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Intermolecular one-pot cyclization of formyl-pyrroles of amino acid esters with norephedrine: stereoselective routes to new tricyclic pyrrole–pyrazine–oxazole fused structures

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Abstract—The treatment of esters of amino acids with dimethoxytetrahydrofuran furnished pyrrole derivatives of amino acid esters. The Wilsmeier–Haack formylation followed by the reaction of the formylated pyrroles with norephedrine afforded a selective formation of the tricyclic pyrrole–pyrazine–oxazole fused structures in one step via the formation of an oxazoline structure and intramolecular lactam formation. Pyrrole–pyrazine–oxazole fused structures were achieved in good yields. The cyclization reaction for the formation of an oxazole ring worked selectively to form only one stereoisomer. The configuration of the newly generated stereogenic center in the oxazole ring is dependent on the stereogenic centers of norephedrine.

1. Introduction

Nitrogen-containing heterocycles have always constituted a subject of great interest due to their wide presence in biologically important compounds.[1] As part of ongoing research directed toward the development of pyrrole-based heterocyclic compounds, we have already reported efficient methods for the construction and functionalization of pyrrole ring systems.[2] In an effort to expand upon access to new heteropolycycles, we studied the reaction of pyrrole derivatives with norephedrine toward inter- and intramolecular cyclizations in order to obtain interesting heteropolycyclic compounds with oxazole–pyrrole–pyrazine structures. These polycyclic structures are present in natural products, especially in alkaloids.[3] Particular interest has come from the selective aspect of the process during intra- and intermolecular cyclizations.

2. Results and discussion

In an initial reaction, alanine methyl ester **2a** was reacted with dimethoxytetrahydrofuran **1** to form the pyrrole derivative of alanine **3a** according to published procedures.[4] This homochiral pyrrole formation process was carried out without racemization. Several procedures are described in the literature for the formylation of a pyrrole ring. The Wilsmeier–Hack formylation of the pyrrole was carried out by using the procedure, given in the experimental, to obtain the highest yield for the desired isomer of the product.[5] 2-Formylpyrrole **4a** was obtained in a 77% yield together with 3-formyl derivative **5a** and undefined products.

2-Formylpyrrole **4a** was refluxed with (−)-norephedrine (−)-**6** to form the corresponding amine via the reduction of the intermediate imine to synthesize the norephedrine-based chiral ligands with multiple stereogenic centers. However, by refluxing norephedrine with 2-formyl pyrrole, the tricyclic fused structure **8** was obtained. Spectral analysis of the product showed that any imine formation failed and the product was identified as a tricyclic pyrrole–pyrazine–oxazole fused structure as shown in Scheme 1. This reaction was repeated several times with the enantiomers of alanine and (−)- and (+)-norephedrine with stereoisomeric products **7** and **8** obtained in comparable yields (72–75%).

As shown in Table 1, the reaction was carried out with the representative esters of amino acids and enantiomers of

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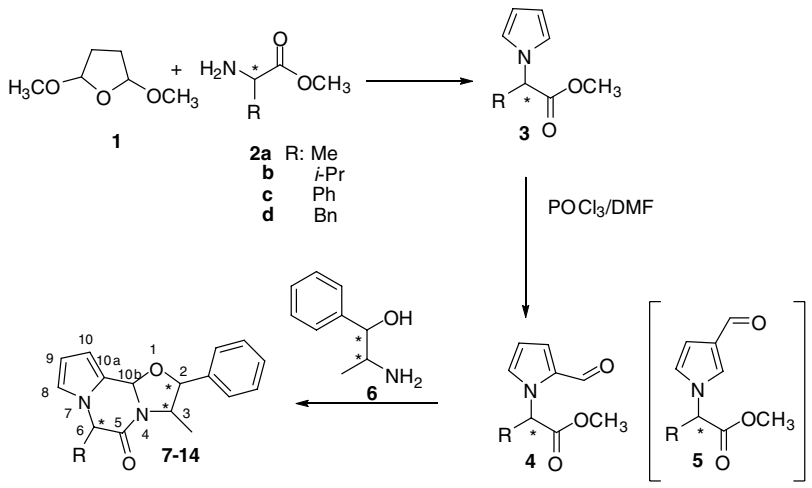


Scheme 1.

norephedrine and the corresponding tricyclic pyrrole–pyrazine–oxazole fused structures were obtained in 71–77% yields.

