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PAPER

1,3-Dipolar cycloadditions from tricyclic hemiaminals. Synthesis of the quinocarcin core through catalyst-free generation of azomethine ylides†

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The generation of azomethine ylides from the readily accessible hemiaminals **3** and **8** or from iminium salt **10** was studied. Compounds **8** gave *anti*- and *syn*-cycloadducts containing the quinocarcin core through a catalyst-free dehydration process.

Introduction

1,3-Dipolar cycloaddition (1,3-DPC) reactions using azomethine ylides as 1,3-dipolar reactive intermediates are powerful tools for the synthesis of substituted pyrrolidine rings. Common methods for the *in situ* generation of these unstable species are: a) proton abstraction or decarboxylation in imino derivatives of α-amino acids promoted by Lewis acids, bases, organocatalysts, or dehydrating agents; b) thermolysis or photolysis of aziridines; and c) dehydrohalogenation or desilylation of iminium salts.[1–5] Other compounds, such as *N*-methoxymethylaminomethyl trimethylsilanes are azomethine ylide equivalents.[6]

Tetrahydroisoquinoline antitumour antibiotics[7,8] exhibit a piperazine moiety and a bicyclic isoquinoline framework where the benzene ring may be a phenol, a hydroquinone, or a quinone. This skeleton, which is common to the whole group, is fused to a pyrrolidine at positions 1–3 in the quinocarcin subfamily. Archetypal members of this subfamily are quinocarcin and its synthetic aminonitrile analogue DX-52-1, lemonomycin, and cyanocycline A (Fig. 1). Quinocarcin is also known as quinocarmycin and its more stable citrate salt as KW2152. Most of these compounds have shown an interesting antineoplastic activity,[9–11] and several synthetic approaches to them have been reported.[12–14]

In the last years we have developed a simple and efficient method to achieve the preparation of tetrahydropyrazino [1,2-*b*]isoquinoline-1,4-diones,[15] which were used as building blocks in the synthesis of compounds with the saframycin subfamily skeleton.[16,17] The key step to afford the pentacyclic system was the partial reduction of the C(1)-carbonyl group to give hemiaminal intermediates, which were precursors of the iminium species involved in Pictet–Spengler type cyclizations.[18] We study here the dehydration of these hemiaminals to give azomethine ylides and their use to efficiently synthesize the quinocarcin core through 1,3-DPC reactions.

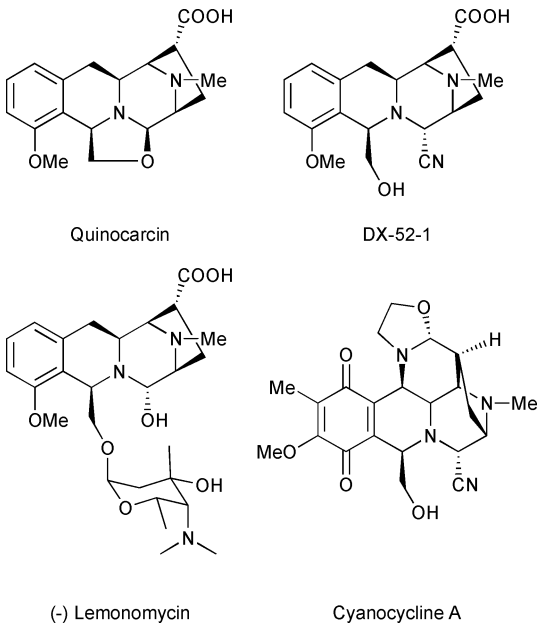

Fig. 1 Examples of natural and synthetic members of the quinocarcin and naphthyridinomycin subfamilies.

Results and discussion

Hemiaminals **3** were obtained by the chemoselective reduction of the C-1 carbonyl group in compounds **2**, that were derived from compounds **1** according to previously reported procedures (Scheme 1).[15,19] Unfortunately, we found that these hemiaminals were not suitable for the generation of azomethine ylides of type **A** through water elimination because of competitive reactions. For instance, attempts to condense compound **3a** with acrolein through the generation of ylide **A**, obtained by thermal dehydration, did not give the desired cycloadduct, affording instead enamide **4**. A similar result was obtained when the generation of ylide **A** was attempted from **3c**, giving enamides **5** and **6** through a two-step dehydration mechanism.

