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Cascade and RCM syntheses of chiral tricyclic alkaloids from (*S*)-1,2,3,4-tetrahydro isoquinoline carboxylic acid

Daniele Muroni, Mauro Mucedda, Antonio Saba *

Dipartimento di Chimica, Facoltà di Scienze, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

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ABSTRACT

Concise syntheses of novel chiral pyrroloazacyclo and chiral tricyclic isoquinoline alkaloids, starting from the readily available (*S*)-1,2,3,4-tetrahydroisoquinoline carboxylic acid methyl ester, by utilizing cascade spiro-to fused and RCM protocols, are reported.

1. Introduction

Chiral pyrroloazacylo and chiral tricyclic isoquinoline alkaloids have been the subject of intense investigation, due to their important biological and therapeutic properties.[1] Recently, we have carried out concise and highly stereoselective syntheses of azabicyclic and tricyclic alkaloids, by using cascade cyclization processes[2] or ring-closing metathesis (RCM),[3] starting from simple and convenient starting materials.

In connection with our previous work, we herein report the syntheses of new medium-sized chiral azacyclic systems and chiral tricyclic isoquinolines performed with the aforementioned protocols, starting from the readily available (*S*)-1,2,3,4-tetrahydro isoquinoline carboxylic acid methyl ester **1**.

The cascade process is a powerful strategy for building complex molecules from relatively simple reagents, due to a combination of two or more distinct reactions into a single transformation.[4] Particularly, the formation of ammonium ylides generated by metallo carbenoids and their spontaneous Stevens [1,2]-shift[5] or [2,3]-sigmatropic rearrangement[6] has been shown to give very rapid access to nitrogen heterocycles with high stereoselectivity.

The diazoketoester **2**, bearing a diazo function at the appropriate position on the ester chain tethered to the tetrahydroisoquinoline nitrogen atom, has been selected as an appropriate carbenoid cyclization precursor (Scheme 1). Initiation of the cascade process is based upon diazo catalytic decomposition. As the nitrogen is part of a pre-existing ring system, an intramolecular carbenoid attack to this heteroatom is expected to furnish the transient spirocyclic ammonium ylide **3**.[7] Due to the presence of two possible migratory groups on the nitrogen atom, this intermediate could reasonably undergo two different [1,2]-shifts.[8] Migration of the ester-substituted carbon atom would lead to pyrrolobenzoazepinones **4** and **5**, while migration of the benzylic carbon would give the pyrrolobenzoazepinone **6**. In previous studies, in which both possibilities were available, the benzylic shift has been observed,[9] while exclusive [1,2]-shift of CH_2CO_2R has been also reported.[10]

2. Results and discussion

The diazocompound **2** was conveniently prepared in two-step one-pot reaction by conjugate addition of **1** to ethyl 3-keto-pent-4-enoate,[11] followed by diazo-transfer reaction with tosyl azide.

The $Cu(acac)_2$-catalyzed decomposition of **2** has been performed in refluxing xylene, affording a 2:2:1 mixture of benzoazepinones **4**, **5,** and **6**. No traces of the intermediate ylide **3** have been observed, its isolation or spectroscopic detection being unsuccessful.

By reduction with $NaBH_4$, compound **4** afforded the tetracyclic lactone **7** (Fig. 1) in mixture with partial and total reduction products. Then, by submitting alkaloid **5** to the same reaction, no lactonization product has been obtained: this result allowed the *trans* and *cis* configuration to be assigned to benzazepinones **4** and **5**, respectively.

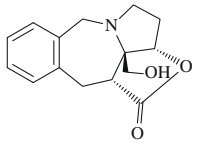

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Figure 1.

Given the stereoselectivity in the nitrogen quaternarization step,[12] the high stereoselectivity of overall process needs high stereoselectivity in the final Stevens [1,2]-shift. The enantioselectivity of the latter step involves intramolecular transfer of chirality from the quaternary asymmetric nitrogen to the adjacent C-position, namely from the ylide spirocycle axis to the newly formed sp^3

* Corresponding author. Tel.: +39 79 229538; fax: +39 79 229559.
E-mail address: saba@uniss.it (A. Saba).

