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Organocatalyzed synthesis of chiral non-racemic 1,4-dihydropyridazines

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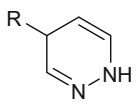
ABSTRACT

Chiral non-racemic 1,4-dihydropyridazines were prepared by the reaction of 1,2-diaza-1,3-dienes with arylacetaldehydes under organocatalytic conditions. L-Proline and (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine coupled with trifluoroacetic acid were used as organocatalysts. Enantiomeric excesses ranged from 25% to 78%.

1. Introduction

The Michael addition of carbon and hetero-nucleophiles to α,β-unsaturated systems is one of the most important bond-forming processes in organic chemistry since it offers an extremely powerful tool for the synthesis of highly functionalized molecules.[1] Therefore, extensive studies have been carried out on the development of catalytic asymmetric Michael procedures for various useful donor–acceptor combinations.[2] Functionalized 1,2-diaza-1,3-dienes (DDs) are reactive species both as acceptors in Michael reactions and as components in cycloadditions. In general, when they are used as electrophilic carbon derivatives, the resulting α-functionalized hydrazone intermediates evolve more or less rapidly towards the formation of five- or six-membered heterocyclic rings, depending on the reaction conditions, the nature of the nucleophile and the electrophile. Among the various possible products that can be prepared by these methods, 1,4-dihydropyridazine derivatives **1** (Fig. 1) are of particular interest, as some of them are known for their biological activity. For example, they act as vasodilators and coronary therapeutic agents, or as spasmolytic agents, particularly when the substituent at C4 is aromatic.[3]



1

Figure 1. 4-Substituted-1,4-dihydropyridazine ring.

Their activities can be correlated with those of 1,4-dihydropyridine derivatives, such as lercanidipine and niphedipine.[4] 1,4-Dihydropyridazines can be prepared by many different methods including formal [4+2] cycloadditions.[5] The particular case of an inverse electron demand Diels–Alder reaction[6] is the synthesis, carried out in hexane, of the 5,6-dihydro-4*H*-pyridazine derivative **4** starting from DD **2a** and the pyrrolidino enamine of phenylacetaldehyde **3**. The subsequent elimination of the amino moiety and the *tert*-butyloxycarbonyl group was carried out by treatment of compound **4** with Amberlyst 15 obtaining the corresponding 1,4-dihydropyridazine system **5** (Scheme 1). Starting from these results, we envisaged the possibility to use asymmetric enamine organocatalysis[7] to prepare compound **5** and other 4-aryl-1,4-dihydropyridazines in optically active forms.

2. Results and discussion

L-Proline (L-Pro) was chosen as the organocatalyst because it was the first organocatalyst used[8] and considering that many studies are present in the literature on the mechanism of its action.[7a,8,9] Freshly distilled phenylacetaldehyde **6** was reacted with DD **2b** in the presence of catalytic amounts of L-Pro (20 mol %) in tetrahydrofuran (THF), at room temperature. After 96 h, the ^{1}H NMR analysis of the crude reaction mixture revealed the almost complete disappearance of **2b** and the concomitant formation of ethyl 6-methyl-4-phenyl-1,4-dihydropyridazine-5-carboxylate **5**, which was purified by column chromatography (Scheme 2).

The enantiomeric excess of (+)-**5** was 39%, as determined by HPLC on a chiral column. The reaction was also performed using DD **2c**, which furnished compound (+)-**12** with 59% ee, determined by HPLC on a chiral column. Using (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (2PMP) and trifluoroacetic acid (TFA) as the organocatalytic mixture,[10] in THF, the ee of compound (+)-**5** was 75% while the ee of (+)-**12** was 46%. In particular, the structure of

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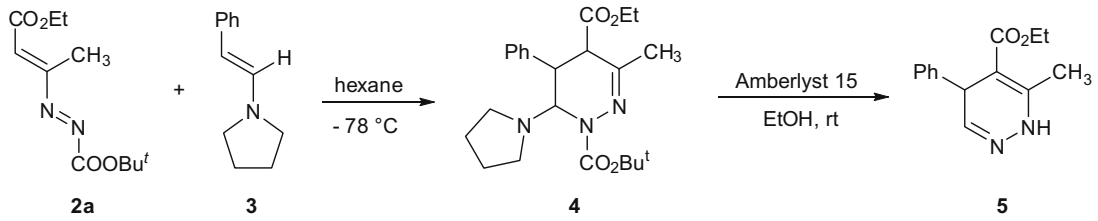


Scheme 1. Formation of 1,4-dihydropyridazine **5** via reaction of 1,2-diaza-1,3-butadiene **2a** and phenylacetaldehyde enamine **3**.