These results moved us to explore alternative 1,3-DPC reactions involving 11,11a-unsaturated hemiaminals **8a**, **8b** and **8d** and

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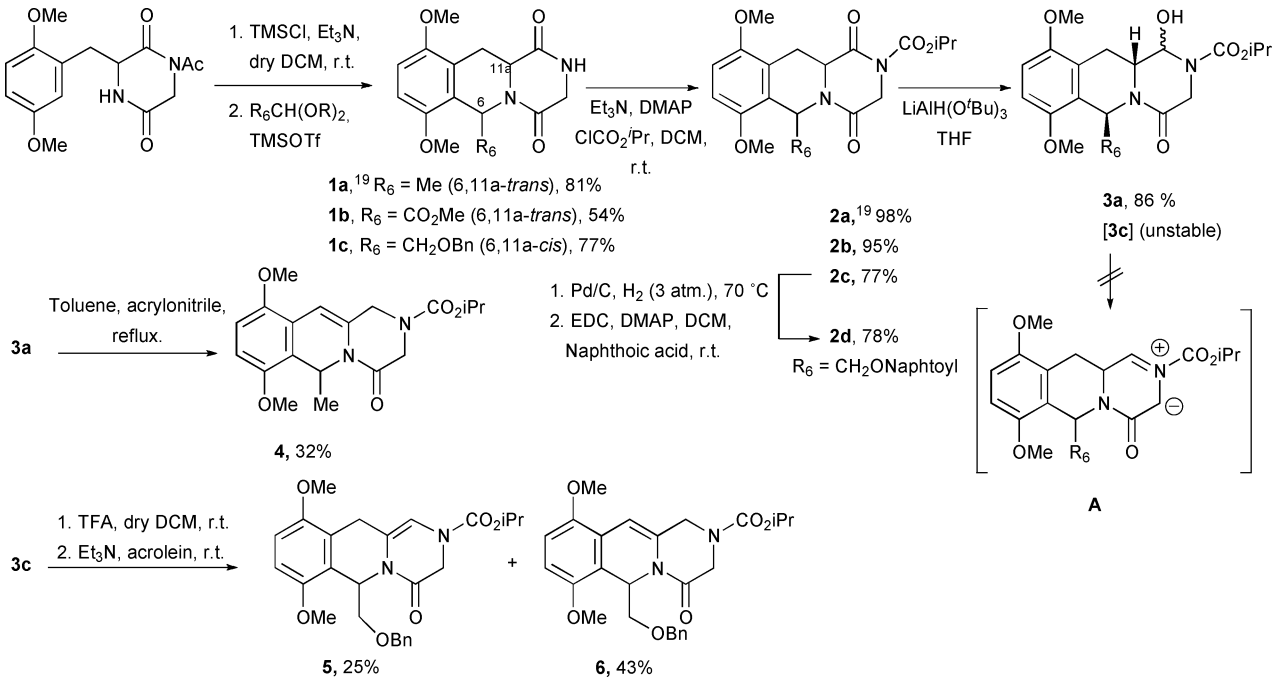


Scheme 1 Synthesis and reactivity of saturated hemiaminals **3**.

iminium salt **10**. Compounds **8** were obtained from **2** by a bromination–dehydrohalogenation reaction tandem with NBS and AIBN in CCl_4, followed by treatment of enamides **7** with $LiAlH(O^tBu)_3$ (Scheme 2). Hydrolytic *N*-deprotection of **8a** gave **9**, which was converted to the iminium salt **10** by reaction with iodomethane in refluxing methanol. The attempted 1,3-DPC reaction between **10** and diethyl acetylenedicarboxylate in the presence of Et_3N was expected to afford a cycloadduct of azomethine ylide **B** (compound **11**) but instead gave a complex mixture from which the only isolated product seemed to arise from the generation of azomethine ylide **C** by a mechanism involving an initial proton abstraction at the exocyclic methyl group as suggested by ^1H–^{13}C NMR correlation studies, although this compound could not be isolated in a pure state. We reasoned that 1,3-DPC reactions starting from hemiaminals **8**, lacking the exocyclic methyl substituent, should not suffer from this problem. Gratifyingly, this expectation was borne out by experiment and, furthermore, we found that the generation of the azomethine ylides **D** from **8** does not require addition of any catalyst, since it proceeds through spontaneous dehydration in refluxing toluene.

The reactions of **8** with activated alkenes or alkynes gave the *exo* adducts **12–20** or their dehydro analogues **21–25**, respectively. The *anti*-isomers, which resulted from the approach of the dipolarophile from the least hindered face of the azomethine ylide, were the major products in most cases and, not unexpectedly and, a higher bulk of the R_6 substituent in **8b** and **8d** improves this selectivity (Scheme 3). We obtained the best results when reactions were carried out at 120 °C in a sealed tube, although for dipolarophiles with a high boiling point such as acrylonitrile or DEAD the reactions can be performed under standard reflux conditions.

