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Concise diastereospecific pyrrolo[1,2-*a*][1,4]benzodiazepinone synthesis

Mauro Mucedda,[a] Daniele Muroni,[a] Antonio Saba[a,*] and Carlo Manassero[b]

[a]*Dipartimento di Chimica, Facoltà di Scienze, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy*
[b]*Dipartimento di Chimica Strutturale e Stereochimica Inorganica, Facoltà di Scienze, Università di Milano, Via Venezian 21, 20133 Milano, Italy*

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Abstract—A concise synthesis of the novel pyrrolo[1,2-*a*]benzodiazepine system, by using the metallo carbenoid/spiro-[6,5]-ammonium ylide/Stevens[1,2]-shift with ring-expansion approach, was reported. The overall cascade process resulted stereospecific.

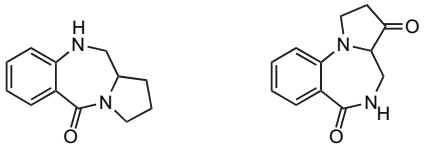
1. Introduction

Amongst the privileged class within medicinal chemistry 1,4-benzodiazepines, most attention has been paid to related tricyclic systems such as pyrrolo[2,1-*c*][1,4]benzodiazepinones **1** (PBDs), due to a broad and ever evolving field of biological activities.[1] PBDs continue to attract great interest. In fact such compounds are potentially therapeutic agents in the treatment of some cancer and as interactive antitumor antibiotics, due to their ability to recognize and bind with specific sequences of the minor groove of DNA.[2]

Instead, in this area, it is surprising that, to date, there are no publications on the synthesis of the other possible isomer bearing the cyclic amine nitrogen engaged in the pyrrolidine ring, namely the pyrrolo[1,2-*a*]benzodiazepinone system **2** (Fig. 1).

As apart of the ongoing program on the tandem carbenoid/ammonium ylide cascade protocol,[3] which is a very concise and powerful approach to construct enantiopure bicyclic and tricyclic alkaloids from easy available starting materials,[4] herein we describe the synthesis of pyrrolo[1,2-*a*]benzodiazepinones **2** by using the metallo carbenoid/spiro-[6,5]-ammonium ylide[5]/Stevens[1,2]-shift with ring-expansion sequence.[6]

Tandem or cascade processes of metallo carbenoids generated by transition metal catalyzed reactions of diazo compounds and leading to ammonium ylides, which undergo sigmatropic rearrangements, has gained significant



1 **2**

Figure 1.

importance in organic synthesis. Moreover, such intermediate metallo carbenoids often show high levels of stereoselectivity despite their high reactivity.[7]

2. Results and discussion

The tetrahydroquinazolinones **4a**–**e**, bearing a diazo function at the proper position on the keto ester chain tethered to the amine nitrogen atom, have been selected as the appropriate carbenoid cyclization precursors for accessing target structures (Scheme 1).

(±)-3-Benzyl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester starting material for diazoesters **4a** and **4b**, and (±)-3-benzyl-5,7-dichloro-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester, for **4d**, have been, respectively, prepared in one step from the corresponding 2-aminobenzamides.[8] The remaining (±)-3-benzyl-2-phenyl-2,3-dihydro-1*H*-quinazolin-4-one, precursor of **4c** and **4e**, has been synthesized from isatoic anhydride, according to a three-component protocol reported recently.[9]

The diazo compounds **4a**–**e** were prepared efficiently in two steps by conjugate addition of **3** to ethyl-3-ketopent-4-enoate[10] or (−)-menthyl-3-ketopent-4-enoate,[4d] followed by diazo group transfer reaction with tosyl azide.

Keywords: Benzodiazepines; Diazo compounds; Cascade process; Stevens[1,2]-shift.
* Corresponding author. Tel.: +39 79 229538; fax: +39 79 229559; e-mail: saba@uniss.it

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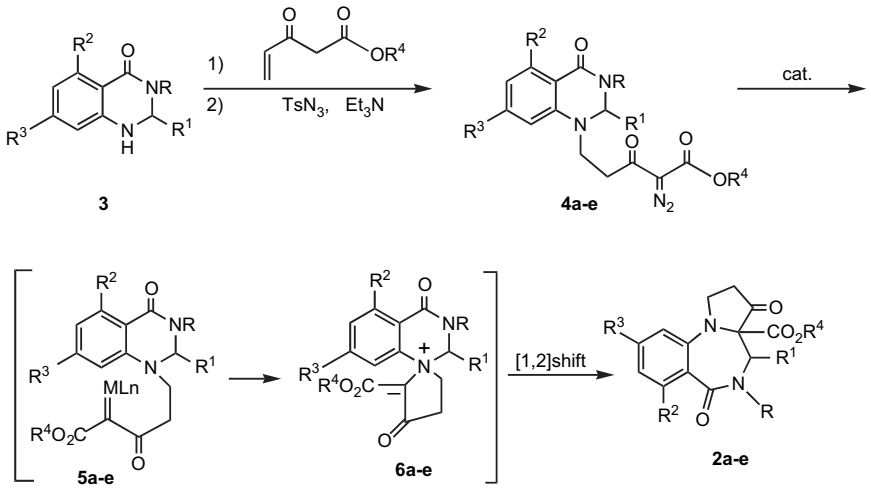


	R	R^1	R^2	R^3	R^4
a	CH_2Ph	CO_2Et	H	H	Et
b	CH_2Ph	CO_2Et	H	H	(-)Ment
c	CH_2Ph	Ph	H	H	(-)Ment
d	CH_2Ph	CO_2Et	Cl	Cl	Et
e	CH_2Ph	Ph	H	H	Et

Scheme 1.

