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Diastereoselective Michael addition of (*S*)-mandelic acid enolate to 2-arylidene-1,3-diketones: enantioselective diversity-oriented synthesis of densely substituted pyrazoles

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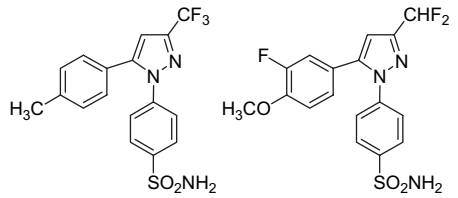
Abstract—A diversity-oriented approach to enantiomerically pure densely substituted pyrazoles, α-aryl-α-pyrazolylatrolactic acid and α-aryl-α-pyrazolylacetophenones has been developed. The approach utilises the conjugated addition of the lithium enolate of the (2*S*,5*S*)-*cis*-1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde to several 2-arylidene-1,3-diketones, which proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. The cyclocondensation of the 1,3-diketone moieties present in Michael adducts with several hydrazines leads to enantiomerically pure densely substituted pyrazoles. Subsequent basic hydrolysis of the dioxolanone moiety present in these products leads to enantiomerically pure α-aryl-α-pyrazolylatrolactic acids. Finally, oxidative decarboxylation of these using oxygen, pivalaldehyde and the Co(III)–Me_2opba complex as catalyst gives α-aryl-α-pyrazolylacetophenones. In this approach four points of diversity are introduced, one of them is the configuration of the (*S*)-mandelic acid, which acts as an umpoled chiral equivalent of the benzoyl anion.

1. Introduction

Substituted pyrazoles constitute an important class of heterocyclic compounds because this ring system is present in numerous compounds of therapeutic importance, including a number of marketed drugs, such as Celecoxib (Celebrex®) or Deracoxib (Fig. 1). These compounds are used with success for the treatment of inflammatory diseases with the advantage they present low ulcerogenic side effects commonly associated with the chronic use of other non-selective non-steroidal anti-inflammatory drugs (NSAIDs).[1] Due to the importance of these pharmacological properties, significant efforts toward the synthesis of this kind of compounds have been carried out in the last years.[2] However, to the best of our knowledge, preparation of optically active substituted pyrazoles has never been reported, despite chiral compounds could be used in pharmacological studies to explore the receptor topology.[3] In this paper we wish to report a general and diversity-oriented approach towards the syntheses of these compounds, including the construction of a stereogenic centre in the side chain.



Celecoxib Deracoxib

Figure 1. Some pyrazole-based marketed drugs.

Our approach to the synthesis of densely substituted pyrazoles, i.e., α-aryl-α-pyrazolylacetophenones, is shown in Figure 2. The pyrazole ring can be obtained by a variety of synthetic methods, including the 1,3-dipolar cycloaddition of diazo compounds onto triple bonds and the cyclocondensation of hydrazines with 1,3-difunctionalized compounds. This last procedure is the most commonly used strategy because of the availability of 1,3-difunctionalized compounds, and it is the one we used in our approach. According to this, we disconnected our target molecules into a hydrazine (fragment D) and a chiral 1,3-dicarbonyl component, which can be prepared from a 1,3-diketone (fragment C), an aromatic aldehyde (fragment B), and mandelic acid (fragment A).

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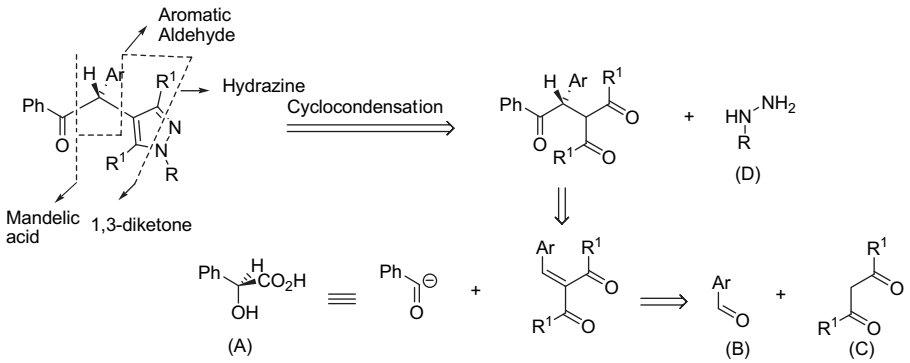


Figure 2. Retrosynthetic analysis.

Therefore, up to four points of diversity are possible in this scheme: R, R^1, Ar and the configuration of the stereogenic centre, which depends on mandelic acid.

The key step in the preparation of the chiral 1,3-dicarbonyl component is the conjugate addition of the enolate of (*S*)-mandelic acid to a 2-arylidene-1,3-diketone. Recently, we have described a highly diastereoselective Michael reaction of the enolate of (*S*)-(+)-mandelic acid to enones and the transformation of the resulting products into highly enantioenriched 2-substituted-1,4-diketones.[4]

2. Results and discussion

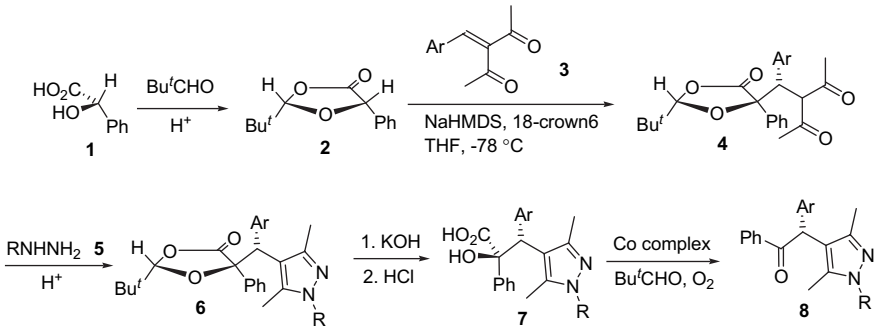
Our synthetic methodology is summarised in Scheme 1. The key step involves a Michael addition of the (*S*)-(+)-mandelic acid enolate to 2-arylidene-1,3-diketones **3**, which are easily prepared from aromatic aldehydes and pentane-2,4-dione via a Knoevenagel reaction.[5] These compounds are excellent Michael acceptors due to the strong anion-stabilising effect of the two carbonyl groups. Although the formation of the mandelic acid enolate leads to loss of chirality at the stereogenic centre, it is possible to regenerate the chiral information if (*S*)-(+)-mandelic acid (**1**) is previously transformed into (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**), according to the principle of self-regeneration of stereocentres,[6] as shown by Seebach[7] and us.[4,8,9]