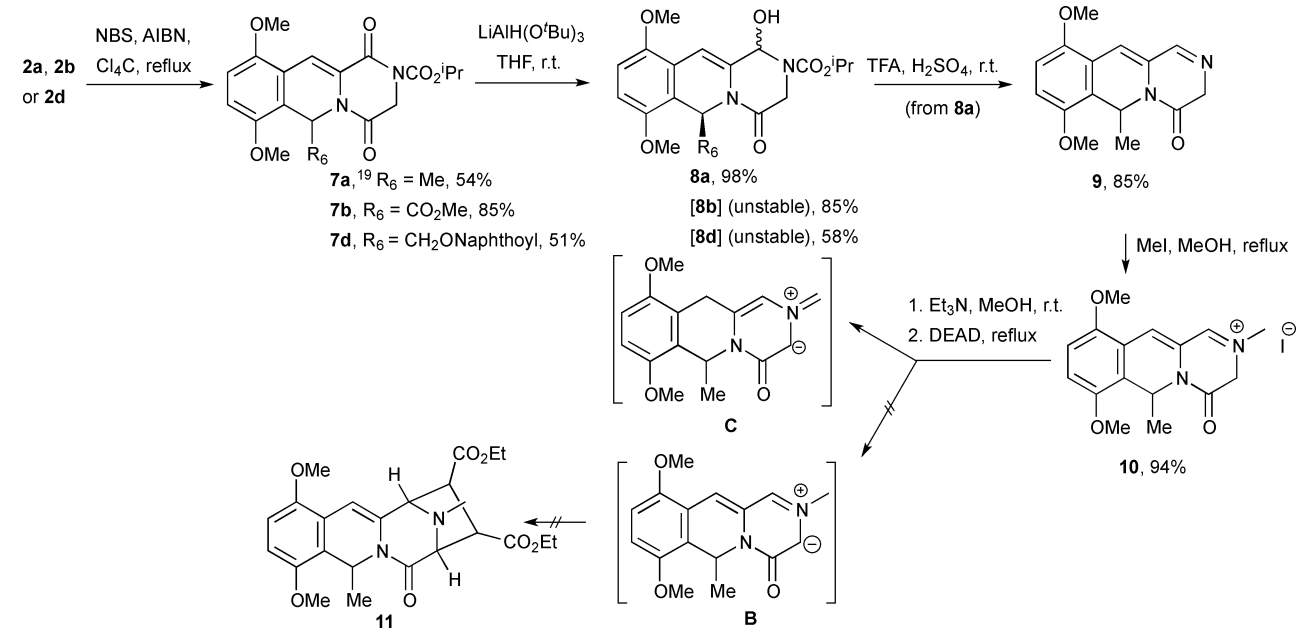
The use of microwave irradiation decreased the reaction time, as compared to conventional heating, but gave similar yields, and the isomer relationship whether the reactions were done in a sealed tube or MW irradiation conditions was always in the same order as when the reaction was performed in reflux conditions (Table 1).

Table 1 Assayed experimental conditions of 1,3-DPC reactions with hemiaminals **8**

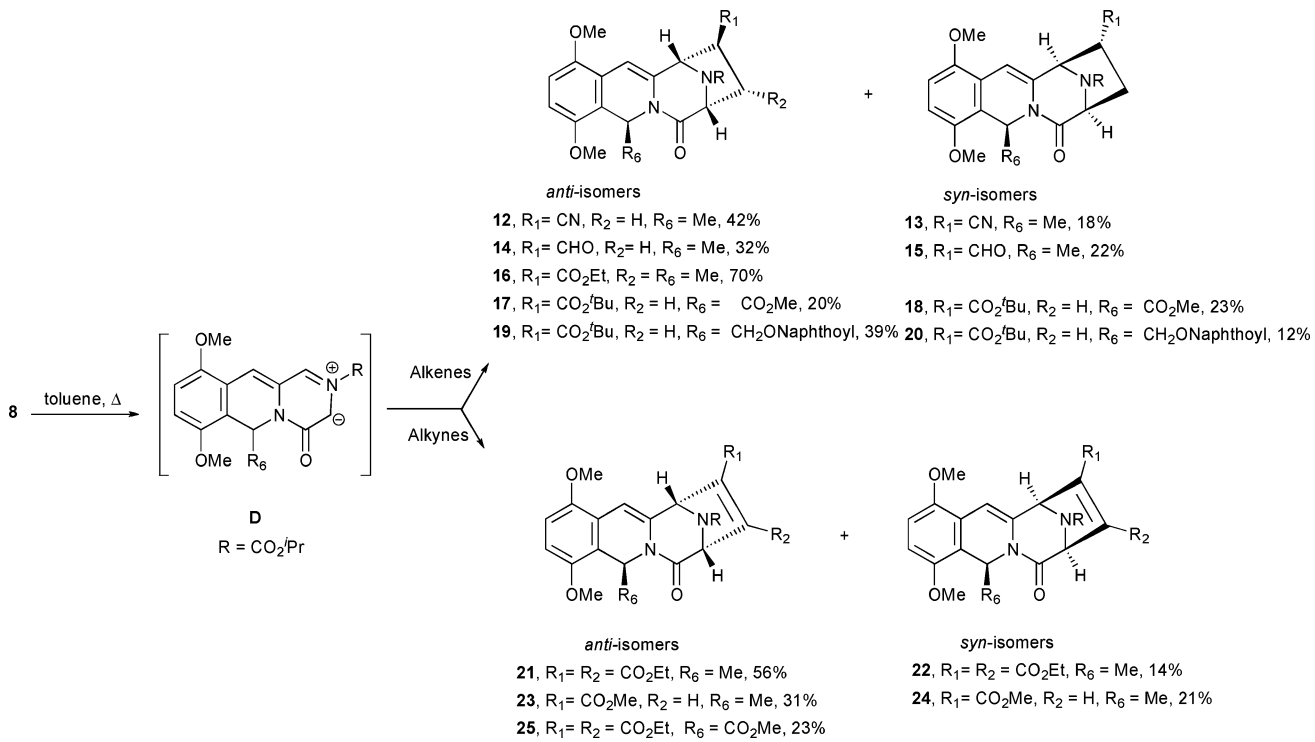
Entry	Compounds	*anti*/*syn* ratio	Overall yield (%)
1	**12** and **13**	7/3	60[a] 62[b] 54[c]
2	**14** and **15**	6/4	11[a] 54[b]
3	**16**	1/0	70[b]
4	**17** and **18**	8/2	70[b]
5	**19** and **20**	10/3	51
6	**21** and **22**	6/4	52[b]
7	**23** and **24**	1/1	58[b]
8	**25**	1/0	23[b]