The configuration of the new stereogenic center was assigned on the basis of the NMR spectroscopic data. The NOE and NOESY showed that in all four isomers **7** and **8**, the (C-10b)–H lies on the same side as the CH_3 and the phenyl groups of norephedrine, any positive NOE being not registered between (C-10b)–H and (C-2)–H nor (C-3)–H. The structural determination experiments were carried out with other amino acid derived products with the stereochemical results in agreement with what was found for alanine derived products. The assignment of the stereochemistry of the newly formed center was also assigned from the X-ray crystallographic data from (*R*,*S*,*S*,*R*)-**12**, as shown in Figure 1. It seems that the stereocenters of norephedrine are responsible for the stereochemical outcome of the products at the newly formed center, but not the stereocenter of the amino acid moiety.[6]

The configuration of the tricyclic structure (*R*,*S*,*S*,*R*)-**12** was determined by X-ray crystal structure analysis (Fig. 1a). The compound crystallizes in the non-centrosymmetric chiral space group $P2_12_12_1$ (no. 19) with $Z = 4$; it contains the C10(*R*), C16(*S*), C8(*S*), C7(*R*) chiral centers. Although it is generally not a stable form, pyrazine ring has the boat conformation; C16 and C10 lie out of the plane and on the same side of the plane containing C15, N2, C11, and N1. Deviation for C16 and C10 from the least square plane is 0.169 and 0.135 Å, respectively. The pyrrole ring is planar but the oxazole ring has a slightly distorted envelope conformation. Maximum deviation from the mean plane is 0.167 Å for C8 [Cremer and Pople puckering parameters[7] $Q(2) = 0.273(3)$ Å, phi(2) = 261.1(5)°]. The chains of molecules running parallel to the short *a* axis are linked by conventional hydrogen bonds (Fig. 1b) [$C10\cdots O2^{i} = 3.194(4)$ Å and $C14\cdots O2^{ii} = 3.342(4)$ Å; symmetry codes: (i) $-1 + x, y, z$; (ii) $2 - x, -1/2 + y, 1/2 - z$].

Most probably, during the cyclization of the imine intermediate, the OH attack preferentially occurs on the *Si* face of the >C=N– planar group. As a result, during the formation of the oxazoline ring, the bulky phenyl and pyrrole can be arranged in the *trans* position, to avoid steric interactions as shown in Scheme 2.

3. Conclusion

The synthesis of the pyrrole derivative of amino acid esters followed by Vilsmeier–Haack formylation furnished C-2 formylated pyrrole derivatives of amino acid esters as the major products. The C-2 formylated pyrroles are refluxed with norephedrine and the products identified as tricyclic pyrrole–pyrazine–oxazole fused structures in high yields. According to the NMR and X-ray experiment, the oxazole ring formation step proceeded selectively to give only one stereoisomer. The configuration of the newly generated stereogenic center in the oxazole ring depends on the chirality centers of norephedrine.

4. Experimental

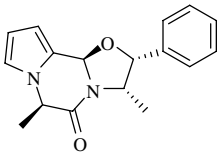
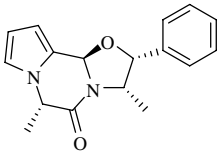
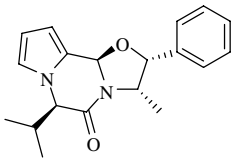
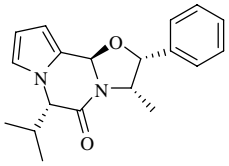
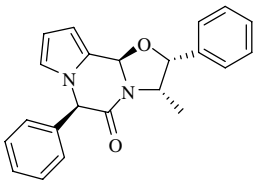
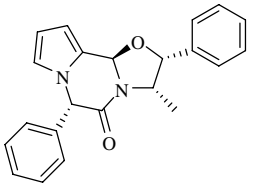
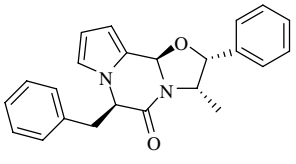
4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (^{1}H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$), and CCl_4 (^{13}C: $\delta = 96.4$) as the internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda = 254$ nm). Optical rotations were measured with a Krüss P3002RS automatic polarimeter.