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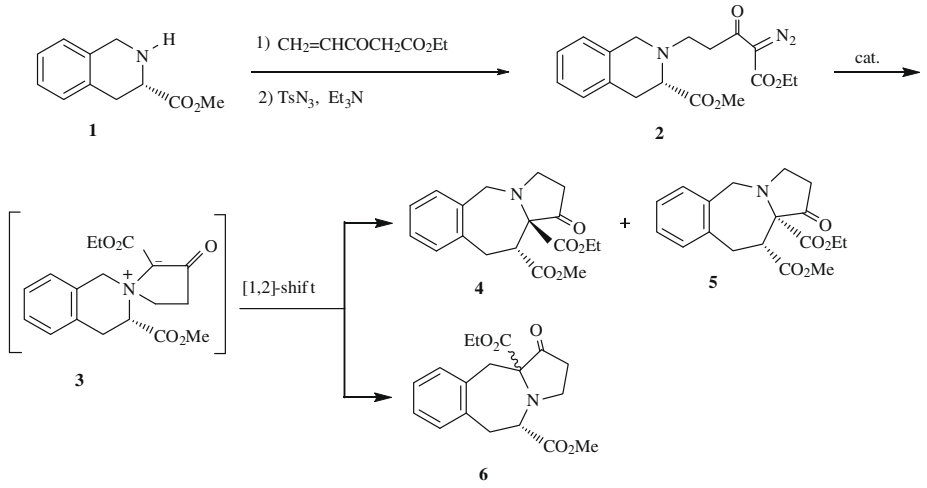


Scheme 1.

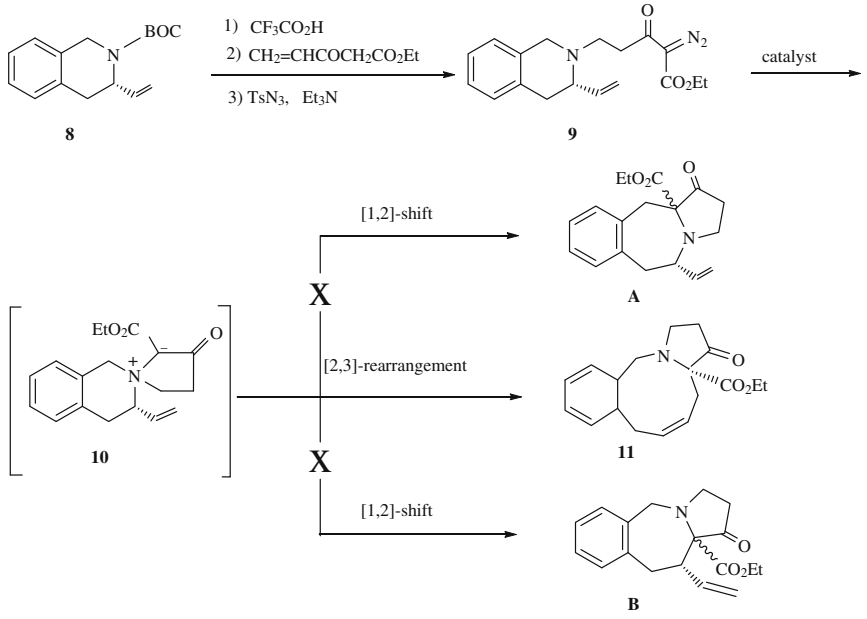
stereogenic center. A transfer of chirality in the [1,2]-Stevens shift could occur, despite the fact that the diradical character is usually accepted for the reaction mechanism.[13]

The enantiomeric excesses for compounds **4** and **5** (52% and 40%, respectively) were measured by using the chiral reagent $Eu(hfc)_3$, and by comparing the shift separations observed in the ^1H NMR spectra to those of the benzazepinones obtained submitting the racemic diazocompound **2** to the same treatment. Current efforts are directed to optimizing the synthetic approach to larger cyclic aminoacids that could prove useful in peptide mimic design.[14]

The cascade strategy based on [2,3]-sigmatropic rearrangement of a spirocyclic ammonium ylide has been then adopted for the synthesis of an optically active nine-membered azacycle,[15] even starting from the ester **1**. For this purpose, the preparation of diazoketoester **9** from tetrahydroisoquinoline **8**, with the requisite vinyl appendage, has been planned (Scheme 2).