The aim of obtaining chiral diastereomers, permitting to attempt their separation, has suggested the preparation of (−)-menthyldiazoesters **4b** and **4c**, both bearing the chiral auxiliary.

All the diazoketocarboxylates **4a–e** are stable compounds and reliable to be handled and safe is their preparation by diazo transfer reaction with tosyl azide.[11]

As depicted in Scheme 1, the intermediates spiro-[6,5]-ammonium ylides **6** might be expected to form, via the nitrogen trapping of the metallo carbenoid group correctly situated on the pendant of **5**, whenever the amine is part of a pre-existing ring system. The ylides' sigmatropic rearrangement would furnish the tricyclic targets **2**. The presence of a conjugative stabilizing phenyl or ester group on the putative migrating carbon was foreseen for the [1,2]-shift to be successful. Such presence was reported to favor an efficient carbon migration in Stevens rearrangement.[12,3d]

Two transition metal catalysts have been studied (Table 1). The $Cu(acac)_2$ or $Rh_2(OAc)_4$ catalyzed diazo-decomposition of **4a–d** has been performed in refluxing toluene, giving the desired benzodiazepinones (**2a–d**) as the sole product. Best yields were achieved when the diazo-decompositions were performed in the presence of $Rh_2(OAc)_4$ as catalyst, in contrast to data previously reported.[13] Only in the case of **4e**, the copper-based catalysis has demonstrated to be more effective.

Notwithstanding the double stabilizing effect applied on the ylide carbon atom by the presence of both carbonyl and ester groups, isolation of the spirocyclic ammonium ylide intermediates **6**, previously observed by us in similar cases,[4c] was unsuccessful.

Interestingly, compounds **2a**, **2d**, and **2e** have been obtained as single diastereoisomers bearing the substituents at C-3a and C-4 trans disposed. As expected, the chiral compounds **2b** and **2c** have been achieved as a 1:1 mixture of trans diastereomers. Unfortunately, all attempts in resolving that mixture by column chromatography failed.

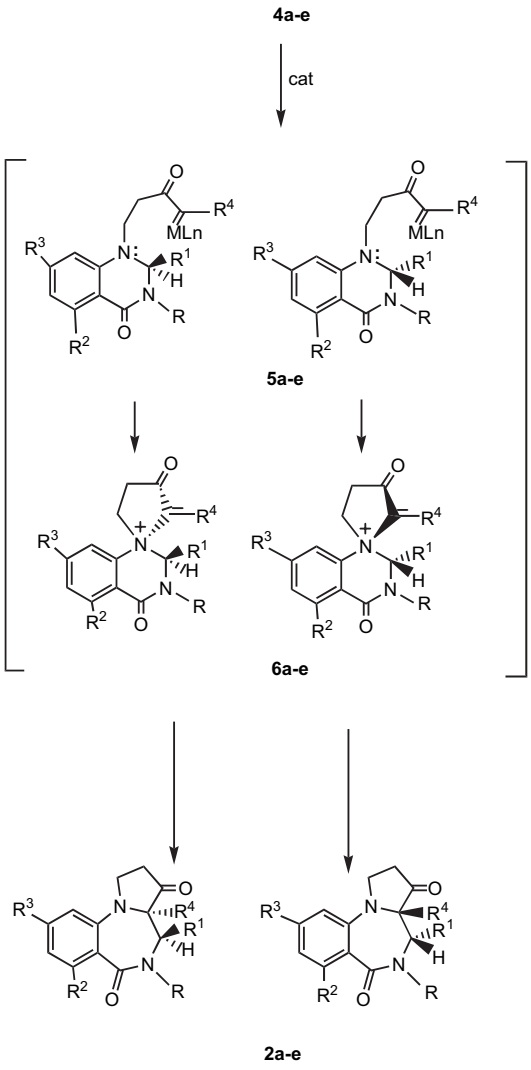
Such high stereoselectivity suggests that a previous formation of ylide **6** could happen, and this is consistent with a probable approach of the electrophilic carbenoid by the nucleophilic amine from the opposite face of the quinazolinone ring such as the ethyl ester or phenyl substituent. In Scheme 2 this attack is depicted by both the enantiomeric forms of the precursor racemic metallo carbenoid.

Isolation of compound **2e** crystals enabled the single crystal X-ray analysis to be performed. As shown in Figure 2, the trans configuration of the substituents at C-3a and C-4 is consequently assigned.