4.2. X-ray crystal structure analysis of (*R*,*S*,*S*,*R*)-12

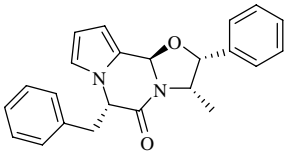
A single crystal suitable for X-ray structural analysis was obtained by EtOAc/hexane. A white crystal of dimensions $0.25 \times 0.17 \times 0.15$ mm was mounted on a glass fiber. X-ray diffraction intensity data collection and cell refinement were performed on Rigaku R-AXIS RAPID IP diffracto-

Table 1. Synthesis of tricyclic heterocycles

Entry	Amino acid ester **2**	2-Formylpyrrole **4**, yield[a] (%)	Norephedrine **6**	Pyrrole–pyrazine–oxazole-product	Yield[a,b] (%)
1	(*R*)-**2a**	(*R*)-**4a**	(1*R*,2*S*)	 (2*R*,3*S*,6*R*,10b*R*)-**7**	72
2	(*S*)-**2a**	(*S*)-**4a**	(1*S*,2*R*)	(2*S*,3*R*,6*S*,10b*S*)-**7**	75
3	(*S*)-**2a**	(*S*)-**4a**, 77	(1*R*,2*S*)	 (2*R*,3*S*,6*S*,10b*R*)-**8**	74
4	(*R*)-**2a**	(*R*)-**4a**, 76	(1*S*,2*R*)	(2*S*,3*R*,6*R*,10b*S*)-**8**	75
5	(*R*)-**2b**	(*R*)-**4b**	(1*R*,2*S*)	 (2*R*,3*S*,6*R*,10b*R*)-**9**	76
6	(*S*)-**2b**	(*S*)-**4b**	(1*S*,2*R*)	(2*S*,3*R*,6*S*,10b*S*)-**9**	77
7	(*S*)-**2b**	(*S*)-**4b**, 76	(1*R*,2*S*)	 (2*R*,3*S*,6*S*,10b*R*)-**10**	71
8	(*R*)-**2b**	(*R*)-**4b**, 73	(1*S*,2*R*)	(2*S*,3*R*,6*R*,10b*S*)-**10**	74
9	(*R*)-**2c**	(*R*)-**4c**	(1*R*,2*S*)	 (2*R*,3*S*,6*R*,10b*R*)-**11**	71
10	(*S*)-**2c**	(*S*)-**4c**	(1*S*,2*R*)	(2*S*,3*R*,6*S*,10b*S*)-**11**	73
11	(*S*)-**2c**	(*S*)-**4c**, 73	(1*R*,2*S*)	 (2*R*,3*S*,6*S*,10b*R*)-**12**	73
12	(*R*)-**2c**	(*R*)-**4c**, 74	(1*S*,2*R*)	(2*S*,3*R*,6*R*,10b*S*)-**12**	72
13	(*R*)-**2d**	(*R*)-**4d**	(1*R*,2*S*)	 (2*R*,3*S*,6*R*,10b*R*)-**13**	74

(*continued on next page*)

Table 1 (*continued*)

Entry	Amino acid ester **2**	2-Formylpyrrole **4**, yield[a] (%)	Norephedrine **6**	Pyrrole–pyrazine–oxazole-product	Yield[a,b] (%)
14	(*S*)-**2d**	(*S*)-**4d**	(1*S*,2*R*)	(2*S*,3*R*,6*S*,10b*S*)-**13**	73
15	(*S*)-**2d**	(*S*)-**4d**, 76	(1*R*,2*S*)	 (2*R*,3*S*,6*S*,10b*R*)-**14**	71
16	(*R*)-**2d**	(*R*)-**4d**, 76	(1*S*,2*R*)	(2*S*,3*R*,6*R*,10b*S*)-**14**	73

[a] Isolated yields.
[b] Newly generated stereogenic centers are assigned according to the unique reaction and the structure information from NOE experiments and the X-ray diffraction structure of (2*R*,3*S*,6*S*,10b*R*)-**12**.