[a] Reflux conditions. [b] Sealed tube. [c] Microwave.

The stereochemical assignment of *anti* and *syn* isomers was based on a correlation between the H-6 proton and CH proton of the isopropyl group in an NOE experiment for the *syn* isomer. The *exo* configuration for the R_1 group in compounds **12–20** was established based on the NOE effect between H-1 and H-12 protons and H-11 and H-12. This diastereoselection, giving compounds with the quinocarcin configuration as the minor products, is in accordance with the findings of Williams's group in the total syntheses of (±)-quinocarcinamide and (–)-tetrazomine.[20,21] In this work analogues of azomethine ylides **D** were generated through the NBS-mediated oxidation of tetrahydropyrazino[1,2-*b*]isoquinoline-4-ones followed by base-promoted deprotonation with simultaneous bromide elimination. The structural study of compounds **12–24** (and also of some of their precursors) was



Scheme 2 Synthesis of iminium salt **10** and 1,3-DPC reactions.



Scheme 3 1,3-DPC reactions with unsaturated hemiaminals **8**.

complicated by the presence of the carbamate group. Carbamates usually contain significant populations of rotamers,[22] leading to the presence of two or more sets of peaks in ^{1}H and ^{13}C NMR spectra of pure samples at ambient temperature. To demonstrate the presence of rotamers in our samples, we have studied the effect of temperature on the ^{1}H-NMR spectrum of compound **18** in $CDCl_3$. We have observed that at 40 °C, only one set of signals was observed, even though some of them were rather broad. A decrease of the temperature to 15 °C leads to clearly duplicated peaks, and this effect is even clearer at 5 °C. These findings confirm the existence of rotamers, and rule out the existence of diastereoisomers in compound **18** (see Supporting Information).

In conclusion, we have developed a new synthetic strategy that permits highly functionalized cycloadducts to be obtained from readily accessible hemiaminals **8** through a catalyst-free dehydration process.

Experimental

General experimental

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as KBr pellets or as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance-250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense) or a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) for the case of compound **13**. For compounds comprising mixtures of rotamers, only the data for major species are given. In some cases, the carbonyl group of the carbamate moiety gives very broad signals that are difficult to distinguish from the background,[23] but can be easily detected in the infrared spectrum. High resolution mass measurements were performed by the CAI de Espectrometria de Masas, Universidad Complutense, using an FTMS Bruker APEX QIV instrument. Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

One-pot synthesis of compounds 1

To a stirred solution of 1-acetyl-3-(2,5-dimethoxybenzyl)-piperazine-2,5-dione (3.26 mmol) in dry DCM (50 mL) were added TMSCl (4.9 mmol) and triethylamine (4.9 mmol) and the mixture was stirred under an argon atmosphere at room temperature for 1 h. Then, the corresponding dimethyl acetal (6.52 mmol) and TMSOTf (9.78 mmol) were added and this mixture was stirred for 12 h at room temperature or for an additional 48 h at reflux conditions (for compound **1b**). The reaction was quenched with a 10% aqueous solution of $NaHCO_3$ (50 mL) and extracted with DCM (30 mL×3). The combined extracts were washed with H_2O (20 mL) and with a saturated aqueous solution of NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*, to give a residue that was purified by flash column chromatography on silica gel.