1,4-dihydropyridazine (+)-**12** was determined by X-ray spectroscopy diffraction (Fig. 2).

Using both L-Pro and 2PMP/TFA as organocatalysts, other arylacetaldehydes, namely compounds **7**–**11**, were also reacted with DD **2c**, with the aim of verifying a possible electronic effect on the outcome of the reaction and on the stability of the products. The resulting methyl 4-aryl-6-methyl-1,4-dihydropyridazine-5-carboxylates (+)-**13**–(+)-**17** were isolated as single reaction products. However, as shown in Table 1, the yields of the products were modest for compounds derived from phenylacetaldehyde, 4-bromophenylacetaldehyde and 4-ethoxy phenylacetaldehyde (entries 1–4), whereas the yields were much higher for those derived from nitrophenylacetaldehydes (entries 5–7). This is probably a consequence of the higher stability of the more conjugated enamine intermediate when the substituent at the phenyl ring is the nitro group.

Low catalyst turnover has already been observed in other cases[11] and it has been ascribed to the formation of unreactive hemiaminal species of relative stability.

A reaction was also performed between phenylacetaldehyde **6** and 4-ethoxycarbonyl-3-methyl-1-phenylaminocarbonyl-2-diaza-1,3-diene **2d**, in the presence of 2PMP/TFA, with the aim of determining whether a substituent on the carbamic nitrogen might have an influence on the course of the reaction. No difference was observed, as the known 1,4-dihydropyridazine (+)-**5** was isolated (25% yield, 47% ee) (Scheme 3).

A possible mechanism for the enamine organocatalysis is shown in Scheme 4, with L-Pro as the catalyst. Taking into account

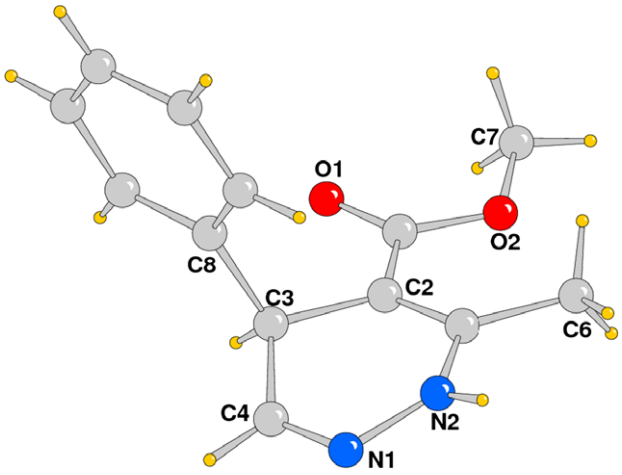
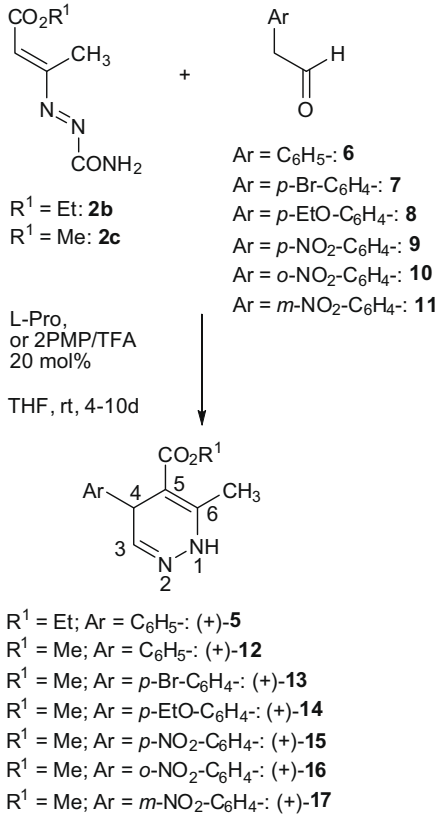


Figure 2. ORTEP drawing of compound **12**.