The initial conditions tested for the Michael addition of **2** to 3-benzylidene-2,4-pentanedione **3a** were identical to those previously established by us for the addition of **2** to simple α,β-unsaturated ketones.[4] Compound **2** was deprotonated with a LDA solution at −78 °C in THF and then Michael acceptor **3a** was added to the resulting enolate solution. However, these conditions provided **4a** only with moderate yield and low diastereoselectivity (Table 1, entry 1). Next, the effect of the enolate aggregation state was examined. In most cases, the use of HMPA as an additive appreciably increases the reactivity as well as substantially modifies the selectivity. However, when 3 equiv of HMPA was used (entry 2) an important drop of the reaction yield was observed. The reaction was also examined in the presence of a crown ether as cation sequestering agent. When we carried out the reaction in the conditions reported recently by Dixon[10] for Michael addition to arylidene malonate esters, using 18-crown-6 and KHMDS as the base, the yield of **4a** was again very low (entry 3). However a change in the order of addition of the reagents brought about a spectacular increase in yield (90%) with a moderately good diastereoselectivity (77:23) (entry 4). Finally, the change of potassium to sodium

Table 1. Michael addition of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) and 3-benzylidene-2,4-pentanedione **3a** (optimisation of the conditions)

Entry	Additive	Base	**4a** Yield (%)[a]	**4a** dr[b]
1[c]	None	LDA	60	60:40
2[c]	HMPA	LDA	26	62:38
3[d]	18-Crown-6	KHMDS	19	80:20
4[e]	18-Crown-6	KHMDS	90	77:23
5[e]	18-Crown-6	NaHMDS	84	94:6

[a] Yield of the major adduct after column chromatography.
[b] Determined by ^{1}H NMR of the mixture prior purification.
[c] Our early protocol. See Ref. 4.
[d] Dixon's protocol. See Ref. 10.
[e] Our present protocol. See Section 3.



Scheme 1. Synthesis of compounds **4**–**8**.

hexamethyldisilazanide as the base increased the diastereoselectivity to 94:6, maintaining a good yield of **4a** (entry 5).

The Michael addition reaction with the enolate of **2** was carried out with several 2-arylidene-1,3-diketones **3** under these optimised conditions. In all cases the corresponding adducts **4** were obtained in good to excellent yields (81–94%) and diastereomeric ratios (from 89:11 to 97:3) (Table 2). It is important to note that the Michael adducts were obtained as only two diastereomers out of the four possible ones attending to the configuration of the two newly created stereogenic centres, one of the diastereomers being strongly predominant. The stereochemical structures of the major Michael adducts **4** were elucidated by NOE experiments. These experiments showed for all major diastereomers **4** a cis-relationship between the *t*-Bu group and the phenyl group from the original (*S*)-mandelic acid. The absolute configuration of the newly formed quaternary carbon atom was then assigned to be *S*, upon the consideration that the absolute configuration of the dioxolanone C-2 carbon atom bearing the *tert*-butyl group in **2** is *S* and remains unaltered from **2** to **4**. Furthermore, in the case of the *p*-chlorophenyl substituted adduct **4b**, the absolute stereochemistry of the major diastereomer was unambiguously determined by single X-ray diffraction (Fig. 3). According to the crystal structure the tertiary chiral carbon in **4b** had the *S* configuration. These results indicate that the major reaction pathway involves the approach of the *Re*-face of the 2-arylidene-1,3-diketone **3** to the *Re*-face of the lithium enolate of **2** (relative topicity *like*), in good agreement with the results reported by Seebach[7] and us[4,8,9] in related reactions.

The second step in our synthetic sequence was the preparation of the pyrazole ring system, which involves the cyclocondensation[11] of the 1,3-diketone moiety present in the Michael adducts **4** with different hydrazines **5**. Reaction of diketones **4a**, **4b** and **4e** with either phenylhydrazine (**5a**), or *p*-nitrophenylhydrazine (**5c**) using concd H_2SO_4 as catalyst in ethanol at reflux[11a] afforded pyrazoles **6aa** and **6ac**, **6ba** and **6bc**, **6ea** and **6ec**, respectively, with good yields (Table 3). The same diketones reacted with methylhydrazine (**5b**) at dioxane reflux in the presence of catalytic acetic acid[11b] to give pyrazoles **6ab**, **6bb** and **6eb** with acceptable yields (93–56%).

Table 2. Michael reaction of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) with 2-arylidene-1,3-diketones **3**

Entry	**3** (Ar)	**4** (Ar)	**4** Yield (%)[a]	**4** dr[b]
1	**3a** (Ph)	**4a** (Ph)	84	94:6
2	**3b** (*p*-ClC_6H_4)	**4b** (*p*-ClC_6H_4)	84	91:9
3	**3c** (*p*-BrC_6H_4)	**4c** (*p*-BrC_6H_4)	81	89:11
4	**3d** (*p*-MeC_6H_4)	**4d** (*p*-MeC_6H_4)	78	97:3
5	**3e** (*p*-$MeOC_6H_4$)	**4e** (*p*-$MeOC_6H_4$)	94	95:5

[a] Yield of the major adduct after column chromatography.
[b] Determined by ^1H NMR of the mixture prior purification.

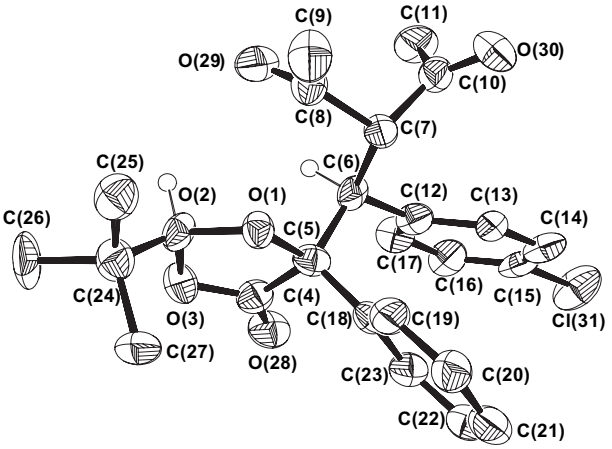


Figure 3. ORTEP drawing for compound **4b**.[14]

Table 3. Preparation of pyrazoles **6** from 1,3-diketones **4** and hydrazines **5**