meter equipped with a graphite monochromator. A total of 5505 unique reflections were collected using Mo Kα ($\lambda = 0.71073$ Å) radiation by the oscillation scan technique at 291(2) K, of which 2891 reflections had $I > 2\sigma(I)$ and were used in the structural solution and refinements. The corrections for Lp factors and empirical absorption were applied to the intensity data. The structure was solved by direct methods and refined on F^2 using a full matrix least-squares technique (SHELXS-97 and SHELXL-97).[8] The non-hydrogen atoms were also refined by a full-matrix least-squares technique, anisotropically, and the hydrogen atoms were included but not refined. The final cycle of the full-matrix least-squares refinement was based on 3741 observed reflections and 237 parameters. Convergence with unweighted and weighted agreement factors was achieved at $R = 0.079$ $Rw = 0.116$ $(w = 1/[\sigma(F_o^2)+(0.0325P)^2 + 0.1214P])$ where $P = (F_o^2 + 2F_c^2)/3$, The maximum and minimum peaks on the final difference Fourier map correspond to 0.120 and −0.120 e Å^3. Crystal data for (*R*,*S*,*S*,*R*)-**7c**: empirical formula, $C_{22}H_{20}N_2O_2$; formula weight, 344.4; calculated density, 1.27 g/cm^3; volume (*V*), 1807.6.(2) Å^3; crystal system, orthorhombic; space group, $P2_12_12_1$ (no: 19); $Z = 4$; unit cell dimensions, $a = 6.569$ (5), $b = 13.099$ (5), $c = 21.007$ (5); absorption coefficient, 0.082 mm −1 ; index ranges, $-9 \leqslant h \leqslant 9$, $-17 \leqslant k \leqslant 18$, $-29 \leqslant l \leqslant 30$; $F(000)$, 728; $\theta_{max} = 30.5$; GOF, 1.077; Flack parameter, 0.05(2).

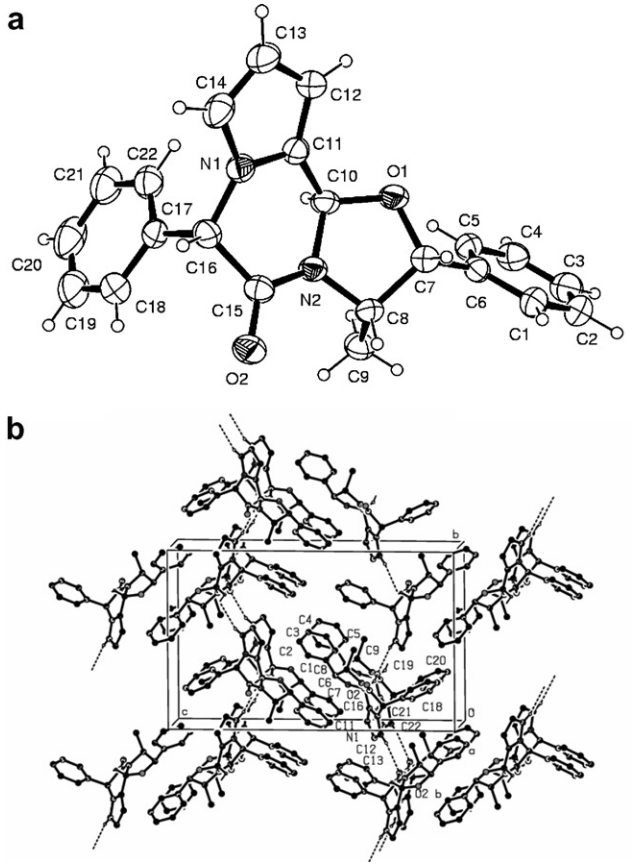
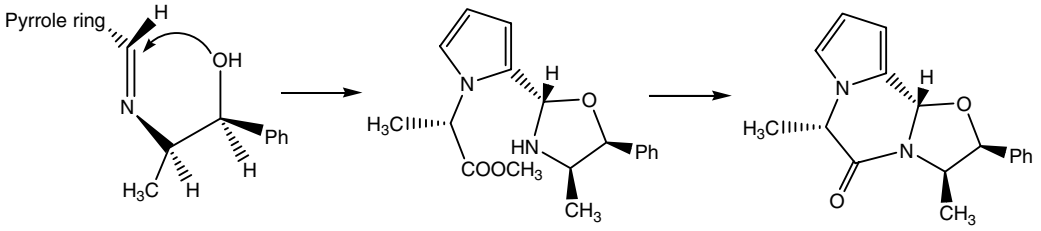