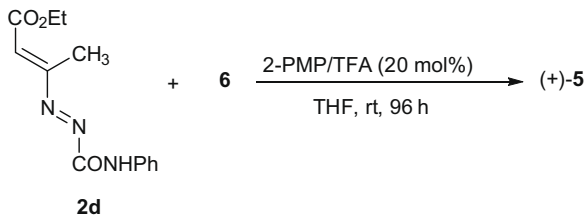
Table 1
Reaction times, yields and ee's for all products

Entry	Product	L-Pro			2PMP/TFA		
		Reaction time (d)	Yield[a] (%)	ee[b] (%)	Reaction time (d)	Yield[a] (%)	ee[b] (%)
1	(+)-**5**	4	35	39	4	40	75
2	(+)-**12**	4	25	59	4	37	46
3	(+)-**13**	5	23	62	5	32	72
4	(+)-**14**	10	18	66	10	15	28
5	(+)-**15**	7	70	69	10	36	25
6	(+)-**16**	5	85	52	5	83	35
7	(+)-**17**	7	87	78	4	62	65

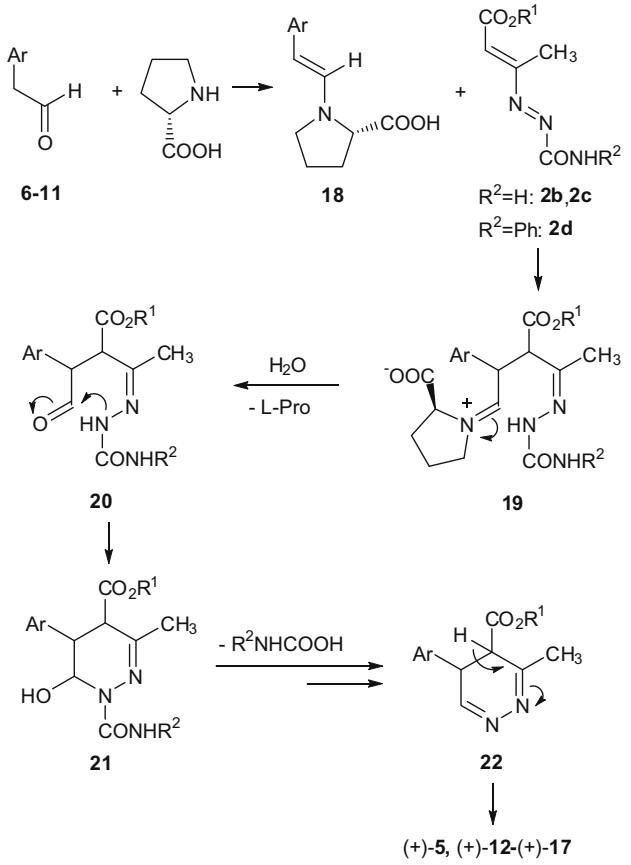
[a] In isolated product.
[b] Determined by HPLC on a chiral column.



Scheme 2. Organocatalyzed formation of 1,4-dihydropyridazines (+)-**5**, (+)-**12**–(+)-**17** from DDs **2b**,**c** and arylacetaldehydes **6**–**11**.



Scheme 3. Organocatalyzed formation of 1,4-dihydropyridazines (+)-**5** from DD **2d** and phenylacetaldehyde **6**.