Entry	**4** (Ar)	**5** (R)	Pyrazoles **6** (Yield %)
1	**4a** (Ph)	**5a** (Ph)	**6aa** (77)
2	**4a** (Ph)	**5b** (Me)	**6ab** (93)
3	**4a** (Ph)	**5c** (*p*-$O_2NC_6H_4$)	**6ac** (74)
4	**4b** (*p*-ClC_6H_4)	**5a** (Ph)	**6ba** (86)
5	**4b** (*p*-ClC_6H_4)	**5b** (Me)	**6bb** (62)
6	**4b** (*p*-ClC_6H_4)	**5c** (*p*-$O_2NC_6H_4$)	**6bc** (74)
7	**4e** (*p*-$MeOC_6H_4$)	**5a** (Ph)	**6ea** (86)
8	**4e** (*p*-$MeOC_6H_4$)	**5b** (Me)	**6eb** (56)
9	**4e** (*p*-$MeOC_6H_4$)	**5c** (*p*-$O_2NC_6H_4$)	**6ec** (56)

The next step in our synthetic sequence was the cleavage of the 1,3-dioxolan-4-one moiety present in compound **6**, which was achieved upon basic hydrolysis with ethanolic KOH and reprotonation to give the corresponding hydroxy acids, α-aryl-α-pyrazolylatrolactic acids **7**, with good yields (Table 4).

Table 4. Hydrolysis of the 1,3-dioxolan-4-one moiety in compounds **6** and oxidative decarboxylation of the hydroxy acid in compounds **7**

Entry	**6**	**6**,**7**,**8** Ar	**6**,**7**,**8** R	**7** (Yield %)	**8** (Yield %)
1	**6aa**	Ph	Ph	**7aa** (94)	**8aa** (66)
2	**6ab**	Ph	Me	**7ab** (77)	**8ab** (87)
3	**6ac**	Ph	*p*-$O_2NC_6H_4$	**7ac** (73)	**8ac** (—)
4	**6ba**	*p*-Cl–C_6H_4	Ph	**7ba** (88)	**8ba** (62)
5	**6bb**	*p*-Cl–C_6H_4	Me	**7bb** (86)	**8bb** (61)
6	**6ea**	*p*-MeO–C_6H_4	Ph	**7ea** (99)	**8ea** (58)
7	**6eb**	*p*-MeO–C_6H_4	Me	**7eb** (93)	**8eb** (74)

Finally, the oxidative decarboxylation of the α-hydroxy acid moiety present in **7** to carbonyl compounds **8** was carried out by using a catalytic system developed in our laboratory that employs oxygen as terminal oxidant in the presence of pivalaldehyde and a catalytic amount of the Co(III)–Me_2opba complex (Fig. 4).[12] Under these conditions α-aryl-α-pyrazolylacetophenones **8** were obtained in good yields from α-aryl-α-pyrazolylatrolactic acids **7**, except in the case of the *N*-(*p*-nitrophenyl)pyrazole **7ac** that gave rise to a complex reaction mixture (Table 4).

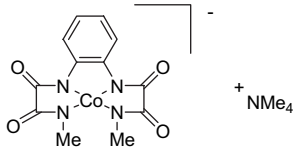


Figure 4. Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex.

In summary, a practical, efficient and diversity-oriented synthesis of enantiomerically pure densely substituted pyrazoles, α-aryl-α-pyrazolylatrolactic acids and α-aryl-α-pyrazolylacetophenones has been developed. The key step in this synthesis is the conjugate addition of the lithium enolate of the (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one to 2-arylidene-1,3-diketones, which proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. The cyclocondensation of the 1,3-diketone moieties present in these adducts with several hydrazines leads to substituted pyrazoles. Subsequent basic hydrolysis of the 1,3-dioxolan-4-one moiety present in these products leads to enantiomerically pure α-aryl-α-pyrazolylatrolactic acids. Finally, oxidative decarboxylation of these using oxygen, pivalaldehyde and the Co(III)–Me_2opba complex as catalyst gives α-aryl-α-pyrazolylacetophenones. In this synthetic sequence four points of diversity, including the configuration of the stereogenic centre of the side chain, are introduced. Furthermore, it should be noted that by using other substituted mandelic acids as starting materials,[13] a fifth point of diversity could be introduced (the substituent of the benzoyl group). In this synthetic sequence (*S*)-mandelic acid acts as an umpoled chiral equivalent of the benzoyl carbanion determining the configuration of the stereogenic centre of the side chain.

3. Experimental

3.1. General

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). Commercial reagents and solvents were of analytical grade or were purified by standard procedures, prior to use. All reactions involving air or moisture sensitive materials were carried out under nitrogen atmosphere. Optical rotations were determined on a Perkin–Elmer 243 polarimeter. NMR spectra were recorded on a Bruker Advance 300 DPX spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz) or a Varian Unity 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) and referenced to TMS as internal standard. The carbon type was determined by DEPT experiments. In the case of some pyrazoles **6** the ^{13}C NMR was registered in DMSO-d_6 at 70 °C in order to observe all the expected signals. Mass spectra were run by electron impact at 70 eV, by chemical ionisation using methane as ionising gas, or FAB+ on a VG Autospec spectrometer (VG Analytical, Micromass Instruments). All new compounds were determined >95% pure by ^{1}H NMR spectroscopy.

3.2. General procedure for the preparation of Michael adducts 4

A solution of 18-crown-6 (0.8 mmol) in dry THF (0.8 mL) was added to a solution of NaHMDS (1.0 mmol) in dry THF (10 mL) at −78 °C. The reaction mixture was then stirred for 15 min at −78 °C before a solution of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolanone (**2**)[7a] (0.8 mmol) in dry THF (4.5 mL) was dropwise added. Stirring was maintained for 30 min at −78 °C before a solution of 2-arylidene-1,3-diketone **3** (0.67 mmol) in dry THF (5 mL) was added. The reaction was kept at this temperature until consumption of the 2-arylidene-1,3-diketone **3** as indicated by TLC. The reaction was then quenched with glacial acetic acid (80 μL, 2 mmol) via syringe at −78 °C. Once the mixture reached room temperature, water (15 mL) was added and extracted with diethyl ether (3×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was flash chromatographed on silica gel (hexane–diethyl ether) to afford adduct **4**.