Figure 1. (a) ORTEP view of (*R*,*S*,*S*,*R*)-**12** with displacement ellipsoids drawn at the 50% probability level. (b) Hydrogen bonded chains, viewed along the *b* axis. Dashed lines represent C–H···O bonds. H atoms not involved in hydrogen bonding have been omitted. Selected bond lengths (Å), bond angles (°) and torsion angles (°): C10–O1 1.403(3), C10–N2 1.460(3), O2–C15 1.231(3), C7–C6 1.513(4), C1–C6 1.379(3), N1–C16 1.449(3), C10–O1–C7 110.7(2), N1–C16–C15 110.2(2), C10–N2–C8 109.8(2), O2–C15–N2 123.1(3), C5–C6–C7–O1 −33.0(2), C7–O1–C10–N2 4.6(2), N2–10–C11–N1 −25.9(3), C10–C11–N1–C14 179.5(2).

Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-609449. Data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.cn; web: http//www.ccdc.cam.ac.uk).

4.3. General procedure for the synthesis of pyrrole derivatives 3

Amino acid ester (10 mmol) was dissolved in 5 mL of water. To this solution 2,5-dimethoxytetrahydrofuran (12 mmol), glacial AcOH (4 mL), and dichloroethane (30 mL) were added at room temperature. The reaction mixture was refluxed for 3 h. The two layers were then sep-



Scheme 2.

arated and the aqueous layer extracted three times with $CHCl_3$. The organic phases were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (1:3, EtOAc/hexane).

4.4. General procedure for the synthesis of pyrrole-2-carboxaldehyde derivatives 4

Phosphoryl chloride (10 mmol) was added to ice-cold DMF (10 mmol) over 15 min. The reaction mixture was allowed to warm to room temperature diluted with CH_2Cl_2 (20 mL) and cooled again to 0 °C. Pyrrole (5 mmol) was dissolved in 10 mL CH_2Cl_2 and this solution added dropwise over 1 h, while the temperature was kept at 0 °C. After the addition was complete, the reaction mixture was refluxed for 30 min. After the reflux was completed, the reaction mixture was cooled to 10 °C and hydrolyzed with sodium acetate solution (3.15 g NaOAc in 15 mL water). The phases were separated and the aqueous phase was extracted three times with ether. The combined organic layer was washed with a saturated sodium carbonate until no CO_2 evolved. The organic layer was then dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography (1:5, EtOAc/hexane).

4.5. (*S*)-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate 4a[5a]

Orange oil (1.40 g, 77% yield). $[\alpha]_D^{25} = -87.5$ (*c* 0.2, $CHCl_3$). IR (neat): 2846, 1660, 1412, 1214, 1085, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67 (d, $J = 7.4$ Hz, 3H), 3.67 (s, 3H), 5.82 (q, $J = 7.3$ Hz, 1H), 6.22 (t, $J = 3.3$ Hz, 1H), 6.88 (d, $J = 3.5$ Hz, 1H), 7.07 (s, 1H), 9.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.0, 52.4, 55.2, 110.2, 113.5, 125.1, 128.5, 171.2, 179.3. Anal. Calcd for $C_9H_{11}NO_3$ (181.19): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.81; H, 6.25; N, 7.61.

4.6. (*S*)-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate 4b

Yellow oil (1.59 g, 76% yield). $[\alpha]_D^{25} = +1.5$ (*c* 1.1, $CHCl_3$). IR (neat): 2966, 1662, 1208, 1030, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.71 (d, $J = 6.7$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H), 2.31 (m, 1H), 3.68 (s, 3H), 5.91 (d, $J = 9.5$ Hz, 1H), 6.21 (dd, $J_1 = 2.9$ Hz, $J_2 = 3.7$ Hz, 1H), 6.82 (dd, $J_1 = 1.6$ Hz, $J_2 = 3.9$ Hz, 1H), 7.30 (s, 1H), 9.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.5, 19.2, 33.1, 52.1, 63.7, 110.6, 125.0, 129.7, 132.0, 170.9, 179.5. Anal. Calcd for $C_{11}H_{15}NO_3$ (209.24): C, 63.14; H, 7.23; N, 6.69. Found: C, 63.35; H, 7.48; N, 6.42.