Table 1. Diazo-decomposition of **4a–e** in refluxing toluene

Substrate	Catalyst	Yield[a] (%)	Product
4a	$Rh_2(OAc)_4$	65	**2a**
4a	$Cu(acac)_2$	54	**2a**
4b	$Rh_2(OAc)_4$	71	**2b**
4b	$Cu(acac)_2$	62	**2b**
4c	$Rh_2(OAc)_4$	83	**2c**
4c	$Cu(acac)_2$	53	**2c**
4d	$Rh_2(OAc)_4$	70	**2d**
4d	$Cu(acac)_2$	58	**2d**
4e	$Rh_2(OAc)_4$	68	**2e**
4e	$Cu(acac)_2$	80	**2e**

[a] Isolated yield after column chromatography.



Scheme 2.

Moreover, by reducing with $NaBH_4$, compound **2d** afforded the racemic tetracyclic lactone **7** resulting in accord with the trans configuration of the ester substituents (Fig. 3).

Given the predicted stereoselectivity in the nitrogen quaternization step,[14] the high diastereoselectivity of the overall process needs elevated stereoselectivity in the subsequent Stevens [1,2]-shift. Within this context, the migration pathway most accepted[15] involves homolytic cleavage of the carbon–nitrogen bond to the most stable potential carbon centered radical, generating a radical pair that is held tightly together by a solvent cage. This is followed by solvent cage/rapid recombination of the radical center with the neighbor ylide carbon to generate the rearranged product, thus accounting for the high degree of stereoselectivity observed.

3. Conclusion

This work reports a very concise and convenient stereospecific synthesis of novel pyrrolo-benzodiazepinone alkaloids in three steps and 45–60% total yield from the readily available tetrahydroquinazolinones, by utilizing the cascade spiro-to-fused strategy.

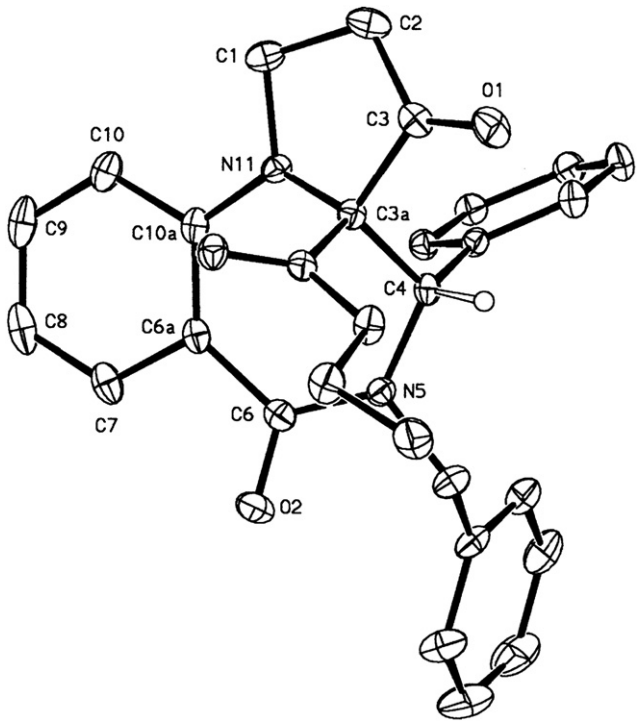


Figure 2. ORTEP view of compound **2e**. Hydrogen atoms omitted for clarity: only the hydrogen atom at C-4 is shown.

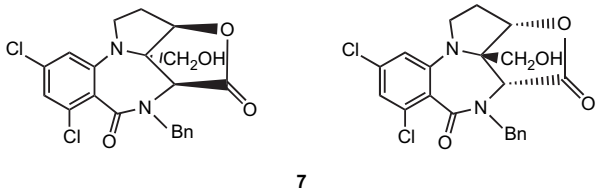


Figure 3.

Due to a combination of two or more distinct reactions into a single transformation, cascade or tandem processes are a powerful method for constructing polycyclic structures from relatively simple starting materials with proper regio- and stereo-chemical control.[16]

It is interesting to note that conformationally constrained amino esters can be recognized in the 1,4-diazepinone frames of **2a**–**e**; conformationally constrained analogs of natural amino acids is a matter of great interest.[17]

Moreover, all the pyrrolo[1,2-*a*][1,4]benzodiazepinones prepared are besides characterized by the presence of a quaternary carbon stereocenter whose construction is still a challenging and dynamic area in organic synthesis.[18]

Biological evaluations and structure–activity relationship (SAR) will be reported in due course.

4. Experimental

4.1. General

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR-300 spectrometer with TMS as

internal standard. Infrared (IR) spectra were performed on a FT/IR-480plus JASCO spectrophotometer. All reagents and solvents employed were reagent grade materials; purified by standard methods and redistilled before use.