3.2.1. Michael adduct 4a. White crystals; mp 177–178 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +296.9 (*c* 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (9H, s), 1.61 (3H, s), 2.25 (3H, s), 4.45 (1H, d, *J*=11.4 Hz), 4.53 (1H, d, *J*=11.4 Hz), 4.92 (1H, s), 7.20–7.35 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 26.9 (q), 30.5 (q), 34.6 (q), 51.8 (d), 70.2 (d), 82.4 (s), 107.8 (d), 126.9 (d), 127.6 (d), 128.0 (d), 128.2 (d), 128.6 (d), 133.7 (s), 134.2 (s), 170.4 (s), 201.1 (s), 202.0 (s); HRMS (CI) *m*/*z* 409.2015 (M^++1, 62, $C_{25}H_{29}O_5$ required 409.2015), 323 (83), 220 (51), 147 (75), 105 (100).

3.2.2. Michael adduct 4b. White crystals; mp 197–198 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +286.3 (*c* 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.64 (3H, s), 2.28 (3H, s), 4.44 (2H, s), 5.01 (1H, s), 7.2–7.35 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 27.0 (q), 30.6 (q), 34.6 (q), 51.2 (d), 70.0 (d), 82.0 (s), 107.9 (d), 126.9 (d), 127.7 (d), 128.2 (d), 128.8 (d), 132.7 (s), 133.3 (s), 134.3 (s), 170.3 (s), 200.8 (s), 201.7 (s); HRMS (CI) *m*/*z* 443.1682 (M^++1, 13, $C_{25}H_{28}ClO_5$ required 443.1625), 445 (4), 359 (15), 357 (43), 220 (68), 219 (61), 105 (100).

3.2.3. Michael adduct 4c. White crystals; mp 202–203 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +272.3 (*c* 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.64 (3H, s), 2.28 (3H, s), 4.41 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.7 Hz), 5.01 (1H, s), 7.25–7.40 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 27.0 (q), 30.5 (q), 34.6 (q), 51.2 (d), 70.0 (d), 81.9 (s), 107.9 (d), 122.5 (s), 126.8 (d), 127.7 (d), 128.8 (d), 131.1 (d), 131.2 (s), 133.2 (s), 170.2 (s), 200.8 (s), 201.6 (s); HRMS (CI) *m*/*z* 487.1147 (M^++1, 1, $C_{25}H_{28}BrO_5$ required 487.1120), 489 (1), 403 (9), 401 (9), 220 (41), 219 (34), 105 (100).

3.2.4. Michael adduct 4d. White solid; mp 164–165 °C; $[\alpha]_D^{25}$ +299.2 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.61 (3H, s), 2.25 (3H, s), 2.30 (3H, s), 4.41 (1H, d, *J*=11.1 Hz), 4.48 (1H, d, *J*=11.4 Hz), 4.95 (1H, s), 7.20–7.35 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (q), 23.1 (q), 26.8 (q), 30.5 (q), 34.5 (q), 51.3 (d), 70.2 (d), 82.3 (s), 107.6 (d), 126.9 (d), 127.5 (d), 128.5 (d), 128.6 (d), 130.9 (d), 133.6 (s), 137.9 (s), 170.4 (s), 201.2 (s), 202.0 (s); HRMS (CI) *m*/*z* 423.2268 (M^++1, 69, $C_{26}H_{31}O_5$ required 423.2171), 337 (93), 220 (38), 203 (76), 161 (100), 105 (5).

3.2.5. Michael adduct 4e. White solid; mp 128–130 °C; $[\alpha]_D^{25}$ +272.0 (*c* 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.62 (3H, s), 2.25 (3H, s), 3.78 (3H, s), 4.40 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.4 Hz), 4.96 (1H, s), 7.20–7.30 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2

(q), 26.7 (q), 30.6 (q), 34.5 (q), 50.9 (d), 55.1 (q), 70.3 (d), 82.4 (s), 107.7 (d), 113.2 (d), 113.3 (d), 125.9 (s), 126.9 (d), 127.5 (d), 128.5 (d), 159.3 (s), 170.5 (s), 201.2 (s), 202.1 (s); HRMS (CI) *m/z* 339.1614 (M^++1−$C_5H_7O_2$, 9, $C_{21}H_{23}O_4$ required 339.1596), 219 (25), 177 (100), 105 (5).

3.3. General procedure for the preparation of pyrazoles 6

3.3.1. Procedure A (reaction with arylhydrazines). To a solution of compound **4** (0.24 mmol) in absolute EtOH (3 mL), acidified with a drop of concd H_2SO_4, was dropwise added a solution of arylhydrazine **5** ($PhNHNH_2$ or *p*-$NO_2PhNHNH_2$) (0.48 mmol) in absolute EtOH (2 mL). The reaction mixture was heated at reflux temperature until complete transformation of compound **4** into pyrazole **6**, as shown by TLC. Then, the reaction mixture was neutralised with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and flash chromatographed on silica gel (hexane–diethyl ether) to afford pyrazoles **6**.

3.3.2. Procedure B (reaction with methylhydrazine). A solution of compound **4** (0.49 mmol), methylhydrazine **5b** (0.98 mmol) and CH_3CO_2H (56 μL, 0.98 mmol) in dioxane (8 mL), was heated at reflux temperature until complete transformation of compound **4** into pyrazole **6**, as shown by TLC (in some cases additional amounts of reagent were added). Then, the dioxane was removed in vacuo, and the residue was diluted with water, extracted with EtOAc, washed with saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4, concentrated and flash chromatographed on silica gel (hexane–diethyl ether) to afford pyrazoles **6**.

3.3.3. Pyrazole 6aa. Yellow oil; $[\alpha]_D^{25}$ +253.0 (*c* 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.15 (3H, br s), 2.41 (3H, br s), 4.97 (1H, s), 5.03 (1H, s), 7.06–7.45 (13H, m), 7.83 (2H, d, *J*=7.2 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (9H, s), 2.13 (3H, s), 2.29 (3H, s), 5.01 (1H, s), 5.03 (1H, s), 7.02 (1H, tt, *J*=7.4, 1.4 Hz), 7.12 (2H, t, *J*=7.6 Hz), 7.20 (2H, dt, *J*=7.6, 1.2 Hz), 7.31 (2H, d, *J*=8 Hz), 7.35 (2H, d, *J*=7.6 Hz), 7.40 (2H, d, *J*=8 Hz), 7.41 (1H, d, *J*=7.2 Hz), 7.5 (2H, t, *J*=7.8 Hz), 7.83 (2H, d, *J*=8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 10.7 (q), 12.5 (q), 23.0 (q), 34.3 (q), 48.5 (d), 86.2 (s), 109.4 (d), 115.0 (s), 124.4 (d), 125.3 (d), 125.5 (d), 126.9 (d), 127.0 (d), 127.2 (d), 127.3 (d), 128.5 (d), 129.4 (d), 137.2 (s), 137.4 (s), 137.5 (s), 139.1 (s), 147.0 (s), 172.4 (s); HRMS (FAB+) *m/z* 481.2497 (M^++1, 33, $C_{31}H_{33}N_2O_3$ required 481.2491), 262 (36), 261 (100), 147 (15).