4.7. (*R*)-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)-2-phenyl acetate 4c

White solid (1.80 g, 74% yield). Mp = 88.7–89.7 °C. $[\alpha]_D^{25} = -104.4$ (*c* 0.2, $CHCl_3$). IR (KBr): 3116, 2960, 2847, 1755, 1651, 1466, 1381, 1212, 1000, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.79 (s, 3H), 6.18 (t, $J = 3.1$ Hz, 1H), 6.84 (s, 1H), 6.97 (m, 2H), 7.35 (m, 2H), 7.41 (m, 3H), 9.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 52.4, 63.2, 109.9, 125.2, 128.8, 129.1, 130.1, 131.7, 134.1, 169.8, 179.4. Anal. Calcd for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.33; H, 5.42; N, 5.62.

4.8. (*S*)-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate 4d

Yellow oil (1.95 g, 76% yield). $[\alpha]_D^{25} = +8.8$ (*c* 0.2, $CHCl_3$). IR (neat): 3116, 2960, 1658, 1412, 1080, 751, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.30 (ddd, $J_1 = 5.6$ Hz, $J_2 = 14.1$ Hz, $J_3 = 19.7$ Hz, 2H), 3.66 (s, 3H), 5.99 (s, 1H), 6.12 (m, 1H), 6.79 (m, 1H), 6.92 (m, 2H), 7.09 (m, 3H), 9.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 40.1, 52.8, 63.9, 109.3, 120.3, 121.6, 122.3, 126.2, 127.4, 127.5, 128.9, 129.3, 136.7, 170.7, 170.8. Anal. Calcd for $C_{15}H_{15}NO_3$ (257.28): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.82; H, 5.61; N, 5.23.

4.9. General procedure for the synthesis of pyrrole–pyrazine–oxazole fused cyclic structures 7–14

Formylated pyrrole (3 mmol) was dissolved in 10 mL of dry benzene. To this solution was added norephedrine (503 mg, 3.33 mmol) in 10 mL dry benzene under argon. The reaction mixture was refluxed under a Dean Stark trapp apparatus and monitored by TLC (24–36 h). The organic layer was separated and dried over $MgSO_4$. After evaporation of solvent, the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6).

4.10. (2*R*,3*S*,6*R*,10b*R*)-3,6-Dimethyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 7

Yellow oil (610 mg, 72% yield). $[\alpha]_D^{25} = -7.2$ (*c* 0.2, $CHCl_3$). IR (neat): 2962, 1659, 1413, 1260, 1087, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (d, $J = 7.0$ Hz, 3H), 1.55 (d, $J = 7.2$ Hz, 3H), 4.63 (q, $J = 7.1$ Hz, 1H),

4.76 (p, $J = 6.7$ Hz, 1H), 5.09 (d, $J = 5.6$ Hz, 1H), 6.15 (t, $J = 3.2$ Hz, 1H), 6.20 (broad s, 1H), 6.24 (s, 1H), 6.56 (s, 1H), 7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.0, 21.4, 54.3, 55.9, 80.6, 81.0, 105.1, 110.0, 118.1, 124.1, 126.2, 127.9, 128.4, 136.4, 166.3. Anal. Calcd for $C_{17}H_{18}N_2O_2$ (282.34): C, 72.32; H, 6.43; N, 9.92. Found: C, 72.44; H, 6.62; N, 9.71.