(6*S,11a*S**)-Methyl 7,10-dimethoxy-1,4-dioxo-1,2,3,4,11,11a-hexahydro - 6*H* - pyrazino[1,2 - *b*]isoquinoline - 6 - carboxylate (1b).** Purification by flash chromatography on silica gel with methanol/dichloromethane (1 : 9) as eluent gave **1b** (54%) as a yellow solid. Mp 160–161 °C; IR ν_{max} (film): 1661, 1628 and 1563 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.74 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.45 (s, 1H), 6.08 (ws, 1H), 4.43 (dd, J = 11.7 and 4.6 Hz, 1H), 4.17 (d, J = 16.5 Hz, 1H), 4.07 (d, J = 16.5 Hz, 1H), 3.76 (s, 6H), 3.72 (s, 3H), 3.42 (dd, J = 17.5 and 4.6 Hz, 1H), 2.80 (dd, J = 17.5 and 11.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 169.5, 167.2, 161.9, 150.9, 150.4, 122.6, 120.1, 109.6, 108.4, 55.8, 55.7, 53.0, 52.9, 51.3, 44.8, 27.4. HRMS (negative ESI), m/z: Calcd for $C_{16}H_{18}N_2O_6$: 334.11649 (M^+). Found: 333.10921 (M^+ – 1). Anal. calcd. for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.05; H, 5.12; N, 7.98%.

General procedure for the synthesis of compounds 2a–c

A solution of compound **1** (9.1 mmol), triethylamine (54 mmol) and 4-dimethylaminopyridine (27 mmol) in dry DCM (140 mL) was cooled in ice water, and isopropyl chloroformate (18 mmol) was added dropwise. The solution was stirred under argon atmosphere for 16 h at room temperature and then, water (50 mL) was added. After extraction with DCM (20 mL × 3), the extracts were washed with HCl (25 mL × 3), H_2O (30 mL) and with saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue that was purified by flash column chromatography on silica gel.

(6*S,11a*S**)-Methyl 2-isopropoxycarbonyl-7,10-dimethoxy-1,4-dioxo-1,2,3,4,11,11a-hexahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-6-carboxylate (2b).** The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7 : 3) as eluent to give **2b** (95%) as a white solid. Mp 164–165 °C; IR ν_{max} (film): 2981, 1921, 1628 and 1501 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.82 (d, J = 9.0 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 6.48 (s, 1H), 5.13 (sept, J = 6.2 Hz, 1H), 4.66 (dd, J = 7.9 and 6.3 Hz, 1H), 4.54 (d, J = 17.2 Hz, 1H), 4.47 (d, J = 17.2 Hz, 1H), 3.82 (s, 6H), 3.76 (s, 3H), 3.31 (dd, J = 17.0 and 7.9 Hz, 1H), 3.20 (dd, J = 17.0 and 6.3 Hz, 1H), 1.37 (d, J = 6.2 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 169.5, 165.7, 163.3, 151.0, 150.7, 150.1, 122.4, 120.6, 110.2, 108.9, 72.5, 55.9, 54.8, 52.9, 50.6, 47.8, 24.5, 21.6. HRMS (negative ESI), m/z: Calcd for $C_{20}H_{24}N_2O_8$: 420.15327 (M^+). Found: 419.14599 (M^+ – 1). Anal. calcd. for $C_{20}H_{24}N_2O_8$: C, 57.14; H, 5.75; N, 6.66. Found: C, 56.85; H, 5.48; N, 6.21%.

(6*R,11a*S**)-2-Isopropoxycarbonyl-7,10-dimethoxy-6-naphthylcarbonyloxymethyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (2d).** To a solution of **2c** (400 mg, 0.83 mmol) was added Pd/C (66 mg) in ethanol (4 mL) and the mixture was stirred under hydrogen atmosphere (3 atm), at 70 °C, for 3.5 h. Then, the mixture was filtered through celite and the solvent was concentrated *in vacuo* to give an oil residue. The unpurified crude was used in the next step. A solution of this crude, EDC (2.3 mmol), 4-dimethylaminopyridine (1.21 mmol) and naphthoic acid (1.2 mmol) in dry DCM (20 mL) was stirred under argon atmosphere for 20 h at room temperature. Then the solvent was evaporated and the residue was dissolved in AcOEt (150 mL), the organic solution was washed with HCl 0.1 N (50 mL), $NaHCO_3$ (50 mL), H_2O (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue that was purified by flash column chromatography on silica gel with hexane/ethyl acetate mixture (8 : 2) as eluent to give **2d** as a brown oil (265 mg, 44%). IR ν_{max} (film): 2981, 1780, 1509 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.80 (d, J = 7.9 Hz, 1H), 8.19 (dd, J = 7.3 and 1.1 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.90 (dd, J = 7.3 and 1.7 Hz, 1H), 7.54 (m, 3H), 6.79 (m, 2H), 6.34 (dd, J = 9.0 and 3.3 Hz, 1H), 5.07 (sept, J = 6.2 Hz, 1H), 4.91 (dd, J = 11.6 and 9.0 Hz, 1H), 4.80 (dd, J = 11.4 and 5.0 Hz, 1H), 4.69 (dd, J = 11.6 and 3.3 Hz, 1H), 4.41 (d, J = 17.8 Hz, 1H), 4.29 (d, J = 17.8 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.52 (dd, J = 17.3 and 5.0 Hz, 1H), 2.95 (dd, J = 17.3 and 11.4 Hz, 1H), 1.33 (d, J = 6.2 Hz, 6H); ^{13}C NMR (63 MHz,