3.3.4. Pyrazole 6ab. Colourless oil; $[\alpha]_D^{25}$ +270.4 (*c* 0.71, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (9H, s), 2.01 (3H, br s), 2.33 (3H, br s), 3.67 (3H, s), 4.85 (1H, s), 4.97 (1H, s), 6.96 (1H, t, *J*=7.2 Hz), 7.05 (2H, t, *J*=7.8 Hz), 7.13 (1H, t, *J*=7.2 Hz), 7.25 (2H, m), 7.81 (2H, dd, *J*=7.5, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1 (q), 13.6 (q), 23.8 (q), 35.1 (q), 36.1 (q), 49.6 (d), 87.0 (s), 110.5 (d), 114.0 (s), 125.7 (d), 125.8 (d), 127.4 (d), 127.6 (d), 127.8 (d), 129.9 (d), 137.5 (s), 137.9 (s), 138.0 (s), 146.4 (s), 173.8 (s); HRMS (FAB+) *m/z* 419.2341 (M^++1, 34, $C_{26}H_{31}N_2O_3$ required 419.2335), 281 (12), 221 (13), 199 (100), 147 (71).

3.3.5. Pyrazole 6ac. Yellow oil; $[\alpha]_D^{25}$ +241.0 (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.13 (3H, br s), 2.54 (3H, br s), 4.97 (1H, s), 5.01 (1H, s), 7.05–7.20 (5H, m), 7.29 (3H, t, *J*=7.5 Hz), 7.65 (2H, d, *J*=8.7 Hz), 7.84 (2H, d, *J*=7.5 Hz), 8.33 (2H, d, *J*=9 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (9H, s), 2.15 (3H, s), 2.45 (3H, s), 5.03 (1H, s), 5.06 (1H, s), 7.03 (1H, t, *J*=7.4 Hz), 7.12 (2H, t, *J*=7.4 Hz), 7.21 (1H, t, *J*=7.2 Hz), 7.32 (2H, t, *J*=7.8 Hz), 7.36 (2H, d, *J*=7.6 Hz), 7.77 (2H, d, *J*=8.8 Hz), 7.85 (2H, dd, *J*=8.4, 1.2 Hz), 8.32 (2H, d, *J*=9.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 11.1 (q), 12.6 (q), 23.0 (q), 34.3 (q), 48.4 (d), 86.0 (s), 109.4 (d), 116.9 (s), 124.0 (d), 124.1 (d), 125.3 (d), 125.6 (d), 127.0 (d), 127.2 (d), 127.3 (d), 129.5 (d), 137.2 (s), 137.3 (s), 138.0 (s), 144.0 (s), 145.3 (s), 148.9 (s), 172.3 (s); HRMS (FAB+) *m/z* 526.2383 (M^++1, 70, $C_{31}H_{32}N_3O_5$ required 526.2342), 306 (100), 260 (15), 105 (14).

3.3.6. Pyrazole 6ba. Colourless oil; $[\alpha]_D^{25}$ +228.9 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (9H, s), 2.03 (3H, s), 2.35 (3H, s), 4.85 (1H, s), 4.94 (1H, s), 7.00 (2H, d, *J*=8.4 Hz), 7.12–7.41 (10H, m), 7.73 (2H, d, *J*=7.5 Hz), ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (9H, s), 2.15 (3H, s), 2.30 (3H, s), 5.00 (1H, s), 5.04 (1H, s), 7.16 (2H, d, *J*=8.8 Hz), 7.22 (1H, td, *J*=7.4, 1.2 Hz), 7.33 (2H, t, *J*=8.4 Hz), 7.37 (2H, d, *J*=8.8 Hz), 7.43–7.39 (3H, m), 7.51 (2H, t, *J*=7.6 Hz), 7.82 (2H, dd, *J*=8.4, 1.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 10.7 (q), 12.5 (q), 23.0 (q), 29.5 (s), 47.9 (d), 86.0 (s), 109.5 (d), 124.4 (d), 125.2 (d), 126.9 (d), 127.0 (d), 127.3 (d), 127.4 (d), 128.6 (d), 130.3 (s), 131.3 (d), 136.5 (s), 137.2 (s), 137.3 (s), 139.0 (s), 146.9 (s), 172.1 (s); HRMS (FAB+) *m/z* 515.2119 (M^++1, 15, $C_{31}H_{32}ClN_2O_3$ required 515.2101), 517 (5), 297 (34), 296 (44), 295 (86), 267 (15), 221 (46), 147 (100).

3.3.7. Pyrazole 6bb. Colourless oil; $[\alpha]_D^{25}$ +260.1 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (9H, s), 2.00 (3H, s), 2.34 (3H, s), 3.71 (3H, s), 4.81 (1H, s), 4.95 (1H, s), 7.03 (2H, d, *J*=8.4 Hz), 7.18–7.30 (5H, m), 7.78 (d, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1 (q), 14.2 (q), 23.8 (q), 35.1 (s), 36.2 (q), 49.1 (d), 86.9 (s), 110.6 (d), 113.6 (s), 125.7 (d), 127.7 (d), 127.9 (d), 128.0 (d), 131.3 (d), 131.7 (s), 137.60 (s), 137.63 (s), 146.3 (s), 173.0 (s); HRMS (FAB+) *m/z* 453.1951 (M^++1, 49, $C_{26}H_{30}ClN_2O_3$ required 453.1945), 455 (16), 235 (33), 233 (100), 147 (44).

