). HRMS (ESI+): *m/z* calcd for [C₂₁H₂₂N₂O₆ + H⁺]: 399.1551; found: 399.1548.
- Synthesis of Pyrrolidines 4; General Procedure:** Michael adduct **3** (0.3 mmol, 1.0 equiv) was dissolved in anhydrous THF (15 mL) and activated zinc powder (2.77 g, 42 mmol, 70.0 equiv) was added followed by acetic acid (15 mL). The mixture was stirred for 2 h at r.t., then the mixture was concentrated and saturated aqueous NaHCO₃ solution (15 mL) was added. The aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL) and the combined organic layers were washed with water (20 mL),

dried over sodium sulfate, and concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc-PE, 40:60).

Methyl 2-[(2S,3R,4R)-3-Ethyl-4-phenylpyrrolidine-2-carboxamido]benzoate (4a): Yield: 55%; colorless oil; *R_f* = 0.5 (PE-EtOAc, 3:2); HPLC (Lux-Cellulose-2; heptane-EtOH, 80:20; flow rate = 1.0 mL/min; λ = 254 nm); *t_R* = 6.75 (major), 8.83 (minor) min; ee = 91%. ¹H NMR (400 MHz, CDCl₃): δ = 12.34 (br s, NH, 1 H), 8.84 (dd, *J* = 8.5, 1.2 Hz, 1 H), 8.05 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.58–7.54 (m, 1 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 7.25–7.20 (m, 1 H), 7.18–7.14 (m, 2 H), 7.13–7.08 (m, 1 H), 3.93 (s, 3 H), 3.80 (d, *J* = 3.7 Hz, 1 H), 3.56 (d, *J* = 2.4 Hz, 1 H), 3.47 (d, *J* = 5.1 Hz, 2 H), 2.52–2.43 (m, 1 H), 1.32–1.29 (m, 1 H), 1.20–1.11 (m, 1 H), 0.92 (t, *J* = 7.3 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 175.1 (C), 168.1 (C), 141.0 (C), 139.9 (C), 134.5 (CH), 131.2 (CH), 128.4 (CH), 128.4 (CH), 126.5 (CH), 122.7 (CH), 120.6 (CH), 116.2 (C), 66.3 (CH₃), 52.4 (CH), 51.1 (CH), 50.0 (CH₂), 47.2 (CH), 21.6 (CH₂), 12.5 (CH₃). HRMS (ESI+): *m/z* calcd for [C₂₁H₂₄N₂O₃ + H⁺]: 353.1860; found: 353.1862.

Synthesis of Pyrrolo[1,4]benzodiazepine-2,5-dione 5;

General Procedure: A reaction vessel equipped with a magnetic stir bar was charged with pyrrolidine **4** (0.2 mmol) and ethylene glycol (0.6 mL), and the mixture was subjected to microwave irradiation at 210 °C for 10–20 min. The crude reaction mixture was extracted with CH₂Cl₂ (2 × 10 mL) and the combined organic layers were washed with water (10 mL), dried over sodium sulfate, and concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc-PE, 40:60).

(1R,2R,11aS)-1-Ethyl-2-phenyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (5a): Yield: 50%; white solid; mp 234 °C; *R_f* = 0.2 (PE-EtOAc, 6:4); HPLC (Chiralpak AD-H; heptane-EtOH, 80:20; flow rate = 1.0 mL/min; λ = 254 nm); *t_R* = 15.47 (major), 19.39 (minor) min; ee = 86%. ¹H NMR (400 MHz, CDCl₃): δ = 8.10–8.06 (m, 2 H), 7.56–7.50 (m, 1 H), 7.28–7.26 (m, 1 H), 7.36–7.31 (m, 3 H), 7.24–7.19 (m, 2 H), 7.03 (dd, *J* = 8.0, 1.1 Hz, 1 H), 4.08 (dd, *J* = 8.7, 1.4 Hz, 2 H), 3.94 (d, *J* = 2.4 Hz, 1 H), 3.81–3.73 (m, 1 H), 3.16–3.09 (m, 1 H), 1.23–1.07 (m, 2 H), 0.77 (t, *J* = 7.4 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.0 (C), 165.7 (C), 138.0 (C), 135.1 (C), 132.7 (CH), 131.4 (CH), 128.6 (CH), 127.9 (CH), 126.9 (CH), 126.8 (C), 125.3 (CH), 121.0 (CH), 60.7 (CH), 49.2 (CH₂), 45.3 (CH), 44.6 (CH), 20.1 (CH₂), 12.3 (CH₃). HRMS (ESI+): *m/z* calcd for [C₂₀H₂₀N₂O₂ + H⁺]: 321.1598; found: 321.1596.

Other examples of compounds **3**, **4** and **5** as well as ¹H and ¹³C NMR spectra and chiral HPLC analyses are available in the Supporting Information.