Therefore compound **8** has been prepared from **1** following a literature route[16] involving *N*-BOC protection; reduction of the ester function to an alcohol; Swern oxidation to an aldehyde and olefination of the latter via standard Wittig conditions to acquire the requisite vinyl appendage. Diazoalkene **9** has been prepared by deprotection of amine **8**, conjugate addition of the latter to ethyl 3-keto-pent-4-enoate followed by a diazo-transfer to the activated methylene with tosyl azide in one pot and in 51% overall yield. Catalytic decomposition of **9** was then performed under the same conditions adopted for the diazo compound **2** to afford the pyrrolo benzoazacyclononenone **11** as the only product. This is the result of a cascade involving the cyclization of a $Cu(acac)_2$-generated metallo carbenoid species to spiricyclic ammonium ylide **10** followed by [2,3]-sigmatropic rearrangement of the latter through the pendant vinyl group. The overall process resulted in a three carbon expansion of the starting amine ring moiety.

This rearrangement regiospecificity is noticeable, due to the migratory aptitude of both the carbon atoms situated at the α- and α′-position relative to the spirocyclic ammonium group, assisted by the presence of stabilizing allylic and benzylic functions, respectively. A Stevens [1,2]-shift with a one carbon ring expansion



Scheme 2.

to afford the pyrrolobenzazepines **A** and **B** as the secondary products, would not be avoided in principle.

As in the case of **3**, the intermediate ylide **10** has never been observed or detected. Olefin *cis* geometry has been assigned to **11** on the basis of spectroscopic data.[17]

Asymmetric variants of ammonium ylides [2,3]-sigmatropic rearrangement have relied on intramolecular chirality transfer.[18] We have found that azacyclononene **11** displays highly efficient transfer of chirality.[19]

Chiral polycyclic systems, which possess the 1,2,3,4-tetrahydro isoquinoline moiety, are useful in medicinal chemistry for their interesting pharmacological activities.[20] With the aim of preparing tricyclic 1,2,3,4-tetrahydro isoquinoline alkaloids starting from **1**, we herein report the syntheses of compounds **13a–c** by ring-closing metathesis of dienes **12a–c** easily obtained from (*S*)-3-ethenyl-isoquinoline **8**.

Thus, deprotection of **8** followed by acylation with acryloyl, ω-butenoyl, and ω-pentenoyl chlorides, in the presence of triethylamine or pyridine, allowed the preparation of the requisite chiral dienes **12a–c** in good overall yields.

It is well documented that Grubb's RCM catalytic protocol may fail in metathesizing compounds containing amino groups, whose nitrogen lone pair may coordinate the metal center, poisoning and deactivating the ruthenium catalyst.[21] Notwithstanding the increasing number of examples of successful metathesized amine compounds are reported,[22] *N*-acyl alkenyl- in the place of *N*-alkenyl-derivatives was selected, in order to prevent this inconvenience. After examining several catalysts and solvents, Grubb's second generation (Grubb's II) and $ClCH_2CH_2Cl$ were chosen, and these gave better efficiency. The catalytic intramolecular cyclizations, performed in refluxing $ClCH_2CH_2Cl$ solutions, in the presence of Grubb's II catalyst (5 mol %) afforded the chiral target alkaloids **13a**, **13b,** and **13c** as the sole products in good yields. The enantiomer of compound **13a** has recently been prepared as a precursor of new benzoanalogs of lentiginosine starting from L-glutamic acid[23] (Scheme 3).

3. Conclusions

Successful RCM and cascade spiro-to fused protocols allow ready access to a variety of nitrogen heterocyclic systems that are widespread in Nature. Novel optically active tricyclic azacycloisoquinolinones in a two-step one-pot reaction and chiral pyrrolo benzoazacyclononenone alkaloids in a three-step two-pot reaction, starting from the readily available (*S*)-1,2,3,4-tetrahydro isoquinoline carboxylic acid, have been prepared by utilizing these procedures.

Moreover, the cascade ylide formation/[2,3]-sigmatropic rearrangement can function as an expedient route to medium-sized nitrogen containing cyclic natural products. It should be noted that an efficient transfer of chirality based on a pool route has been accomplished in this rearrangement.