4.11. (2*R*,3*S*,6*S*,10b*R*)-3-Methyl-6-isopropyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-(2*R*,3*S*,6*S*,10b*R*)-3,6-dimethyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]-pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 8

Yellow oil (627 mg, 74% yield). $[\alpha]_D^{25} = -58.1$ (*c* 0.1, $CHCl_3$). IR (neat): 2962, 1659, 1413, 1260, 1087, 802 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (d, $J = 7.0$ Hz, 3H), 1.56 (d, $J = 7.2$ Hz, 3H), 4.64 (q, $J = 7.1$ Hz, 1H), 4.76 (p, $J = 6.7$ Hz, 1H), 5.10 (d, $J = 5.5$ Hz, 1H), 6.16 (t, $J = 3.2$ Hz, 1H), 6.20 (broad s, 1H), 6.24 (s, 1H), 6.58 (s, 1H), 7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.1, 21.4, 54.3, 55.9, 80.5, 81.0, 105.1, 110.0, 119.7, 123.3, 126.2, 127.9, 128.4, 136.3, 166.4. Anal. Calcd for $C_{17}H_{18}N_2O_2$ (282.34): C, 72.32; H, 6.43; N, 9.92. Found: C, 72.51; H, 6.61; N, 9.69.

4.12. (2*R*,3*S*,6*S*,10a*R*)-3-Methyl-6-isopropyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one

Yellow oil (661 mg, 71% yield). $[\alpha]_D^{25} = -57.4$ (*c* 0.4, $CHCl_3$). IR (neat): 2969, 1666, 1452, 1358, 1200, 1068, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (dd, $J_1 = 6.8$ Hz, $J_2 = 9.5$ Hz, 6H), 1.0 (d, $J = 6.9$ Hz, 3H), 2.12 (sextet, $J = 6.7$, 1H), 4.29 (d, $J = 6.2$ Hz, 1H), 4.75 (p, $J = 6.8$ Hz, 1H), 5.05 (d, $J = 5.6$ Hz, 1H), 6.12 (t, $J = 3.1$ Hz, 1H), 6.19 (d, $J = 3.3$ Hz, 1H), 6.24 (s, 1H), 6.54 (t, $J = 1.8$ Hz, 1H), 7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.1, 17.4, 18.4, 33.1, 53.1, 65.2, 79.3, 80.3, 103.6, 108.1, 118.9, 124.7, 125.1, 126.8, 127.3, 135.3, 164.1. Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.31; H, 7.11; N, 8.86.

4.13. (2*R*,3*S*,6*R*,10b*R*)-3-Methyl-6-isopropyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 10

Yellow oil (707 mg, 76% yield). $[\alpha]_D^{25} = -28.2$ (*c* 0.1, $CHCl_3$). IR (neat): 2969, 1666, 1452, 1358, 1200, 1068, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82 (d, $J = 6.4$ Hz, 3H), 0.96 (dd, $J = 6.9$ Hz, 6H), 2.21 (sextet, $J = 6.7$, 1H), 4.31 (d, $J = 5.8$ Hz, 1H), 4.77 (p, $J = 6.3$ Hz, 1H), 5.07 (d, $J = 5.6$ Hz, 1H), 6.14 (t, $J = 2.9$, 1H), 6.22 (br s, 1H), 6.25 (s, 1H), 6.56 (s, 1H), 7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 18.9, 20.2, 34.4, 55.9, 67.3, 82.7, 82.4, 104.2, 109.4, 120.4, 126.6, 126.6, 128.5, 128.7, 135.4, 165.3. Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.39; H, 7.23; N, 8.78.

4.14. (2*R*,3*S*,6*R*,10b*R*)-2,6-Diphenyl-3-methyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 11

White solid (723 mg, 71% yield). Mp = 140.5–141.5 °C. $[\alpha]_D^{25} = -63.0$ (*c* 0.1, $CHCl_3$). IR (KBr): 3059, 1664, 1449, 1313, 1199, 1071, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.79 (d, $J = 6.8$ Hz, 3H), 4.77 (p, $J = 6.6$ Hz, 1H), 5.16 (d, $J = 5.5$ Hz, 1H), 5.78 (s, 1H), 6.14 (s, 1H), 6.29 (m, 1H), 6.34 (br s, 1H), 6.68 (s, 1H), 6.98 (d, $J = 7.3$ Hz, 2H), 7.31 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.0, 54.5, 63.5, 80.6, 81.2, 105.1, 110.3, 125.1, 125.3, 126.2, 126.6, 127.9, 128.2, 128.4, 128.4, 129.0, 129.1, 136.2, 136.6, 164.4. Anal. Calcd for $C_{22}H_{20}N_2O_2$ (344.41): C, 76.72; H, 5.85; N, 8.13. Found: C, 76.61; H, 5.77; N, 7.88.