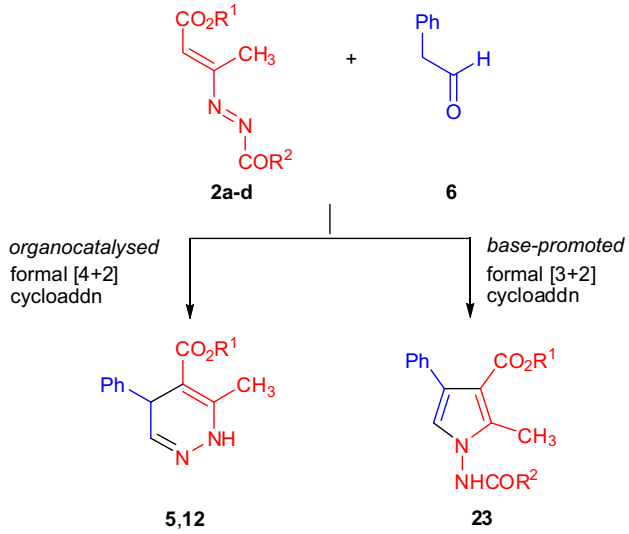


Scheme 4. Plausible mechanism of 1,4-dihydropyridazine formation.

what is proposed by several authors,[7a,9] L-Pro reacts with aldehydes **6**–**11** forming in situ their enamine derivatives **18**. The regioselective Michael-type reaction of the β-carbon atom of enamines **18** to the electrophilic terminal carbon atom of the azo-ene system produces the zwitterionic hydrazone intermediates **19**, which is then hydrolyzed in situ to give the corresponding aldehyde **20**.

Intramolecular nucleophilic attack of the nitrogen atom onto the carbonyl group determines the formation of the tetrahydropyridazine (intermediates **21**). The loss of either the carbamic acid (R^2 = H) or its phenyl derivative (R^2 = Ph), induced by L-Pro (or by TFA for the 2PMP-TFA pair), yields alkyl 4-aryl-6-methyl-1,4-dihydropyridazine-5-carboxylates (+)-**5** and (+)-**12**–(+)-**17**, after rearrangement of the 4,5-dihydropyridazine intermediates **22**. Under our reaction conditions, no traces of oxazolidinone systems have ever been detected, different to that found by Seebach and Eschenmoser et al. in the reaction between cyclohexanone and superelectrophiles such as (*E*)-β-nitrostyrene and chloral, organocatalyzed by L-Pro.[9c]

In this case the cyclization process occurred by means of formal [4+2] cyclization and all four atoms (C=C–N=N) of the former azo-ene system of starting DDs are incorporated into the 1,4-dihydropyridazine derivatives. It is noteworthy that the base-mediated reaction of the same starting phenylacetaldehyde **6** with the DDs **2a**–**d** produces the corresponding pyrrole derivatives **23** through formal [3+2] cycloaddition in which three atoms (C=C–N) of the azo-ene system are involved.[12] The same compounds **23** were obtained when the reaction between the DD **2a** and the pyrrolidino enamine of phenylacetaldehyde **3** was performed in methanol, firstly at −78 °C and then under heating (Scheme 5).[6] Under the conditions used for organocatalysis, no traces of pyrrole derivatives were found.



Scheme 5. Possible reaction pathways.

All optically active 1,4-dihydropyridazines (+)-**5**, (+)-**12**–(+)-**17** molecules exhibited very high positive specific rotation values. A direct comparison of the CD spectra of our 1,4-dihydropyridazines cannot be made, owing to their different enantiopurities. However, 1,4-dihydropyridazines (+)-**5**, (+)-**12**, (+)-**13**, (+)-**14** and (+)-**17** show two strong positive bands at about 250 nm and 320 nm (Fig. 3). These bands can be attributed to $\pi \rightarrow \pi^*$ transitions of the aromatic ring and to the enaminoester moiety. A third band (shoulder) around 260 nm showing fine structure can also be assigned to the aromatic ring. The *p*- and *o*-nitrophenyl derivatives (+)-**15** and (+)-**16** exhibit the same bands, shifted, however, the former to higher wavelengths, above 250 nm, and the latter to shorter wavelengths, around 300 nm, as a consequence of a strong electronic effect exerted by the nitro group.