4.1.1. (±)-3-Benzyl-1-(4-diazo-4-ethoxycarbonyl-3-oxobutyl)-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester 4a. To a stirred solution of (±)-3-benzyl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester (0.856 g, 2.16 mmol), and 3-oxo-pent-4-enoic acid ethyl ester (0.45 g, 3.17 mmol), in CH_2Cl_2 (10 mL), few drops of aqueous 50% HCl were added and stirred at room temperature for 1 day. The solvent was evaporated and to the residue a solution of tosyl azide (0.638 g, 3.2 mmol) and Et_3N (0.44 mL, 3.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (light petroleum ether/ethyl acetate 7:3), the *diazo compound* **4a** (0.742 g, 72%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.14 (t, 3H, J=8.0 Hz), 1.30 (t, 3H, J=8.0 Hz), 2.95–3.04 (m, 1H), 3.14–3.25 (m, 1H), 3.57–3.73 (m, 2H), 4.07 (dq, 2H, J=6.6, 1.3 Hz), 4.20 (AB system, 1H), 4.24 (q, 2H, J=6.6 Hz), 5.14 (s, 1H), 5.51 (AB system, 1H), 6.75 (d, 1H, J=8.7 Hz), 6.87 (t, 1H, J=8.7 Hz), 7.27–7.41 (m, 6H), 8.00 (dd, 1H, J=8.7, 2.0 Hz). ^{13}C NMR ($CDCl_3$): δ 13.9, 14.2, 38.7, 43.9, 48.6, 61.4, 61.7, 62.1, 73.0, 76.0, 111.8, 117.1, 118.9, 127.5, 128.4, 128.5, 129.3, 133.7, 136.3, 137.3, 145.3, 160.9, 162.7, 169.3, 190.4. IR (neat): 2981, 2136, 1716, 1655, 1606, 1493, 1374, 1307, 1173, 1051, 754, 726, 702 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_4O_6$: C, 66.65; H, 5.82; N, 6.22%. Found: C, 66.23; H, 5.65; N, 6.07%.

4.1.2. (±)-Diethyl 5-benzyl-3,6-dioxo-2,3,5,6-tetrahydro-1*H*-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-3a,4-dicarboxylate 2a. A solution of the diazoketoester **4a** (0.440 g, 0.92 mmol) in toluene (10 mL) was refluxed for 40 min in the presence of $Rh_2(OAc)_4$ (0.013 g, 0.029 mmol). The solvent was evaporated and the residue gave, after flash chromatography (light petroleum ether/ethyl acetate 7:3), the *dicarboxylate* **2a** (0.269 g, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.61 (t, 3H, J=8.0 Hz), 1.21 (t, 3H, J=8.0 Hz), 2.74–2.98 (m, 2H), 3.46 (dq, 1H, J=8.0, 4.0 Hz), 3.61 (dq, 1H, J=8.0, 4.0 Hz), 3.76 (dt 1H, J=10.0, 4.0 Hz), 3.90 (dt, 1H, J=10.0, 5.7 Hz), 4.04 (AB system, 1H), 4.10–4.28 (m, 2H), 5.15 (s, 1H), 5.82 (AB system, 1H), 6.84 (d, 1H, J=8.4 Hz), 6.90 (t, 1H, J=8.1 Hz), 7.27–7.35 (6H, m), 8.29 (1H, dd, J=8.1, 1.8 Hz). ^{13}C NMR ($CDCl_3$): δ 13.1, 14.0, 33.0, 44.4, 55.41, 61.8, 63.2, 64.4, 77.9, 113.7, 118.3, 119.6, 127.5, 128.2, 129.6, 132.6, 135.2, 136.4, 142.1, 165.6, 167.5, 168.3, 201.8. IR (Nujol): 2929, 1773, 1731, 1626, 1492, 1478, 1453, 1372, 1241, 1153, 1020, 750, 704 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 5.82; N, 6.22%. Found: C, 66.42; H, 5.59; N, 5.97%.

4.1.3. (±)-3-Benzyl-1-(4-diazo-4-ethoxycarbonyl-3-oxobutyl)-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid (−)-menthyl ester 4b. To a stirred solution of (±)-3-benzyl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester (0.275 g, 0.85 mmol), and 3-oxo-pent-4-enoic acid (−)-menthyl ester (0.236 g, 0.93 mmol), in CH_2Cl_2 (5 mL), two drops of aqueous 50% HCl were added and stirred at room temperature for 2 days. The solvent was evaporated and to the residue a solution of tosyl azide (0.25 g, 1.26 mmol) and Et_3N (0.2 mL, 1.42 mmol) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (hexanes/ethyl ether 8:2), the *diazo compound* **4b** (0.355 g, 71.7%), yellow crystals, mp 41–43 °C (mixture of diastereomers). ^{1}H NMR ($CDCl_3$): δ 0.77 (d, 3H, J=7.8 Hz), 0.87–0.93 (m, 6H), 0.97–1.01 (m, 1H), 1.14 (t, 3H, J=7.8 Hz), 1.09–1.25 (m, 1H), 1.32–1.56 (m, 3H), 1.68–1.83 (m, 3H), 2.0–2.04 (m, 1H), 2.92–3.04 (m, 1H), 3.15–3.28 (m, 1H), 3.57–3.73 (m, 2H), 4.00–4.10 (m, 2H), 4.24 (AB system, 1H), 4.77 (4.78) (dt, 1H, J=10.2, 5.0 Hz), 5.14 (5.16) (s, 1H), 5.47 (5.52) (AB system, 1H), 6.73 (dd, 1H, J=8.6, 2.0 Hz), 6.87 (t, 1H, J=8.3 Hz), 7.26–7.41 (m, 6H), 7.99 (d, 1H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$): δ 13.9, 16.4, 20.6, 21.8 (21.9), 23.4, 26.4, 31.3, 33.9, 38.8 (38.8), 40.9, 43.8 (43.9), 48.6 (48.7), 61.7, 73.0 (73.1), 75.8, 111.7, 117.0, 118.8, 127.5, 127.4, 128.3, 128.4, 128.7, 129.3, 133.7, 136.3, 145.3, 160.5, 162.7, 190.4 (190.5). IR (Nujol): 2957, 2870, 2136, 1742, 1710, 1658, 1606, 1493, 1476, 1455, 1423, 1370, 1303, 1214, 1133, 999, 736, 701 cm^{-1}. Anal. Calcd for $C_{33}H_{40}N_4O_6$: C, 67.33; H, 6.85%; N, 9.52. Found: C, 67.24; H, 6.64; N, 9.27%.