In addition, amino esters, conformationally constrained analogs to aspartic acid,[24] and other aminoacids,[25] can be envisioned in azepinone and azacyclononenone frames, respectively. Finally, by deoxygenation and catalytic dihydroxylation of azacycloisoquinolinones, new enantiopure epimers benzoanalogs of lentiginosine, a glycosidase inhibitor, could be concisely and conveniently prepared. Biological evaluations and structure-activity relationship will be reported in due course.

4. Experimental

4.1. General

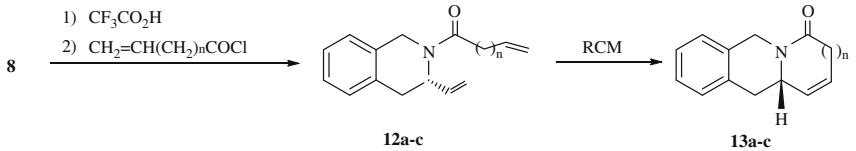
^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR-300 spectrometer with TMS as internal standard. Infrared (IR) spectra were performed on a FT/IR-480plus JASKO spectrophotometer. The optical rotations were measured by a polarimeter P-1010 JASCO in a 1 dm tube. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

4.1.1. (*S*)-Methyl 2-(4-diazo-5-ethoxy-3,5-dioxopentyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 2

A solution of (*S*)-1,2,3,4-tetrahydroisoquinolinecarboxylic acid methyl ester hydrochloride **1** (1.50 g, 6.60 mmol), 3-oxo-pent-4-enoic acid ethyl ester (1.22 g, 8.58 mmol), and Et_3N (1.02 mL, 7.20 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 2 h. Tosyl azide (1.69 g, 8.58 mmol) and Et_3N (1.85 mL, 13.2 mmol) were then added at 0 °C. After completion of the addition, the solution was stirred at rt for 6 h. The solvent was evaporated and the residue gave, after flash chromatography on silica gel (light petroleum ether/ethyl acetate 8:2), the diazo compound **2**, (1.395 g, 59%), yellow oil, $[\alpha]_D^{25} = +5.8$ (*c* 0.65, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.31 (t, 3H, *J* = 7.2 Hz), 3.05–3.19 (m, 6H), 3.65 (s, 3H), 3.86 (t, 1H, *J* = 5.1 Hz), 3.91 (AB system, 1H), 4.07 (AB system, 1H), 2.28 (q, 2H, *J* = 7.2 Hz), 7.01–7.13 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.2, 31.1, 38.4, 49.9, 50.8, 51.3, 59.6, 61.2, 76.1, 125.8, 125.9, 126.3, 128.3, 131.9, 133.8, 161.2, 172.8, 191.5. IR (neat): 2982, 2951, 2134, 1715, 1652, 1455, 1372, 1299, 1197, 1172, 1127, 1100, 1071, 1015, 744 cm^{-1}. Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.08; H, 5.91; N, 11.73.

4.1.2. Diazo-decomposition of 2

A solution of the diazoketoester **2** (0.693 g, 1.93 mmol) in 20 ml anhydrous xylene was added dropwise to a solution of $Cu(acac)_2$ (0.022 g, 5 mol %) in dry xylene (40 mL) over 30 min. After stirring for other 40 min at reflux, the solvent was evaporated and the residue gave, after silica gel column chromatography (light petroleum ether/ethyl acetate 9.5:0.5), the (9*R*,9a*S*)-9a-ethyl-9-methyl-1-oxo-2,3,5,8,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]benzo[*c*]azepine-9, 9a-dicarboxylate **4**, (0.182 g, 28%) as white crystals mp 117–119 °C, $[\alpha]_D^{25} = -103.5$ (*c* 0.39, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2 Hz), 2.50–2.60 (m, 1H), 2.75–2.86 (m, 1H), 3.25–3.27 (m, 2H), 3.43 (dd, 2H, *J* = 7.8, 4.5 Hz), 3.49 (s, 3H), 3.81 (AB system, 1H), 4.03 (dd, 1H, *J* = 5.7, 1.8 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 4.30 (AB system, 1H), 7.12 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 14.1, 33.7, 36.9, 47.6, 48.5, 51.5, 54.1, 61.9, 76.1, 126.6, 127.1, 128.2, 130.4, 137.0, 139.1, 169.6, 171.9, 210.5. IR ($CHCl_3$): 2953, 2929, 1759, 1730,



12a, **13a**, n = 0; **12b**, **13b**, n = 1; **12c**, **13c**, n = 2

Scheme 3.