3.3.8. Pyrazole 6bc. Yellow oil; $[\alpha]_D^{25}$ +236.2 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.10 (3H, br s), 2.55 (3H, br s), 4.92 (1H, s), 5.00 (1H, s), 7.1 (2H, d, *J*=8.7 Hz), 7.23 (3H, t, *J*=6.9 Hz), 7.31 (2H, t, *J*=7.5 Hz), 7.66 (2H, d, *J*=8.7 Hz), 7.81 (2H, d, *J*=9 Hz), 8.34 (2H, d, *J*=9 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (9H, s), 2.17 (3H, s), 2.46 (3H, s), 5.02 (1H, s), 5.07 (1H, s), 7.17 (2H, d, *J*=8.8 Hz), 7.23 (1H, tt, *J*=7.4, 1.2 Hz), 7.34 (2H, t, *J*=7.6 Hz), 7.38 (2H, d, *J*=8.4 Hz), 7.77 (2H, d, *J*=9.2 Hz), 7.84 (2H, dd, *J*=8.8, 1.2 Hz), 8.32 (2H, d, *J*=9.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 11.1 (q), 12.6 (q), 22.9 (q), 34.3 (q), 47.8 (d), 85.8 (s), 109.5 (d), 116.3 (s), 124.1 (d), 124.2 (d), 125.3 (d), 127.0 (d), 127.39 (d), 127.42 (d), 130.4 (s), 131.3 (d), 136.2 (s), 137.0 (s), 138.1 (s), 143.9 (s), 145.3 (s), 148.8 (s), 172.0 (s); HRMS (FAB+) *m/z* 560.1956 (M^++1, 81, $C_{31}H_{31}ClN_3O_5$ required 560.1952), 562 (33), 342 (42), 340 (100), 169 (38).

3.3.9. Pyrazole 6ea. Yellow oil; $[\alpha]_D^{25}$ +270.8 (*c* 0.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.14 (3H, br s), 2.40 (3H, br s), 3.68 (3H, s), 4.91 (1H, s), 5.02 (1H, s), 6.63 (2H, d, *J*=8.7 Hz), 7.15–7.3 (5H, m), 7.35–7.48 (5H, m), 7.82 (2H, d, *J*=7.5 Hz); ^1H NMR (400 MHz, DMSO-d_6) δ 1.00 (9H, s), 2.15 (3H, s), 2.29 (3H, s), 3.64 (3H, s), 4.97 (1H, s), 5.01 (1H, s), 6.68 (2H, d, *J*=9.2 Hz), 7.21 (1H, tt, *J*=8.6, 1.4 Hz), 7.26 (2H, d, *J*=8.4 Hz), 7.32 (2H, t, *J*=7.6 Hz), 7.37–7.43 (3H, m), 7.47–7.53 (2H, m), 7.82 (2H, dd, *J*=8.4, 1.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 10.7 (q), 12.5 (q), 23.0 (q), 34.2 (q), 47.8 (d), 54.4 (q), 86.3 (s), 109.4 (d), 112.6 (d), 115.3 (s), 124.4 (d), 125.2 (d), 126.9 (d), 127.1 (d), 127.3 (d), 128.5 (d), 129.5 (s), 130.5 (d), 137.0 (s), 137.5 (s), 139.1 (s), 147.0 (s), 156.9 (s), 172.4 (s); HRMS (FAB+) *m/z* 511.2584 (M^++1, 70, $C_{32}H_{35}N_2O_4$ required 511.2597), 291 (100), 169 (12).

3.3.10. Pyrazole 6eb. Colourless oil; $[\alpha]_D^{25}$ +246.9 (*c* 0.82, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (9H, s), 1.97 (3H, br s), 2.25 (3H, br s), 3.59 (3H, s), 3.63 (3H, s), 4.72 (1H, s), 4.89 (1H, s), 6.52 (2H, d, *J*=9.0 Hz), 7.09 (1H, t, *J*=6.9 Hz), 7.10 (2H, d, *J*=9 Hz), 7.19 (2H, d, *J*=7.5 Hz), 7.72 (2H, d, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2 (q), 14.1 (q), 23.9 (q), 35.1 (q), 36.1 (q), 48.9 (d), 54.9 (q), 87.2 (s), 110.5 (d), 112.8 (d), 114.3 (s), 125.7 (d), 127.6 (d), 127.9 (d), 130.2 (s), 130.9 (d), 137.4 (s), 138.0 (s), 146.4 (s), 157.4 (s), 173.9 (s); HRMS (FAB+) *m/z* 449.2447 (M^++1, 11, $C_{27}H_{33}N_2O_4$ required 449.2440), 281 (40), 229 (18), 221 (54), 147 (100).

3.3.11. Pyrazole 6ec. Yellow oil; $[\alpha]_D^{25}$ +288.4 (*c* 0.70, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (9H, s), 2.13 (3H, br s), 2.54 (3H, br s), 3.69 (3H, s), 4.90 (1H, s), 5.00 (1H, s), 6.65 (2H, d, *J*=6.9 Hz), 7.20 (3H, t, *J*=7.2 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.66 (2H, d, *J*=8.7 Hz), 7.82 (2H, d, *J*=7.5 Hz), 8.33 (2H, d, *J*=9.3 Hz); ^1H NMR (400 MHz, DMSO-d_6, 70 °C) δ 1.00 (9H, s), 2.16 (3H, s), 2.45 (3H, s), 3.64 (3H, s), 4.99 (1H, s), 5.02 (1H, s), 6.68 (2H, d, *J*=8.8 Hz), 7.22 (1H, t, *J*=7.2 Hz), 7.26 (2H, d, *J*=8.8 Hz), 7.33 (2H, t, *J*=7.6 Hz), 7.77 (2H, d, *J*=9.2 Hz), 7.83 (2H, d, *J*=7.6 Hz), 8.32 (2H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 11.2 (q), 12.6 (q), 23.0 (q), 34.3 (q), 47.6 (d), 54.4 (q), 86.2 (s), 109.4 (d), 112.6 (d), 117.2 (s), 124.1 (d), 124.1 (d), 125.3 (d), 127.2 (d), 127.3 (d), 129.1 (s), 130.5 (d), 137.4 (s), 137.9 (s), 144.0 (s), 145.2 (s), 148.9 (s), 157.0 (s), 172.3 (s). HRMS (FAB+) *m/z* 556.2436 (M^++1, 71, $C_{32}H_{34}N_3O_6$ required 556.2448), 336 (100), 238 (27), 169 (62).

3.4. General procedure for the hydrolysis of the 1,3-dioxolan-4-one moiety in compound 6

Compound **6** (0.5 mmol) was treated with 5% ethanolic KOH (1.1 mL, 1 mmol) at 60 °C until complete reaction of the starting material (TLC). The reaction mixture was poured into ice and acidified with 1 M HCl until pH ~2. The aqueous mixture was extracted with EtOAc (4×25 mL), and the organic layers were washed with brine (2×15 mL), dried ($NaSO_4$), filtered and concentrated under reduced pressure to give α-hydroxy acids **7**.