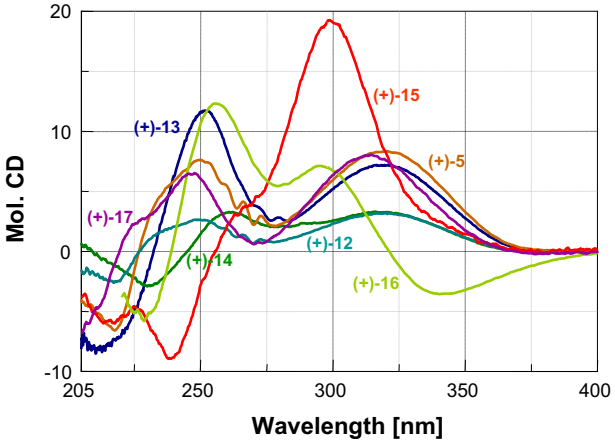


Figure 3. CD spectra for 1,4-dihydropyridazines (+)-**5**, (+)-**12**–(+)-**17**.

The assignment of the absolute configuration to the 1,4-dihydropyridazines (+)-**5** and (+)-**12**–(+)-**17** was tentatively made as (*S*), on the basis of the well-accepted catalysis mechanism of L-Pro, that is, a preferential *re*–*si* facial attack of the enamine intermediate, formed in situ from the aldehyde and proline (or protonated 2PMP), onto the electrophile, with formation of the transition state **24** (Fig. 4).

Transition states having 9–11-membered hydrogen-bonded ring have already been proposed for L-Pro and other pyrrolidine-based organocatalysts for a variety of carbon–carbon bond formations.[9a,13]

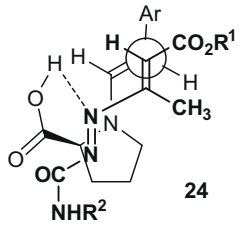
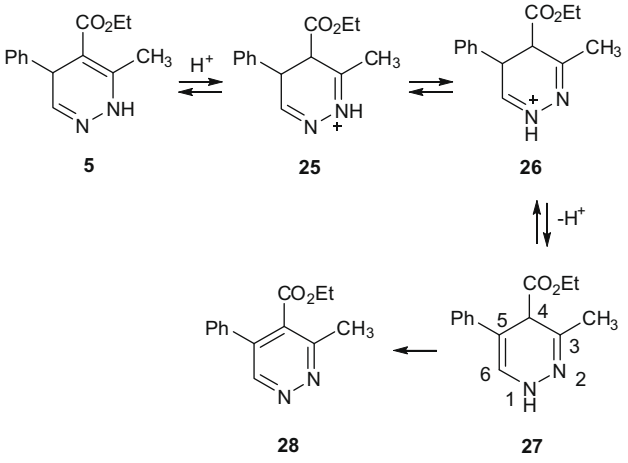


Figure 4. Transition state for proline-mediated reactions of aldehydes with DDs.

Under slightly acidic conditions, by traces of hydrochloric acid present in chloroform, 1,4-dihydropyridazines underwent a series of transformations that could be followed by ^{1}H NMR. For example, ethyl 6-methyl-4-phenyl-1,4-dihydropyridazine-5-carboxylate **5** was converted into its isomer ethyl 3-methyl-5-phenyl-1,4-dihydropyridazine-4-carboxylate **27**, through protonation of C5 to yield the intermediate **25**, prototropy to **26** and loss of proton to give compound **27**. Analogous isomerization, although under basic conditions, between methyl 3,5-dimethyl-1,4-dihydropyridazine-4-carboxylate and methyl 4,6-dimethyl-1,4-dihydropyridazine-5-carboxylate was proposed by Razin and co-workers.[14] These latter heterocycles can be eventually oxidized with potassium permanganate to the corresponding aromatic molecules. In the present case, the oxidation is presumably due to the air, occurring without addition of any oxidant and giving the pyridazine derivative **28**, even in the solid state (Scheme 6).



Scheme 6. Transformations of 1,4-dihydropyridazine (+)-**5** under slightly acidic conditions ($CDCl_3$).

On the other hand, the formation of the pyridazine derivatives is a common fate for all our 1,4-dihydropyridazines, when stored at room temperature.[5b] The process is more or less rapid, depending on the aryl substituent.