1448, 1437, 1384, 1354, 1259, 1211, 1177, 1132, 1101, 1021 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.08; H, 6.41; N, 4.21.

Further chromatographic elution (light petroleum ether/ethyl acetate 9:1) afforded (9*R*,9a*R*)-9a-ethyl-9-methyl-1-oxo-2,3,5, 8,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]benzo[*c*]azepine-9,9a-dicarbo- xylate **5** (0.185 g, 29%), colorless oil, $[\alpha]_D^{25} = -33.4$ (*c* 0.16, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H, *J* = 7.2 Hz), 2.39–2.50 (m, 1H), 2.56–2.67 (m, 1H), 2.99 (AB system, 1H), 3.07–3.19 (m, 2H), 3.27 (q, 1H, *J* = 6.3 Hz), 3.63 (s, 3H), 3.73 (AB system, 1H), 3.76 (AB system, 1H), 4.27 (q, 2H, *J* = 7.2 Hz), 4.88 (AB system, 1H), 7.15 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 14.1, 34.1, 35.5, 46.9, 47.7, 51.9, 53.1, 61.3, 73.4, 126.7, 127.1, 128.3, 130.2, 137.7, 139.0, 167.4, 172.6, 206.9. IR (neat): 2981, 2951, 2856, 1752, 1738, 1438, 1366, 1319, 1272, 1235, 1183, 1129, 1103, 1018, 755 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.12; H, 6.45; N, 4.33.

Final chromatographic elution (light petroleum ether/ethyl acetate 8:2) gave (*S*)-9a-ethyl-5-methyl-1-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]benzo[*c*]azepine-5,9a-dicarboxylate **6** (0.091 g, 14%), colorless oil, $[\alpha]_D^{25} = -5.7$ (*c* 0.15, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.06 (t, 3H, *J* = 7.2 Hz), 2.41–2.63 (m, 2H), 2.95 (dd, 1H, *J* = 14.7, 2.1), 3.13 (Ab system, 1H), 3.13–3.32 (m, 3H), 3.53 (Ab system, 1H), 3.82 (s, 3H), 3.91 (q, 2H, *J* = 7.2 Hz), 4.36 (dd, 1H, *J* = 9.9, 1.8 Hz), 7.10–7.21 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 13.9, 34.1, 39.0, 40.0, 44.5, 52.2, 61.2, 61.3, 73.4, 126.9, 127.2, 129.4, 130.4, 135.8, 138.2, 167.1, 172.8, 206.2. IR (neat): 2951, 1762, 1728, 1438, 1273, 1234, 1183, 1129, 1017, 756 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.27; H, 6.29; N, 4.20.

4.1.3. (2a*S*,4a*R*,10b*R*)-10b-Hydroxymethyl-1,2,2a,4a,5,10,10b-heptahydro-3-oxa-10a-aza-benzo [*e*]-cyclopenta-[*cd*]azulene-4-one 7

$NaBH_4$ (0.039 g, 1.03 mmol) was added to a solution of **4** (0.114 g, 0.34 mmol), in anhydrous MeOH (8 mL), and the resulting mixture was stirred at rt under nitrogen for 2 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (light petroleum ether/ethyl acetate 7:3), to afford the tetracyclic lactone **7** (0.057 g, 64%), white crystals, mp 152–154 °C, $[\alpha]_D^{25} = -35.4$ (*c* 0.20, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.93–1.98 (m, 2H), 2.53 (q, 1H, *J* = 8.1 Hz), 2.67 (t, 1H, *J* = 4.5 Hz), 2.89 (m, 2H), 3.15 (dd, 2H, *J* = 15, 3.9 Hz), 3.29 (dd, 2H, *J* = 15.0, 4.8 Hz), 3.52 (AB system, 1H), 3.77 (AB system, 1H), 3.82 (AB system, 1H), 4.37 (AB system, 1H), 4.74 (s, 1H), 7.11–7.26 (m, 3H), 7.35 (d, 1H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 29.9, 31.0, 42.5, 48.6, 49.7, 63.3, 70.8, 87.7, 126.9, 127.9, 128.9, 131.2, 136.3, 137.3, 175.3. IR ($CHBr_3$): 3382, 2642, 1765, 1453, 1361, 1318, 1251, 1200, 1177, 1141, 1089, 1018, 754, 651 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.37; H, 6.58; N, 5.42.