3.4.1. Compound 7aa. White solid; mp 225–227 °C (from ether–methanol); $[\alpha]_D^{25}$ +179.6 (*c* 0.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.25 (3H, s), 5.10 (1H, s), 6.93–6.97 (3H, m), 7.06–7.18 (10H, m), 7.60 (2H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (q), 12.4 (q), 47.3 (d), 81.3 (s), 117.8 (s), 125.6 (d), 126.5 (d), 127.0 (d), 127.48 (d), 127.78 (d), 128.0 (d), 128.78 (d), 128.83 (d), 130.0 (d), 138.0 (s), 139.34 (s), 139.99 (s), 141.7 (s), 148.0 (s), 176.2 (s); HRMS (FAB+) *m/z* 413.1875 (M^++1, 5, $C_{26}H_{25}N_2O_3$ required 413.1865), 282 (22), 261 (100), 147 (74).

3.4.2. Compound 7ab. White solid; mp 255–257 °C (from chloroform–methanol); $[\alpha]_D^{25}$ +261.0 (*c* 1.8, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (3H, s), 2.49 (3H, s), 3.58 (3H, s), 5.23 (1H, s), 6.98–7.04 (3H, m), 7.16–7.27 (5H, m), 7.76 (2H, d, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$–MeOH-d_4) δ 10.5 (q), 11.9 (q), 34.9 (q), 46.8 (d), 80.8 (s), 115.5 (s), 125.0 (d), 126.1 (d), 126.8 (d), 127.0 (d), 127.5 (d), 129.6 (d), 138.6 (s), 139.4 (s), 141.0 (s), 146.1 (s), 176.1 (s); HRMS (FAB+) *m/z* 351.1711 (M^++1, 41, $C_{21}H_{23}N_2O_3$ required 351.1709), 281 (36), 221 (45), 199 (38), 147 (100).

3.4.3. Compound 7ac. Oil; $[\alpha]_D^{25}$ −150.0 (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (3H, s), 2.20 (3H, s), 5.12 (1H, s), 6.90–7.00 (3H, m), 7.10–7.30 (7H, m), 7.57 (2H, d, *J*=7.2 Hz), 7.93 (2H, d, *J*=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7 (q), 12.8 (q), 47.0 (d), 81.3 (s), 119.4 (s), 124.4 (d), 124.9 (d), 125.9 (d), 126.3 (d), 127.4 (d), 127.6 (d), 128.0 (d), 129.9 (d), 138.6 (s), 140.0 (s), 141.2 (s), 143.5 (s), 146.0 (s), 150.2 (s), 176.2 (s); HRMS (FAB+) *m/z* 458.1711 (M^++1, 7, $C_{26}H_{24}N_3O_5$ required 458.1716), 412 (8), 281 (32), 147 (100).

3.4.4. Compound 7ba. White solid; mp 240–243 °C (from chloroform–methanol); $[\alpha]_D^{25}$ +201.8 (*c* 1.2, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (3H, s), 2.24 (3H, s), 5.11 (1H, s), 6.99 (2H, d, *J*=8.1 Hz), 7.10–7.25 (10H, m), 7.64 (2H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (q), 12.3 (q), 46.8 (d), 81.1 (s), 115.3 (d), 117.2 (s), 125.6 (d), 126.4 (d), 127.6 (d), 127.9 (d), 128.9 (d), 129.5 (d), 131.4 (d), 137.9 (s), 139.9 (s), 141.3 (s), 147.9 (s), 155.9 (s), 176.1 (s); HRMS (FAB+) *m/z* 447.1495 (M^++1, 20, $C_{26}H_{24}ClN_2O_3$ required 447.1475), 449 (5), 294 (44), 281 (29), 154 (100).

3.4.5. Compound 7bb. Pale yellow solid; mp 230–232 °C (from ether–methanol); $[\alpha]_D^{25}$ +202.1 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.33 (3H, s), 3.44 (3H, s), 5.09 (1H, s), 6.93 (2H, d, *J*=9.0 Hz), 7.05–7.19 (5H, m), 7.66 (2H, d, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4 (q), 11.6 (q), 34.9 (q), 46.6 (d), 81.2 (s), 116.5 (s), 126.4 (d), 127.14 (d), 127.64 (d), 127.95 (d), 131.24 (d), 131.32 (s), 138.3 (s), 140.3 (s), 141.8 (s), 145.1 (s), 177.2 (s); HRMS (FAB+) *m/z* 385.1316 (M^++1, 9, $C_{21}H_{22}ClN_2O_3$ required 385.1319), 387 (3), 281 (40), 221 (40), 207 (45), 147 (100).

3.4.6. Compound 7ea. Pale yellow solid; mp 248–251 °C (from ether–methanol); $[\alpha]_D^{25}$ +164.8 (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$-25% CD_3OD) δ 2.14 (3H, s), 2.24 (3H, s), 3.57 (3H, s), 5.09 (1H, s), 6.51 (2H, d, *J*=8.4 Hz), 7.07–7.31 (10H, m), 7.65 (2H, d, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$-25% CD_3OD) δ 12.4 (q), 12.5 (q), 46.7 (d),

54.9 (q), 81.3 (s), 112.8 (d), 117.5 (s), 124.4 (d), 125.4 (d), 127.1 (d), 127.6 (d), 128.8 (d), 130.45 (d), 130.90 (d), 131.5 (s), 138.5 (s), 139.1 (s), 141.3 (s), 148.5 (s), 157.1 (s), 176.5 (s); HRMS (FAB+) *m/z* 443.1944 (M^++1, 25, $C_{27}H_{27}N_2O_4$ required 443.1971), 281 (92), 207 (100), 147 (100).

3.4.7. Compound 7eb. Pale yellow solid; mp 230–231 °C (from ether–methanol); $[\alpha]_D^{25}$ +203.9 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.13 (3H, s), 2.38 (3H, s), 3.49 (3H, s), 3.66 (3H, s), 5.14 (1H, s), 6.58 (2H, d, *J*=8.7 Hz), 7.08–7.26 (5H, m), 7.76 (2H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (q), 11.7 (q), 34.9 (q), 46.4, (d), 54.9 (q), 81.5 (s), 112.8 (d), 117.2 (s), 126.5 (d), 126.9 (d), 127.8 (d), 130.8 (d), 131.8 (s), 140.1 (s), 142.3 (s), 145.2 (s), 157.2 (s), 177.7 (s); HRMS (FAB+) *m/z* 381.1823 (M^++1, 54, $C_{22}H_{25}N_2O_4$ required 381.1814), 281 (86), 229 (83), 207 (63), 147 (100).