$CDCl_3$) δ: 167.2, 165.8, 162.5, 151.1, 151.0, 149.9, 133.7, 133.6, 131.3, 130.6, 128.5, 127.8, 126.4, 126.2, 125.6, 124.6, 122.9, 120.6, 109.4, 108.4, 72.4, 63.1, 55.7, 55.6, 53.5, 48.4, 47.6, 27.2, 21.6. HRMS (negative ESI), *m/z*: Calcd for $C_{30}H_{30}N_2O_8$: 546.20022 (M^+). Found: 545.19305 (M^+ - 1). Anal. calcd. for $C_{30}H_{30}N_2O_8$ C, 65.92; H, 5.53; N, 5.13; Found: C, 65.50; H, 5.46; N, 5.22%.

General procedure for the synthesis of hemiaminals 3 and 8

To a stirred solution of lithium tri-*tert*-butoxyaluminum hydride (8.12 mmol) in dry THF (50 mL) cooled in ice water was added a solution of compounds **2** or **7** (2.7 mmol) in dry THF, and the mixture was stirred under argon atmosphere at room temperature for 16 h. The reaction mixture was quenched by addition of ice, filtered over celite, and extracted with ethyl acetate. The organic phases were washed with H_2O and with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*.

(1*R,6*R**,11a*S** and 1*S**,6*R**,11a*S**)-1-Hydroxy-2-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,6,11,11a-hexahydropyrazino[1,2-*b*]isoquinolin-4-one (3a).** According to the general procedure compound **3a** (86%) was obtained as a crude product in a 7/3 diasteroisomer mixture. IR ν_{max} (film): 3325, 2979, 1704 and 1634 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.67 (s, 2H), 5.93 (q, J = 6.4 Hz, 1H), 5.84 (ws, 1H), 4.93 (sept, J = 6.1 Hz, 1H), 4.34 (m, 1H), 4.30 (d, J = 17.5 Hz, 0.3H), 4.02 (m, 2H), 3.78 (s, 4.2H), 3.76 (s, 1.8 H), 3.20 (dd, J = 17.2 and 8.0 Hz, 0.3H), 2.96 (dd, J = 17.2 and 7.5 Hz, 1H), 2.49 (m, 1H), 1.52 (d, J = 7.2, 2.1H), 1.40 (d, J = 6.5, 1.3H), 1.31 (d, J = 6.5, 6H), 1.27 (m, 6H), 1.20 (d, J = 6.0, 1.3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 176.8, 165.2, 163.0, 150.8, 150.3, 149.8, 149.2, 127.7, 126.5, 122.3, 121.5, 107.8, 107.7, 107.6, 76.3, 76.2, 70.1, 70.0, 55.5, 55.4, 52.6, 50.8, 44.8, 44.1, 43.9, 43.4, 23.8, 21.8, 18.9, 18.3. HRMS (negative ESI), *m/z*: Calcd for $C_{19}H_{26}N_2O_6$: 378.17909 (M^+). Found: 377.17181 ($M^+ - 1$).

2-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,6-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one (4)

Compound **3a** (0.26 mmol) was dissolved in toluene (5 mL) and acrylonitrile (5 eq) was added. The reaction was carried out in a sealed tube for 48 h at 120 °C. Then the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (7 : 3) as eluent to give the compound **4** (32%) as a yellow oil. IR ν_{max} (film): 2979, 1702 and 1648 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.71 (s, 2H), 6.23 (ws, 1H), 6.05 (q, J = 6.5 Hz, 1H), 4.95 (sept, J = 6.4 Hz, 1H), 4.71 (m, 1H), 4.54 (d, J = 18.4 Hz, 1H), 4.11 (d, J = 18.4 Hz, 1H), 3.96 (m, 1H), 3.81 (s, 6H), 1.28 (m, 3H), 1.27 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 163.4, 154.0, 148.8, 148.2, 128.8, 123.1, 119.1, 109.7, 109.5, 101.3, 69.7, 55.9, 55.6, 48.3, 44.4, 22.1, 18.8. HRMS (negative ESI), *m/z*: Calcd for $C_{19}H_{24}N_2O_5$: 360.16852 (M^+). Found: 383.15774 (M^+ + Na). Anal. calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.03; H, 6.42; N, 7.35%.

Synthesis of 5 and 6

To a solution of compound **3c** (140 mg, 0.3 mmol) in anhydrous DCM (3 mL) was added TFA (1.16 mL, 15 mmol). The reaction was stirred for 3.5 h at room temperature and, then the reaction was concentrated to dryness *in vacuo*. The residue was dissolved in anhydrous DCM (3 mL) and cooled in ice water. After addition of acrolein (0.4 mL, 6 mmol) and Et_3N (0.42 mL, 3 mmol) the mixture was stirred at room temperature for 3.5 h and extracted with AcOEt (20 mL × 2). The extracts were washed with NH_4Cl (30 mL), H_2O (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, that was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7 : 3) as eluent to give **5** as an orange solid (25%) and **6** as a yellow solid (43%).