4.1.4. (*S*)-Ethyl 2-diazo-3-oxo-5-[3-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl] pentanoate 9

A solution of **8** (0.514 g, 1.98 mmol) and CF_3COOH (0.76 mL, 9.9 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at rt for 4 h, evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). Then Et_3N (1.38 mL, 9.8 mmol) and 3-oxo-pent-4-enoic acid ethyl ester (0.36 g, 2.57 mmol) were added and the reaction mixture was stirred at rt for 16 h. Tosyl azide (0.51 g, 2.58 mmol) in CH_2Cl_2 (2 mL) was then added dropwise at 0 °C. The resulting solution was stirred at rt for 4 h. The solvent was evaporated and the residue gave, after flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2), the diazo compound **9**, (0.33 g, 51%), yellow oil, $[\alpha]_D^{25} = -21.8$ (*c* 0.63, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.32 (t, 3H, *J* = 7.2 Hz), 2.76–2.89 (m, 2H), 2.96 (dd, 1H, *J* = 16.5, 4.8 Hz), 3.04–3.18 (m, 3H), 3.40 (q, 1H, *J* = 5.1 Hz), 3.74 (AB system, 1H), 3.89 (AB system, 1H), 4.29 (q, 2H, *J* = 7.2), 5.17–5.27 (m, 2H), 5.80–5.92 (m, 1H), 7.01–7.13 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.2, 34.3, 37.5, 48.6, 52.5, 61.1, 61.2, 76.0, 117.0, 125.5, 126.0, 126.1, 128.4, 133.1, 133.9, 137.6, 161.1, 191.5. IR (neat): 2980, 2925, 2134, 1717, 1654, 1447, 1372, 1299, 1213, 1121, 1067, 1015, 743 cm^{-1}. Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.21; H, 6.51; N, 12.85.

4.1.5. Diazo-decomposition of 9

A solution of the diazoketoester **9** (0.157 g, 0.48 mmol) and $Cu(acac)_2$ (0.006 g, 5 mol%) in xylene (11 mL) was refluxed for 20 min. The solvent was evaporated and the residue gave, after silica gel column chromatography (light petroleum ether/ethyl acetate 8:2), the (*R*,*Z*)-ethyl-1-oxo-2.3.4,5,10,13,13a-heptahydro-1*H*-pyrrolo-benzo[*c*]-azonine-13a-carboxylate **11** (0.10 g, 70%), as yellow crystals, mp 57–59 °C, $[\alpha]_D^{25} = -6.4$ (*c* 0.44, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.31 (t, 3H, *J* = 7.2 Hz), 1.73–1.81 (m, 1H), 2.42–2.62 (m, 2H), 3.05–3.23 (m, 2H), 3.10 (AB system, 1H), 3.45–3.55 (m, 2H), 3.71–3.79 (m, 1H), 4.12 (AB system, 1H), 4.14–4.31 (m, 2H), 5.67 (dd, 2H, *J* = 8.1, 3.9 Hz), 7.07–7.25 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.4, 36.3, 41.0, 41.6, 47.8, 56.3, 61.3, 76.3, 125.7, 126.3, 127.8, 131.2, 132.7, 137.7, 137.8, 138.6, 169.4, 211.4. IR (neat): 2977, 2918, 2833, 1757, 1729, 1450, 1269, 1216, 1196, 1172, 1123, 1096, 1046, 1027, 982, 755 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 6.48. Found: C, 72.33; H, 7.09; N, 6.46.