4.1.4. (−)-Menthyl (±)-5-benzyl-3,6-dioxo-2,3,5,6-tetrahydro-1*H*-4*H*-pyrrolo[1,2-*a*][1,4]benzo diazepine-4-carboxyethyl-3a-carboxylate 2b. A solution of the diazoketoester **4b** (0.840 g, 1.42 mmol) in toluene (15 mL) was refluxed for 40 min in the presence of $Rh_2(OAc)_4$ (0.016 g, 0.036 mmol). The solvent was evaporated and the residue gave, after flash chromatography (hexanes/Et_2O 1:1), the *dicarboxylate* **2b** (0.568 g, 71%), white crystals, mp 44–46 °C (mixture of diastereomers). ^{1}H NMR ($CDCl_3$): δ 0.51 (d, 3H, J=7.8 Hz), 0.59 (dt, 3H, J=7.8, 3.0 Hz), 0.69 (dd, 2H, J=7.8, 2.8 Hz), 0.75–1.02 (m, 6H), 1.23–1.40 (m, 3H), 1.58–1.76 (m, 3H), 1.95–2.04 (m, 1H), 2.68–2.98 (m, 2H), 3.43–3.67 (m, 2H), 3.74–3.85 (m, 2H), 4.02 (4.04) (AB system, 1H), 4.53–4.70 (m, 1H), 5.13 (5.14) (s, 1H), 5.90 (5.92) (AB system, 1H), 6.81 (d, 1H, J=9.6 Hz), 6.90 (t, 1H, J=8.3 Hz), 7.13–7.46 (m, 6H), 8.31 (8.42) (dd, 1H, J=9.6, 1.6 Hz). ^{13}C NMR ($CDCl_3$): δ 13.1 (13.2), 15.4, 16.0, 20.6 (20.7), 21.7 (21.8), 22.7 (23.2), 25.3, 26.4, 29.6, 31.2 (31.3), 33.0, 33.7 (33.9), 39.8 (40.3), 44.3 (44.5), 46.7 (46.9), 55.3 (55.9), 61.6 (61.7), 64.2 (64.6), 77.6 (77.7), 77.8 (77.9), 113.0 (113.1), 118.2 (118.3), 119.3 (119.6), 127.5, 128.1 (128.4), 129.6 (129.7), 132.5 (132.6), 135.3 (135.6), 136.5 (136.6), 141.9 (142.1), 165.7 (165.9), 167.4 (167.6), 201.9 (202.4). IR ($CHBr_3$): 3406, 1725, 1623, 1452, 1374, 1371, 1244, 1142, 748 cm^{-1}. Anal. Calcd for $C_{33}H_{40}N_2O_6$: C, 70.69; H, 7.19; N, 5.00%. Found: C, 70.44; H, 7.05; N, 4.77%.

4.1.5. (±)-5-(3-Benzyl-4-oxo-2-phenyl-3,4-dihydro-2*H*-quinazolin-1-yl)-2-diazo-3-oxo-pentanoic acid (−)-menthyl ester 4c. To a stirred solution of (±)-3-benzyl-2-phenyl-2,3-dihydro-1*H*-quinazolin-4-one (1.30 g, 4.14 mmol), and 3-oxo-pent-4-enoic acid (−)-menthyl ester (1.15 g, 4.56 mmol), in CH_2Cl_2 (15 mL), few drops of aqueous 50% HCl were added and stirred at room temperature for 3 days. The solvent was evaporated and to the residue a solution of tosyl azide (1.22 g, 6.2 mmol) and Et_3N (1.03 mL,