6-Benzyloxymethyl-2-isopropoxycarbonyl-7,10-dimethoxy-2,3,6,11-tetrahydropyrazino[1,2-*b*]isoquinoline-4-one (5). Mp 64–65 °C; IR ν_{max}(film): 2980, 1649 and 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.19 (m, 5H), 6.63 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.31 (dd, J = 7.0 and 3.0 1H), 6.12 (ws, 0.7H), 6.00 (ws, 0.3H), 4.84 (sept, J = 6.5 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.45 (m, 2H), 4.33 (d, J = 12.0 Hz, 1H), 4.06 (d, J = 18.6 Hz, 1H), 3.89 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.37 (dd, J = 10.8 and 3.3 Hz, 1H), 1.17 (m, 6H). ^{13}C NMR (85 MHz, $CDCl_3$) δ: 164.6, 154.4, 149.6, 148.6, 138.6, 128.4, 127.9, 127.6, 120.9, 118.8, 116.2, 110.4, 109.7, 102.4, 72.5, 69.6, 68.9, 55.8, 55.5, 47.9, 46.6, 35.9, 21.8. HRMS (negative ESI), *m/z*: Calcd for $C_{26}H_{30}N_2O_6$: 466.21039 (M^+). Found: 489.19961 (M^+ + Na). Anal. calcd. for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.71; H, 6.23; N, 5.84%.

6-Benzyloxymethyl-2-isopropoxycarbonyl-7,10-dimethoxy-1,2,3,6-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one (6). Mp 64–65 °C; IR ν_{max} (film): 2934, 1649 and 1452 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.23–7.00 (m, 5H), 6.41 (m, 2H), 6.26 (m, 1H), 6.13 (ws, 0.7H), 6.00 (ws, 0.3H), 4.85 (sept, J = 5.2 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.51 (m, 1H), 4.34 (d, J = 11.9 Hz, 1H), 4.08 (d, J = 12.3 Hz, 1H), 3.92 (m, 2H), 3.64 (s, 3H), 3.62 (s, 3H), 3.60 (m, 1H), 3.35 (m, 1H), 1.19 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 164.3, 154.1, 150.5, 148.4, 140.5, 138.4, 138.2, 133.7, 128.8, 128.5, 128.3, 127.8, 127.7, 127.6, 127.3, 126.2, 119.2, 112.5, 111.7, 72.8, 69.7, 69.5, 62.1, 55.8, 55.6, 48.2, 47.2, 35.9, 31.6, 22.7, 22.2. Anal. calcd. for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.61; H, 6.19; N, 5.79%.

General procedure for compounds 7

A solution of **2a**, **2b** or **2d** (6.9 mmol), AIBN (0.69 mmol) and NBS (8.3 mmol) in CCl_4 (70 mL) was refluxed under an argon atmosphere for 16 h. The unreacted NBS was filtered from the cooled reaction, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel. Characterization data for one representative example are given here. For full data, see the Supporting Information.

2-Isopropoxycarbonyl-7,10-dimethoxy-6-naphtycarbonyloxymethyl-2,3-dihydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (7d). IR ν_{max} (film): 2360, 1717, 1489 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 8.88 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 7.2, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 7.4, 1H), 7.69 (s, 1H), 7.57 (m, 3H), 6.93 (d, J = 8.9, 1H), 6.84 (d, J = 8.9, 1H), 6.65 (dd, J = 7.8 and 3.5 Hz, 1H), 5.10 (sept, J = 6.2 Hz, 1H), 4.76 (d, J = 17.3 Hz, 1H), 4.58 (dd, J = 11.4 and 7.8 Hz, 1H), 4.41 (dd, J = 11.4 and 3.5 Hz, 1H), 4.16 (d, J = 17.3 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 1.33 (m,

6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 166.9, 162.8, 158.9, 151.6, 150.2, 149.3, 133.7, 133.6, 133.5, 131.4, 130.8, 128.4, 127.7, 126.1, 125.8, 125.7, 124.6, 119.7, 119.0, 114.5, 113.0, 111.0, 72.3, 63.6, 56.0, 55.8, 47.6, 47.5, 21.6. HRMS (negative ESI), *m/z*: Calcd for $C_{30}H_{28}N_2O_8$: 544.18457 (M^+). Found: 543.17958 (M^+ - 1). Anal. calcd. for $C_{30}H_{28}N_2O_8$: C, 66.17; H, 5.18; N, 5.14. Found: C, 66.50; H, 5.46; N, 5.24%.