4.1.6. (*S*)-2-[1-Oxo-propenyl]-3-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl 12a

A solution of **8** (0.4 g, 1.54 mmol) and CF_3COOH (0.6 mL, 7.90 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at rt for 2.5 h, evaporated under reduced pressure and the residue was dissolved in anhydrous CH_2Cl_2 (5 mL). Triethyl amine (1.1 mL, 7.70 mmol) and acroleyl chloride (0.112 g, 2.31 mmol) were then added under nitrogen at 0 °C. The reaction mixture was allowed to warm at rt, stirred for 1 h, and washed with water (3 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (light petroleum ether/ethyl acetate 7:3), gave the *isoquinolinone diene* **12a** (0.25 g, 78%) as a pale yellow oil, $[\alpha]_D^{25} = +56.4$ (c 0.37, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.89 (dd, 1H, *J* = 15.6, 2.7 Hz), 3.08–3.20 (m, 1H), 4.54 (d, 1H, *J* = 17.7 Hz), 4.75–5.17 (m, 3H), 5.07 (d, 1H, *J* = 9.6 Hz), 5.58–5.80 (m, 2H), 6.36 (dd, 1H, *J* = 16.8, 1.8 Hz), 6.59 (dd, 1H, *J* = 16.8, 1.8 Hz), 7.06–7.30 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 34.2, 43.0, 53.7, 116.5, 126.1, 126.5, 127.6, 127.9, 128.1, 132.1, 132.8, 135.4, 136.6, 166.4. IR (neat): 3422, 1646, 1610, 1427, 1286, 1240, 976, 925, 793, 747 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.75; H, 7.13; N, 6.50.

4.1.7. (*S*)-2-[1-Oxo-3-butenyl]-3-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl 12b

A solution of **8** (0.412 g, 1.59 mmol) and CF_3COOH (0.61 mL, 7.90 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at rt for 2.5 h, evaporated under reduced pressure and the residue was dissolved in anhydrous CH_2Cl_2 (5 mL). Triethyl amine (1.1 mL, 7.70 mmol) and freshly prepared 3-butenoyl chloride (0.217 g, 2.34 mmol) were then added under nitrogen at 0 °C. The reaction mixture was allowed to warm at rt, stirred for 15 h, washed with water (3 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (light petroleum ether/ethyl acetate 7:3), gave the isoquinolinone diene **12b** (0.199 g, 55%) as a pale yellow oil, $[\alpha]_D^{25} = +52.9$ (*c* 0.46, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.87 (dd, 1H, *J* = 13.2, 2.4 Hz), 3.05–3.34 (m, 3H), 4.58 (AB system,

1H), 4.61 (AB system, 1H), 4.74 (s,1H), 5.00–5.24 (m, 4H), 5.61–5.74 (m, 1H), 5.94–6.10 (m, 1H), 7.03–7.24 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 34.1, 38.8, 42.6, 53.6, 116.4, 117.5, 126.1, 126.5, 126.8, 128.1, 131.5, 131.8, 132.7, 136.3, 170.5. IR (neat): 3079, 3024, 2980, 1647, 1409, 1241, 992, 921, 745 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.15; H, 7.49; N, 6.18.

4.1.8. (*S*)-2-[1-Oxo-4-pentenyl]-3-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl 12c

A solution of **8** (0.510 g, 1.97 mmol) and CF_3COOH (0.75 mL, 9.80 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at rt for 2.5 h, evaporated under reduced pressure and the residue was dissolved in anhydrous CH_2Cl_2 (15 mL). Pyridine (0.68 mL, 8.40 mmol), DMAP (0.024 g, 0.19 mmol), and 4-pentenoyl chloride (0.310 g, 2.95 mmol) were then added under nitrogen at 0 °C. The reaction mixture was allowed to warm at rt, stirred for 2 h, and washed with water (5 mL), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (light petroleum ether/ethyl acetate 7:3), gave the isoquinolinone diene **12c** (0.350 g, 75%) as a pale yellow oil, $[\alpha]_D^{25} = +44.6$ (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.35–2.57 (m, 4H), 2.84–2.87 (m, 1H), 3.09 (ddd, 1H, *J* = 15.6, 9.6, 5.4 Hz), 4.38–5.08 (m, 7H), 5.55–5.69 (m, 1H), 5.81–5.94 (m, 1H), 7.02–7.20 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 28.9, 32.5, 34.1, 42.5, 53.3, 114.9, 116.2, 126.0, 126.4, 126.7, 127.9, 131.8, 132.8, 136.3, 137.2, 171.8. IR (neat): 2978, 2922, 2850, 1645, 1420, 1304, 1205, 993, 917, 747 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.51; H, 7.90; N, 5.81.