3. Conclusion

The formation of enantiomerically enriched polysubstituted 1,4-dihydropyridazines through a single reaction between DDs and arylacetaldehydes by organocatalysis is an interesting route, although enantiomeric excesses range from 25% to 78%. The use of different organocatalysts should be considered. As to the absolute configuration assignment, a computational investigation is currently in progress concerning the specific rotation, as successfully carried out in other cases.[15]

4. Experimental

4.1. General

Separation by column chromatography was achieved on silica gel for flash-chromatography (BDH) with conditions described by Still.[16] Thin layer chromatograms were run on 0.25 mm EM precoated plates of silica gel Polygram® Sil G/UV$_{254}$. Light petroleum refers to the fraction with bp 40–70 °C. High performance liquid chromatograms (HPLCs) were obtained on a Hewlett Packard Series 1100 instrument from a chiral column Lux 5μ Cellulose-2 (Phenomenex) with a Cellulose tris(3-chloro-4-methylphenylcarbammate) chiral stationary phase, eluent: *n*-hexane/isopropanol 75:25, detector UV 220 nm. IR spectra were recorded on a Jasco FT/IR 200 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained from a Jeol EX-400 spectrometer (400 MHz for proton, 100.1 MHz for carbon) using deuteriochloroform as the solvent and tetramethylsilane as an internal standard. Chemical shifts are expressed in parts per million (δ). Coupling constants are given in hertz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. CD spectra were recorded on a Jasco J-710 spectropolarimeter. Mass spectra were recorded on an ion trap instrument Finnigan GCQ (70 eV). Elemental analyses were determined on a Carlo Erba 1106 instrument at the Department of Chemical Sciences and Technologies of the University of Udine, Italy. Phenylacetaldehyde **6**, L-proline and (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine were purchased from Sigma–Aldrich; 4-bromophenylacetaldehyde **7** and 4-ethoxyphenylacetaldehyde **8** were prepared according to the literature;[17] 2-nitrophenylacetaldehyde was prepared from phenylacetaldehyde by nitration according to the literature;[18] 4-nitrophenylacetaldehyde **9** and 3-nitrophenylacetaldehyde **11** were prepared according to the literature;[19] 1-aminocarbonyl-3-methyl-4-ethoxycarbonyl-1,2-diaza-1,3-diene **2b**, 1-aminocarbonyl-3-methyl-4-methoxycarbonyl-1,2-diaza-1,3-diene **2c** and 1-phenylaminocarbonyl-3-methyl-4-ethoxycarbonyl-1,2-diaza-1,3-diene **2d** were prepared according to the literature.[20]

4.2. General procedure for the reactions between DDs and arylacetaldehydes

To a solution of the appropriate aldehyde (1.0 mmol) and DD (1.0 mmol) in anhydrous THF (10 mL), L-Pro (20 mol %) or 2PMP associated with TFA (20 mol %) was added.[9c,10b] The mixture was stirred for 4–10 days, until completion of the reaction. The solvent was eliminated and the crude reaction mixture was chromatographed on silica gel (eluent: light petroleum–ethyl acetate, gradient).

4.2.1. (*S*)-(+)-Ethyl 6-methyl-4-phenyl-1,4-dihydropyridazine-5-carboxylate 5

Mp 132–133 °C; R_f 0.77 (eluent: ethyl acetate–light petroleum 1:1). IR (nujol) 3322.3, 1670.4, 1604.6, 1259.7, 1100.0, 1057.6, 765.7, 724.0, 701.9 cm^{-1}; ^{1}H NMR δ 7.38 (br s, 1H, NH), 7.25 (m, 5H, Ph), 6.91 (d, *J* 4.0, 1H, H-3), 4.53 (d, *J* 4.0, 1H, H-4), 4.09 (dq, 2H, OCH_2), 2.33 (s, 3H, CH_3), 1.20 (t, 3H, OCH_2CH_3); ^{13}C NMR δ 167.2 (s), 146.2 (s), 143.2 (s), 141.8 (d), 128.6 (2d), 127.7 (2d), 126.9 (d), 95.2 (s), 59.6 (t), 39.1 (d), 18.1 (q), 14.2 (q); MS *m*/*z* 244 ($M^{+\cdot}$, 18), 215 (100), 198 (31), 172 (46), 167 (68), 139 (65). 75% ee; $[\alpha]_D^{20} = +548.8$ (*c* 0.25, MeOH); CD (0.001 M, MeOH) $\Delta\varepsilon_{321}$ = +8.3; $\Delta\varepsilon_{273}$ = +2.9; $\Delta\varepsilon_{266}$ = +4.1; $\Delta\varepsilon_{259}$ = +5.6; $\Delta\varepsilon_{250}$ = +7.6; $\Delta\varepsilon_{218}$ = −6.6). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.10; H, 6.29; N, 12.01.