7,10-Dimethoxy-6-methyl-3,6-dihydropyrazino[1,2-*b*]isoquinolin-4-one (9)

A solution of compound **8a** (100 mg, 0.26 mmol) in 5 mL of a mixture of TFA/H_2SO_4 (20 : 1) was stirred at room temperature for 16 h. Then the mixture was dropped over a saturated aqueous solution of $NaHCO_3$. The aqueous residue was extracted with dichloromethane (20 mL × 3) and the organic extracts were washed with H_2O and with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the unstable imine **9** (60 mg, 85%) as a brown oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.99 (ws, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 6.48 (s, 1H), 6.10 (q, J = 6.5 Hz, 1H), 4.69 (d, J = 23.2 Hz, 1H), 4.40 (d, J = 23.2 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 164.1, 155.4, 149.2, 148.9, 127.6, 124.3, 118.7, 111.8, 109.5, 108.2, 108.6, 56.0, 55.7, 44.0, 24.0, 19.7.

7,10-Dimethoxy-2,6-dimethyl-4-oxo-3,4-dihydro-6*H*-pyrazino[1,2-*b*]isoquinolinium iodide (10)

To a solution of unpurified compound **9** in anhydrous methanol (5 mL), methyl iodide (0.03 mL, 0.44 mmol) was added and the mixture was stirred at reflux for 2 h. Then the solvent was removed *in vacuo* to give **10** (50 mg, 94%) as a green oil. IR ν_{max} (film): 2933, 1575, 1489 and 1261 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.40 (s, 1H), 6.80 (m, 2H), 6.37 (q, J = 6.7 Hz, 1H), 4.33 (d, J = 19.2 Hz, 1H), 3.82 (m, 9H), 3.71 (d, J = 19.2 Hz, 1H), 1.52 (d, J = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 156.1, 149.7, 149.1, 145.6, 137.2, 126.3, 122.6, 120.2, 109.8, 108.9, 55.9, 46.6, 24.1, 18.5. Anal. Calcd for $C_{16}H_{19}IN_2O_3$: C, 46.39; H, 4.62; N, 6.76. Found: C, 46.23; H, 4.26; N, 6.45%.

General procedure for the 1,3-DPC reactions with hemiaminals 8

Compounds **8a**, **8b** or **8d** (0.26 mmol) were dissolved in toluene (5 mL) and the corresponding dipolarophile (alkene or alkyne) (5 eq) was added. The reaction was carried out in a sealed tube or, alternatively, refluxed for 48 h at 120 °C or under microwave heating at 140 °C for 2 h. Then the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel. Characterization data for the compounds arising from one representative cycloaddition are given here. For full data, see the Supporting Information.

Synthesis of compounds 12 and 13

The reaction of compound **8a** (100 mg, 0.26 mmol) and acrylonitrile (0.037 mL, 1.3 mmol) as described earlier, gave a mixture that was purified by column chromatography on silica gel with hexane/ethyl acetate (8 : 2) as eluent to give compounds **12** (42%) and **13** (18%) as brown oils.

(1*S,3*R**,12*S**,6*S**)-13-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carbonitrile (12).** IR ν_{max} (film): 3369, 2981, 1713 and 1692 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.72 (s, 2H), 6.21 (s, 1H), 6.00 (q, J = 6.4 Hz, 1H), 5.23 (s, 1H), 5.00 (sept, J = 6.1 Hz, 1H), 4.81 (d, J = 5.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.09 (dd, J = 9.2 and 4.0, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 1.30 (d, J = 6.1 Hz, 6H), 1.23 (d, J = 6.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.6, 154.2, 148.9, 148.1, 147.6, 132.4, 122.6, 120.1, 119.0, 109.9, 109.6, 100.5, 70.6, 61.3, 59.5, 55.9, 55.6, 44.5, 35.3, 34.0, 21.9, 19.1. HRMS (negative ESI), *m/z*: Calcd for $C_{22}H_{25}N_3O_5$: 411.17942 (M^+). Found: 410.17214 (M^+ -1). Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 64.18; H, 6.06; N, 10.15%.

(1*S,3*S**,12*R**,6*S**)-13-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carbonitrile (13).** IR ν_{max} (film): 3279, 1713 and 1489 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.72 (s, 2H), 6.25 (s, 1H), 5.88 (q, J = 6.3 Hz, 1H), 5.19 (s, 1H), 4.95 (sept, J = 6.3 Hz, 1H), 4.84 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.20 (m, 1H), 2.63 (m, 2H), 1.28 (m, 6H), 1.23 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.3, 148.8, 148.6, 130.9, 122.7, 120.0, 118.5, 110.3, 109.8, 100.8, 77.1, 70.5, 59.9, 56.0, 55.7, 44.2, 32.6, 21.9, 18.5. HRMS (negative ESI), *m/z*: Calcd for $C_{22}H_{25}N_3O_5$: 411.17942 (M^+). Found: 410.17214 (M^+ -1). Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 64.02; H, 5.87; N, 9.96%.

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