4.15. (2*R*,3*S*,6*S*,10b*R*)-2,6-Diphenyl-3-methyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 12

White solid (754 mg, 73% yield). Mp = 139.8–140.8 °C. $[\alpha]_D^{25} = -75.4$ (*c* 0.1, $CHCl_3$). IR (KBr): 3059, 1664, 1449, 1313, 1199, 1071, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82 (d, $J = 6.9$ Hz, 3H), 4.77 (p, $J = 6.7$ Hz, 1H), 5.16 (d, $J = 5.4$ Hz, 1H), 5.79 (s, 1H), 6.14 (s, 1H), 6.31 (m, 1H), 6.35 (br s, 1H), 6.70 (s, 1H), 6.98 (d, $J = 7.5$ Hz, 2H), 7.31 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9, 54.5, 63.5, 80.5, 81.2, 105.1, 110.3, 119.6, 125.1, 126.2, 126.5, 127.9, 128.4, 128.4, 128.9, 129.0, 129.0, 136.2, 136.5, 164.4. Anal. Calcd for $C_{22}H_{20}N_2O_2$ (344.41): C, 76.72; H, 5.85; N, 8.13. Found: C, 76.55; H, 5.70; N, 7.97.

4.16. (2*R*,3*S*,6*R*,10b*R*)-6-Benzyl-3-methyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 13

Orange oil (795 mg, 74% yield). $[\alpha]_D^{25} = -8.3$ (*c* 0.8, $CHCl_3$). IR (neat): 3059, 1660, 1451, 1214, 1079, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.64 (d, $J = 6.8$ Hz, 3H), 3.22 (ddd, $J_1 = 4.2$ Hz, $J_2 = 13.5$ Hz, $J_3 = 47.2$ Hz, 2H), 4.67 (m, 2H), 4.88 (t, $J = 4.4$ Hz, 1H), 4.98 (d, $J = 5.7$ Hz, 1H), 6.03 (m, 1H), 6.19 (t, $J = 3.4$ Hz, 1H), 6.58 (t, $J = 2.1$ Hz, 1H), 6.66 (d, $J = 7.1$ Hz, 2H), 7.06 (t, $J = 7.6$ Hz, 2H), 7.18 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.3, 41.6, 53.9, 60.7, 80.2, 80.6, 104.4, 110.4, 117.7, 125.9, 126.16, 126.4, 127.1, 127.6, 127.8, 128.2, 128.3, 129.1, 134.4, 136.6, 163.7. Anal. Calcd for $C_{23}H_{22}N_2O_2$ (358.43): C, 77.07; H, 6.19; N, 7.82. Found: C, 76.88; H, 6.23; N, 7.52.

4.17. (2*R*,3*S*,6*S*,10b*R*)-6-Benzyl-3-methyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one 14

Orange oil (763 mg, 71% yield). $[\alpha]_D^{25} = -23.0$ (*c* 0.3, $CHCl_3$). IR (neat): 3059, 1660, 1451, 1214, 1079, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.73 (d, $J = 6.9$ Hz, 3H), 3.32 (ddd, $J_1 = 4.1$ Hz, $J_2 = 13.5$ Hz, $J_3 = 49.6$ Hz, 2H), 4.76 (m, 2H), 4.99 (t, $J = 4.3$ Hz, 1H), 5.07 (d, $J = 5.8$ Hz, 1H), 6.14 (m, 1H), 6.30 (t, $J = 3.1$ Hz, 1H), 6.69 (m, 1H), 6.76 (d, $J = 7.4$ Hz, 2H), 7.17 (t, $J = 7.4$ Hz, 2H), 7.30 (m, 6H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ (ppm): 13.3, 41.6, 53.8, 60.6, 80.1, 80.6, 104.4, 110.4, 117.7, 125.9, 126.2, 126.4, 127.1, 127.6, 127.8, 128.2, 128.3, 129.1, 134.4, 136.6, 163.7. Anal. Calcd for $C_{23}H_{22}N_2O_2$ (358.43): C, 77.07; H, 6.19; N, 7.82. Found: C, 76.82; H, 5.91; N, 7.61.

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