4.2.2. (*S*)-(+)-Methyl 6-methyl-4-phenyl-1,4-dihydropyridazine-5-carboxylate 12

Mp 136–137 °C; R_f 0.69 (eluent: ethyl acetate–light petroleum 1:1). IR ($CDCl_3$) 3350.6, 1678.6, 1612.7 1490.7, 1255.6, 1100.3,

1061.0, 698.8 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 6H, Ph, NH), 6.91 (d, *J* 4.0, 1H, H-3), 4.52 (d, *J* 4.0, 1H, H-4), 3.62 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^1H NMR (CD_3CN) δ 8.34 (br s, 1H, NH), 7.30 (m, 2H, Ph), 7.20 (m, 3H, Ph), 6.88 (d, *J* 4.0, 1H, H-3), 4.47 (d, *J* 4.0, 1H, H-4), 3.54 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR δ 167.6 (s), 146.4 (s), 142.9 (s), 141.8 (d), 128.7 (2d), 127.6 (2d), 127.0 (d), 94.9 (s), 50.9 (q), 39.1 (d), 18.2 (q); MS *m*/*z* 230 ($M^{+\cdot}$, 28), 215 (50), 198 (72), 171 (52), 153 (100). 46% ee; $[\alpha]_D^{20} = +211.2$ (*c* 0.34, MeOH); CD (0.0015 M, MeOH) $\Delta\varepsilon_{319} = +3.2$; $\Delta\varepsilon_{273} = +1.0$; $\Delta\varepsilon_{266} = +1.4$; $\Delta\varepsilon_{249} = +2.6$; $\Delta\varepsilon_{218} = -2.5$). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.92; H, 6.18; N, 12.33.

4.2.3. (*S*)-(+)-Methyl 4-(4-bromophenyl)-6-methyl-1,4-dihydropyridazine-5-carboxylate (13)

Mp 142–143 °C; R_f 0.65 (eluent: ethyl acetate–light petroleum 1:1). IR ($CDCl_3$) 3337.8, 1679.5, 1613.5, 1485.1, 1254.2, 1099.6, 1067.0, 1010.4 cm^{-1}; ^1H NMR δ 7.41 (br d, 2H, ArH), 7.32 (br s, 1H, NH), 7.09 (br d, 2H, ArH), 6.89 (d, *J* 4.1, 1H, H-3), 4.49 (d, *J* 4.1, 1H, H-4), 3.64 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR δ 167.4 (s), 146.5 (s), 141.8 (s), 141.2 (d), 131.7 (2d), 129.3 (2d), 120.9 (s), 94.7 (s), 51.0 (q), 38.6 (d), 18.2 (q); MS *m*/*z* 308, 310 ($M^{+\cdot}$, 58), 293, 295 (50), 276, 278 (23), 249, 251 (38), 229 (15), 197 (30), 169 (22), 153 (100). 72% ee; $[\alpha]_D^{20} = +403.3$ (*c* 0.45, MeOH), $[\alpha]_D^{25} = +404.4$ (*c* 0.045, MeOH); CD (0.0015 M, MeOH): $\Delta\varepsilon_{318} = +7.2$; $\Delta\varepsilon_{252} = +11.7$; $\Delta\varepsilon_{210} = -8.5$). Anal. Calcd for $C_{13}H_{13}BrN_2O_2$: C, 50.50; H, 4.24; N, 9.06. Found: C, 50.42; H, 4.16; N, 9.28.