7.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (hexanes/ethyl acetate 8:2), the *diazo compound* **4c** (1.65 g, 70.5%), yellow crystals, mp 51–53 °C (mixture of diastereomers). ^{1}H NMR ($CDCl_3$): δ 0.76 (d, 3H, J=7.8 Hz), 0.87–0.93 (m, 7H), 0.9–1.13 (m, 2H), 1.21–1.83 (m, 5H), 1.98–2.05 (m, 1H), 2.74–2.86 (m, 1H), 3.11–3.22 (m, 1H), 3.34–3.58 (m, 2H), 3.65 (AB system, 1H), 4.76 (ddt, 1H, J=10.2, 2.6, 2.3 Hz), 5.58 (5.59) (s, 1H), 5.62 (5.63) (AB system, 1H), 6.61 (6.62) (d, 1H, J=9.0 Hz), 6.86 (t, 1H, J=8.3 Hz), 7.25–7.38 (m, 11H), 8.06 (8.07) (d, 1H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$): δ 16.4, 20.6, 21.9, 23.4, 26.4, 31.3, 33.9, 38.1, 40.9, 43.1 (43.2), 46.8 (46.9), 75.7 (75.8), 112.1, 116.6, 118.1, 126.5, 127.4, 128.1, 128.5, 128.7, 128.9, 129.1, 133.8, 136.5, 138.4 (138.5), 145.2, 160.5, 162.2, 190.31. IR (Nujol): 2925, 2134, 1713, 1654, 1605, 1457, 1376, 1303, 1132, 1042, 996, 700 cm^{-1}. Anal. Calcd for $C_{36}H_{40}N_4O_4$: C, 72.95; H, 6.80; N, 9.45%. Found: C, 73.24; H, 6.65; N, 9.65%.

4.1.6. (−)-Menthyl-(±)-5-benzyl-3,6-dioxo-4-phenyl-2,3,5,6-tetrahydro-1*H*-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-3a-carboxylate 2c. A solution of the diazoketoester **4c** (0.620 g, 1.02 mmol) in toluene (15 mL) was refluxed for 40 min in the presence of $Rh_2(OAc)_4$ (8.8 mg, 0.020 mmol). The solvent was evaporated and the residue gave, after flash chromatography (hexanes/Et_2O 1:1), the *carboxylate* **2c** (0.49 g, 83%), white crystals, mp 61–63 °C (mixture of diastereomers). ^{1}H NMR ($CDCl_3$): δ 0.40 (d, 1H, J=7.1 Hz), 0.59 (t, 2H, J=7.1 Hz), 0.66–1.03 (m, 9H), 1.25–1.79 (m, 6H), 2.37–2.53 (m, 1H), 3.50–3.56 (m, 1H), 3.57 (AB system, 1H), 4.43–4.53 (m, 1H), 4.70 (AB system, 2H), 4.79 (s, 1H), 5.35 (5.39) (s, 1H), 6.90–7.06 (m, 4H), 7.10–7.29 (m, 8H), 7.43–7.49 (m, 1H), 8.72 (t, 1H, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 15.1 (15.9), 20.6 (20.8), 21.7 (21.8), 23.4, 26.2, 29.6, 30.9 (31.2), 33.8 (33.9), 34.6 (34.9), 39.5 (39.9), 44.4 (44.6), 46.4 (46.7), 54.3 (55.0), 66.9 (67.0), 78.5 (78.7), 113.5 (113.8), 119.2, 119.5, 126.9 (127.0), 127.9 (128.0), 128.1 (128.2), 128.8, 129.2, 129.5, 132.6 (132.8), 136.1 (136.2), 136.8, 136.9 (137.0), 165.8 (165.9), 166.0 (166.1), 205.5. IR (neat): 2956, 2869, 1770, 1732, 1617, 1492, 1478, 1451, 1379, 1307, 1153, 949, 749, 700 cm^{-1}. Anal. Calcd for $C_{36}H_{40}N_2O_4$: C, 76.57; H, 7.14; N, 4.96%. Found: C, 76.34; H, 6.95; N, 5.17%.

4.1.7. (±)-3-Benzyl-5,7-dichloro-1-(4-diazo-4-ethoxycarbonyl-3-oxo-butyl)-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester 4d. To a stirred solution of (±)-3-benzyl-5,7-dichloro-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester (1.32 g, 3.36 mmol), and 3-oxo-pent-4-enoic acid ethyl ester (0.936 g, 6.6 mmol), in CH_2Cl_2 (20 mL), few drops of aqueous 50% HCl were added and stirred at room temperature for 9 days. The solvent was evaporated and to the residue a solution of tosyl azide (0.99 g, 5.0 mmol) and Et_3N (0.90. mL, 6.6 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (petroleum ether/ethyl acetate 7:3), the *diazo compound* **4d** (1.43 g, 77.9%) as a yellow oil. ^{1}H NMR: δ 1.18 (t, 3H, J=8.0 Hz), 1.28 (t, 3H, J=8.0 Hz), 2.95–3.16 (m, 2H), 3.59 (t, 2H, J=6.3 Hz), 4.09 (q, 2H, J=8.0 Hz), 4.24 (AB system, 1H), 4.27 (q, 2H, J=8.0 Hz), 5.14 (s, 1H), 5.48 (AB system, 1H), 6.70 (d, 1H, J=0.2 Hz), 6.90 (d, 1H, J=0.2 Hz), 7.27–7.35 (5H, m). ^{13}C NMR ($CDCl_3$): δ 13.9, 36.5, 44.4, 48.4, 61.5, 62.1, 72.2, 111.0, 113.2, 122.3, 127.7, 128.4, 128.5, 136.0, 137.3, 138.7, 159.6, 160.8, 168.7, 190.0. IR (neat): 2923, 2854, 2152, 1736, 1698, 1671, 1643, 1586, 1452, 1382, 1316, 1249, 1217, 1142, 1087, 1056, 1021, 835, 746, 726, 696 cm^{-1}. Anal. Calcd for $C_{25}H_{24}Cl_2N_4O_6$: C, 54.85; H, 4.42; Cl, 12.95; N, 10.24%. Found: C, 55.03; H, 4.25; Cl, 12.78; N, 9.97%.