4.1.9. (*S*)-10,10a-Dihydro-5*H*-pyrrolo[1,2-*b*]isoquinolin-3-one 13a

A solution of diene **12a** (0.166 g, 0.77 mmol) and Grubb's II catalyst (0.014 g, 2.2 mol %) in anhydrous CH_2ClCH_2Cl (12 mL) was refluxed under argon for 2 h. After filtration on silica gel, the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (light petroleum ether/ethyl acetate 1:1), gave the pyrroloisoquinolinone **13a** (0.131 g, 91%) as a colorless oil, $[\alpha]_D^{25} = -116$ (*c* 0.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.56 (dd, 1H, *J* = 15.0, 2.7 Hz), 3.15 (dd, 1H, *J* = 15.6, 4.2 Hz), 4.22 (dd, 1H, *J* = 12.0, 3.9 Hz), 4.42 (AB system, 1H), 5.12 (AB system, 1H), 6.30 (dd, 1H, *J* = 5.7, 1.5 Hz), 7.16–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 33.5, 41.7, 58.2, 126.8, 126.9, 127.0, 128.3, 129.0, 131.6, 131.7, 147.1, 169.8. IR (neat): 3446, 2853, 1680, 1580, 1495, 1453, 1422, 1266, 809, 752 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.71; H, 5.95; N, 7.54.

4.1.10. (*S*)-11,11a,3-Trihydro-6*H*-pyridino[1,2-*b*]isoquinolin-4-one 13b

A solution of diene **12b** (0.169 g, 0.74 mmol) and Grubb's II catalyst (0.014 g, 2.2 mol %) in anhydrous CH_2ClCH_2Cl (12 mL) was refluxed under argon for 1 h. After filtration on silica gel, the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (light petroleum ether/ethyl acetate 7:3), gave the pyridinoisoquinolinone **13b** (0.140 g, 95%) as a pale yellow oil, $[\alpha]_D^{25} = -124.6$ (*c* 0.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.74–2.85 (m, 1H), 2.95 (dd, 1H, *J* = 15.9, 3.6 Hz), 3.04 (d, 2H, *J* = 4.5 Hz), 4.17–4.23 (m, 1H), 4.20 (AB system, 1H), 5.57 (AB system, 1H), 5.82 (s, 2H), 7.06–7.25 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 31.7, 37.1, 43.9, 54.6, 121.7, 124.6, 126.2, 126.3, 126.6, 128.3, 132.4, 132.9, 166.2. IR (neat): 3460, 2892, 1640, 1466, 1447, 1407, 1329, 1250, 755, 729, 695 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 77.99; H, 6.62; N, 7.01.

4.1.11. (*S*)-3,4,12,12a-Tetrahydro-7*H*-azepino[1,2-*b*]isoquinolin-5-one 13c

A solution of diene **12c** (0.106 g, 0.43 mmol) and Grubb's II catalyst (0.008 g, 2.2 mol %) in anhydrous CH_2ClCH_2Cl (8 mL) was refluxed under argon for 14 min. After filtration on silica gel, the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (light petroleum ether/ethyl acetate 7:3), gave the azepinoisoquinolinone **13c** (0.080 g, 86%) as a brown oil, $[\alpha]_D^{25} = +35.1$ (*c* 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.37–2.50 (m, 3H), 2.81 (dd, 1H, *J* = 15.0, 7.2 Hz), 3.04–3.16 (m, 2H), 4.58 (AB system, 1H), 4.72 (AB system, 1H), 4.80–4.86 (m, 1H), 5.44 (dd, 1H, *J* = 11.1, 2.7 Hz), 5.65 (dd, 1H, *J* = 11.1, 2.4 Hz), 7.20–7.27 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 25.1, 33.8, 35.6, 42.7, 49.9, 126.1, 126.9, 127.0, 127.3 130.7, 131.4, 134.8, 135.7, 173.5. IR (neat): 3020, 2896, 2841, 1640, 1453, 1433, 1415, 1235, 1200, 1158, 763, 747, 729, 607 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.72; H, 7.10; N, 6.60.

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