3.5. General procedure for the oxidative decarboxylation of α-hydroxy acid moiety of compound 7

A solution of compound **7** (0.22 mmol), Co(III)–Me_2opba complex (5.3 mg, 0.013 mmol) and pivalaldehyde (74 μL, 0.66 mmol) in acetonitrile (1.5 mL) and DMF (0.2 mL) was stirred under an oxygen atmosphere until consumption of the starting material (TLC). Water was added, the mixture was extracted with ethyl ether (3×20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (2×10 mL) and dried ($MgSO_4$). The reaction products were purified by flash chromatography on silica gel (hexane–ethyl acetate) to afford compound **8**.

3.5.1. Compound 8aa. Orange oil; $[\alpha]_D^{25}$ −34.8 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (3H, s), 2.22 (3H, s), 5.92 (1H, s), 7.19 (2H, d, *J*=6.6 Hz), 7.55–7.26 (13H, m), 8.00 (2H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5 (q), 12.5 (q), 50.0 (d), 125.2 (d), 125.5 (d), 126.7 (d), 127.6 (d), 128.5 (d), 128.89 (d), 128.94 (d), 129.2 (d), 133.2 (d), 136.1 (s), 136.7 (s), 137.6 (s), 138.4 (s), 139.4 (s), 147.9 (s), 198.1 (s); HRMS (FAB+) *m/z* 367.1829 (M^++1, 100, $C_{25}H_{23}N_2O$ required 367.1810), 277 (20), 261 (64).

3.5.2. Compound 8ab. Yellow oil; $[\alpha]_D^{25}$ −71.0 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, s), 2.14 (3H, s), 3.70 (3H, s), 5.83 (1H, s), 7.11 (2H, d, *J*=6.6 Hz), 7.55–7.25 (8H, m), 7.95 (2H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1 (q), 12.1 (q), 27.1 (q), 35.9 (q), 49.9 (d), 126.9 (d), 128.30 (s), 128.4 (d), 128.6 (d), 128.9 (d), 130.0 (s), 133.0 (d), 136.7 (s), 138.6 (s), 145.7 (s), 198.2 (s); HRMS (FAB+) *m/z* 305.1643 (M^++1, 100, $C_{20}H_{21}N_2O$ required 305.1654), 215 (25), 199 (62).

3.5.3. Compound 8ba. Yellow oil; $[\alpha]_D^{25}$ −19.1 (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (3H, s), 2.21 (3H, s), 5.86 (1H, s), 7.11 (2H, d, *J*=8.4 Hz), 7.30–7.37 (5H, m), 7.41–7.47 (4H, m), 7.56 (1H, t, *J*=7.4 Hz), 7.98 (2H, d, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4 (q), 12.5 (q), 49.5 (d), 111.3 (s), 114.5 (s), 125.2 (d), 127.7 (d), 128.6 (d), 128.7 (d), 129.0 (d), 130.3 (d), 132.9 (s), 133.3 (s), 136.5 (s), 136.9 (s), 137.5 (s), 147.7 (s), 197.7 (s); HRMS (EI) *m/z* 400.1317 (M^+, 2, $C_{25}H_{21}ClN_2O$ required 400.1342), 297 (33), 295 (100).

3.5.4. Compound 8bb. Yellow oil; $[\alpha]_D^{25}$ −35.4 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.13 (3H, s), 3.69 (3H, s), 5.77 (1H, s), 7.04 (2H, d, *J*=8.7 Hz), 7.28 (2H, d, *J*=8.7), 7.41 (2H, t, *J*=7.5 Hz), 7.53 (1H, tt, *J*=7.8, 1.5 Hz), 7.92 (2H, dd, *J*=7.2, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1 (q), 12.2 (q), 36.0 (q), 49.4 (d), 112.6 (s), 128.47 (d), 128.55 (d), 128.63 (d), 130.2 (d), 130.3 (s), 132.7 (s), 133.2 (d), 136.5 (s), 137.1 (s), 145.6 (s), 197.8 (s); HRMS (EI) *m/z* 338.1168 (M^+, 2, $C_{20}H_{19}ClN_2O$ required 338.1186), 247 (15), 233 (100).

3.5.5. Compound 8ea. Pale yellow oil; $[\alpha]_D^{25}$ −52.2 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.13 (3H, s), 3.72 (3H, s), 5.78 (1H, s), 6.80 (2H, d, *J*=8.7 Hz), 7.02 (2H, d, *J*=9.3 Hz), 7.23–7.38 (7H, m), 7.45 (1H, tt, *J*=7.8, 1.5 Hz), 7.91 (2H, d, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4 (q), 12.6 (q), 49.4 (d), 55.2 (q), 113.9 (d), 115.2 (s), 125.2 (d), 127.5 (d), 128.6 (d), 128.9 (d), 130.0 (d), 130.4 (d), 133.0 (d), 136.8 (s), 137.3 (s), 139.6 (s), 147.9 (s), 158.5 (s), 198.4 (s); HRMS (EI) *m/z* 396.1847 (M^+, 1, $C_{26}H_{24}N_2O_2$ required 396.1838), 336 (11), 291 (100).

3.5.6. Compound 8eb. Pale yellow oil; $[\alpha]_D^{25}$ −70.5 (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.13 (3H, s), 3.69 (3H, s), 3.77 (3H, s), 5.77 (1H, s), 6.84 (2H, d, *J*=8.7 Hz), 7.04 (2H, d, *J*=8.7 Hz), 7.40 (2H, t, *J*=7.2 Hz), 7.51 (1H, t, *J*=7.5 Hz), 7.94 (2H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1 (q), 12.2 (q), 35.9 (q), 49.2 (d), 55.2 (q), 113.5 (s), 113.8 (d), 128.52 (d), 128.54 (d), 129.8 (d), 130.6 (s), 132.9 (d), 136.7 (s), 137.3 (s), 145.6 (s), 158.4 (s), 198.4 (s); HRMS (EI) *m/z* 334.1678 (M^+, 1, $C_{21}H_{22}N_2O_2$ required 334.1681), 244 (21), 149 (63).

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