4.1.8. (±)-Diethyl 5-benzyl-3,6-dioxo-7,9-dichloro-2,3,5,6-tetrahydro-1*H*-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-3a,4-dicarboxylate 2d. A solution of the diazoketoester **4d** (0.290 g, 0.52 mmol) in toluene (8 mL) was refluxed for 40 min in the presence of $Rh_2(OAc)_4$ (6.8 mg, 0.015 mmol). The solvent was evaporated and the residue gave, after flash chromatography (hexanes/Et_2O 1:1), the *dicarboxylate* **2d** (0.198 g, 70%), white crystals, mp 128–130 °C. ^{1}H NMR: δ 0.81 (t, 3H, J=8.0 Hz), 1.29 (t, 3H, J=8.0 Hz), 2.83–2.94 (m, 1H), 3.60 (q, 1H, J=8.0 Hz), 3.70 (q, 1H, J=10.0 Hz), 3.84–3.92 (m, 1H), 3.96 (AB system, 1H), 4.20–4.33 (m, 2H), 5.04 (s, 1H), 5.69 (AB system, 1H), 6.74 (d, 1H, J=3.0 Hz), 6.94 (d, 1H, J=3.0 Hz), 7.26–7.36 (5H, m), 7.47 (d, 2H, J=7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 13.2, 14.0, 32.5, 45.2, 53.8, 62.26, 62.3, 63.8, 79.3, 111.5, 120.5, 128.2, 128.3, 129.5, 135.4, 136.4, 136.9, 143.6, 165.4, 165.8, 167.3, 199.9. IR (neat): 2923, 2853, 1771, 1737, 1666, 1582, 1438, 1408, 1240, 1140, 1053, 1021, 827, 753, 712, 656 cm^{-1}. Anal. Calcd for $C_{25}H_{24}Cl_2N_2O_6$: C, 57.81; H, 4.66; Cl, 13.65; N, 5.39%. Found: C, 57.62; H, 4.59; Cl, 13.48; N, 5.12%.

4.1.9. (±)-5-(3-Benzyl-4-oxo-2-phenyl-3,4-dihydro-2*H*-quinazolin-1-yl)-2-diazo-3-oxo-pentanoic acid ethyl ester 4e. To a stirred solution of (±)-3-benzyl-2-phenyl-2,3-dihydro-1*H*-quinazolin-4-one (0.860 g, 2.73 mmol), and 3-oxo-pent-4-enoic acid ethyl ester (0.77 g, 5.46 mmol), in CH_2Cl_2 (15 mL), few drops of aqueous 50% HCl were added and stirred for 3 days at room temperature. The solvent was evaporated and to the residue a solution of tosyl azide (0.806 g, 4.09 mmol) and Et_3N (0.76 mL, 5.46 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. After the addition was complete, the solution was stirred at room temperature overnight. The solvent was evaporated and the residue gave, after flash chromatography (hexanes/ethyl acetate 8:2), the *diazo compound* **4e** (0.874 g, 66.4%), as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J=8.0 Hz), 2.78–2.87 (m, 1H), 3.09–3.20 (m, 1H), 3.36–3.56 (m, 2H), 3.63 (AB, 1H), 4.21 (q, 2H, J=8.0 Hz), 5.59 (s, 1H), 5.63 (AB, 1H), 6.62 (d, 1H, J=9.0 Hz), 6.84 (t, 1H, J=8.3 Hz), 7.25–7.33 (m, 11H), 8.06 (dd, 1H, J=8.3, 1.3 Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 37.9, 42.9, 46.8, 61.3, 75.6, 76.0, 112.0, 116.5, 118.0, 126.4, 127.3, 128.0, 128.4, 128.6, 128.8, 128.9, 133.7, 136.4, 138.4, 145.1, 160.7, 162.1, 190.1. IR (neat): 2924, 2854, 2125, 1716, 1650, 1601, 1464, 1455, 1397, 1301, 1227, 1177, 998, 752, 700 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61%. Found: C, 69.92; H.55; N, 11.78%.

4.1.10. (±)-Ethyl 5-benzyl-3,6-dioxo-4-phenyl-2,3,5,6-tetrahydro-1*H*-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepine-

3a-carboxylate 2e. A solution of the diazoketoester **4e** (0.210 g, 0.43 mmol) in toluene (7 mL) was refluxed for 5 min in the presence of $Cu(acac)_2$ (3.5 mg, 0.013 mmol). The solvent was evaporated under reduced pressure and the residue gave, after flash chromatography (hexanes/ethyl acetate 8:2), the *carboxylate* **2e** (0.158 g, 80.2%), white crystals, mp 160–161 °C. ^{1}H NMR: δ 0.92 (t, 3H, J=8.0 Hz), 1.59–1.73 (m, 1H), 2.43–2.53 (m, 1H), 3.51–3.63 (m, 1H), 3.81 (dq, 1H, J=8.0, 2.7 Hz), 4.04 (dq, 1H, J=8.0, 2.7 Hz), 4.64 (AB system, 1H), 4.87 (AB system, 1H), 5.41 (s, 1H), 6.86 (d, 1H, J=8.0 Hz), 6.93 (d, 2H, J=8.0 Hz), 7.01 (t, 1H, J=8.3 Hz), 7.13–7.30 (m, 9H), 7.45 (dt, 1H, J=9.0, 1.7 Hz), 8.70 (dd, 1H, J=9.0, 1.7 Hz). ^{13}C NMR ($CDCl_3$): δ 13.7, 34.7, 44.2, 54.6, 62.5, 66.9, 78.7, 113.6, 119.2, 119.3, 127.1, 128.0, 128.2, 128.8, 129.4, 132.9, 135.9, 136.4, 136.6, 144.4, 165.4, 165.8, 166.3, 205.3. IR (Nujol): 2924, 2853, 1766, 1729, 1617, 1491, 1452, 1374, 1241, 1153, 1019, 752, 701 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16%. Found: C, 73.74; H, 5.49; N, 6.32%.

4.1.11. Crystal data and structure refinement for compound 2e. Suitable crystals for X-ray structure determination of compound **2e** were obtained by recrystallization from ethyl acetate/light petroleum ether 10:1. The substance ($C_{28}H_{26}N_2O_4$, M_r=454) crystallized in the monoclinic space group $P2_1/c$, a=15.107(1), b=10.3999(9), c=14.662(1)Å; α=90°, β=99.105(1)°, γ=90°; V=2274.6(4) Å^3, Z=4, D_{calcd}=1.327 g/cm^3, F (000)=960, T=150 K; crystal size 0.25×0.35×0.40 mm, θ=3–27°, reciprocal space explored: full sphere, reflections collected=18,950, independent reflections=5352 [R_{int}=0.0311], completeness to θ=27°: 100%, max. and min. transmissions: 1.000 and 0.689, refinement method: full-matrix least-squares on F^2, data=5352, restrains=0, parameters=411, goodness-of-fit on F^2=0.972, final R indices [$I>2\sigma(I)$]: R^1=0.037, wR^2=0.035, R indices (all data, F^2): R^2=0.054, wR^2=0.074, largest diff. peak and hole=0.310(109) and −0.320(109) eÅ^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (deposition number: CCDC 648,015).

4.1.12. (±)-5-Benzyl-7,9-dichloro-10c-hydroxymethyl-1,2,2a,4a,5,10c-hexahydro-3-oxa-5,10b-diaza-benzo[*f*]-cyclopenta[*cd*]azulene-4,6-dione 7. To a solution of **2d** (0.100 g, 0.19 mmol), in anhydrous MeOH (5 mL), $NaBH_4$ (0.77 g, 0.57 mmol) was added and the resulting mixture stirred at room temperature under nitrogen for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (hexanes/ethyl acetate 1:1), to afford the *tetracyclic lactone* **7** (0.063 g, 73.7%), white crystals, mp 230–231 °C. ^{1}H NMR: δ 2.0–2.09 (m, 1H), 2.23–2.29 (m, 1H), 2.74 (dt, 1H, J=9.0, 2.7 Hz), 3.12 (q, 1H, J=9.0 Hz), 3.62–3.69 (m, 1H), 3.79 (AB system, 1H), 4.06 (AB system, 1H), 4.08–4.15 (m, 1H), 4.30 (s, 1H), 4.31 (AB system, 1H), 5.69 (AB system, 1H), 6.77 (s, 1H,), 7.21–7.45 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 29.7, 31.7, 43.1, 49.4, 50.4, 69.3, 75.6, 77.1, 80.6, 117.9, 126.4, 126.6, 127.8, 128.6, 128.8, 135.6, 136.4, 137.5, 144.4, 165.8, 171.2. IR (Nujol): 3406, 2923, 2853, 1780, 1645, 1577, 1463, 1376, 1253, 1107, 983, 827, 734 cm^{-1}. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_4$: C, 58.21; H, 4.19; Cl, 16.36; N, 6.47%. Found: C, 57.92; H, 4.01; Cl, 16.07; N, 6.71%.

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