4.2.4. (*S*)-(+)-Methyl 4-(4-ethoxyphenyl)-6-methyl-1,4-dihydropyridazine-5-carboxylate 14

Oil; R_f 0.61 (eluent: ethyl acetate–light petroleum 1:1). IR (neat) 3342.1, 1734.4, 1682.8, 1608.7, 1510.4, 1477.4, 1259.0, 1096.6, 1045.4, 799.8 cm^{-1}; ^1H NMR δ 7.42 (br s, 1H, NH), 7.04 (br d, 2H, ArH), 6.85 (d, *J* 4.0, 1H, H-3), 6.80 (br d, 2H, ArH), 4.42 (d, *J* 4.0, 1H, H-4), 3.98 (q, 2H, OCH_2), 3.62 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3), 1.38 (t, 3H, OCH_2CH_3); ^{13}C NMR δ 167.7 (s), 158.0 (s), 146.3 (s), 142.0 (d), 135.2 (s), 128.6 (2d), 114.5 (2d), 95.1 (s), 63.3 (t), 51.0 (q), 38.1 (d), 18.2 (q), 14.8 (q); MS *m*/*z* 273 ($M^{+\cdot}-1$, 18), 258 (85), 227 (40), 213 (100), 199 (60), 183 (48). 66% ee; $[\alpha]_D^{20} = +198.0$ (*c* 0.295, MeOH); CD (0.0011 M, MeOH) $\Delta\varepsilon_{316} = +3.3$; $\Delta\varepsilon_{279} = +2.0$; $\Delta\varepsilon_{262} = +3.3$; $\Delta\varepsilon_{230} = -2.9$). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.72; H, 6.30; N, 10.28.

4.2.5. (*S*)-(+)-Methyl 6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridazine-5-carboxylate 15

Mp 148–149 °C; R_f 0.50 (eluent: ethyl acetate–light petroleum 1:1). IR ($CDCl_3$) 3337.1, 3107.7, 1681.8, 1604.7, 1518.7, 1489.8, 1252.9, 1188.0, 1101.5, 854.9 cm^{-1}; ^1H NMR δ 8.16 (br d, 2H, ArH), 7.38 (br d, 3H, ArH, NH), 6.91 (d, *J* 4.0, 1H, H-3), 4.68 (d, *J* 4.0, 1H, H-4), 3.65 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3); ^{13}C NMR δ 167.1 (s), 149.8 (s), 147.0 (s), 146.9 (s), 140.1 (d), 128.4 (2d), 124.0 (2d), 94.1 (s), 51.2 (q), 39.2 (d), 18.2 (q); MS *m*/*z* 275 ($M^{+\cdot}-1$, 15), 260 (100), 246 (10), 216 (30), 198 (10), 153 (25), 121 (10). 69% ee; $[\alpha]_D^{20} = +492.7$ (*c* 0.055, MeOH); CD (0.0002 M, MeOH) $\Delta\varepsilon_{299} = +19.2$; $\Delta\varepsilon_{265} = +3.0$; $\Delta\varepsilon_{239} = -8.9$. Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.34; H, 4.26; N, 15.13.

4.2.6. (*S*)-(+)-Methyl 6-methyl-4-(2-nitrophenyl)-1,4-dihydropyridazine-5-carboxylate 16

Mp 148–149 °C; R_f 0.57 (eluent: ethyl acetate–light petroleum 1:1). IR (nujol) 3335.7, 1697.2, 1613.6 1525.6, 1251.8, 1187.8, 1098.4, 736.3 cm^{-1}; ^1H NMR δ 7.82 (dd, 1H, ArH), 7.55 (br dt, 2H, ArH, NH), 7.42 (dd, 1H, ArH), 7.36 (dt, 1H, ArH), 7.08 (d, *J* 4.1, 1H, H-3), 5.12 (d, *J* 4.1 Hz, 1H, H-4), 3.50 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR δ 166.9 (s), 148.4 (s), 147.6 (s), 140.8 (d), 137.6 (s), 133.6 (d), 131.0 (d), 127.8 (d), 124.0 (d), 94.3 (s), 51.1 (q), 35.0 (d), 17.9 (q); MS *m*/*z* 275 ($M^{+\cdot}$, 8), 258 (80), 227 (10), 213 (100), 199 (60), 183 (45). 52% ee; $[\alpha]_D^{20} = +71.5$ (*c* 0.595, MeOH); CD (0.002 M, MeOH): $\Delta\varepsilon_{340} = -3.7$; $\Delta\varepsilon_{294} = +6.8$; $\Delta\varepsilon_{279} = +5.2$; $\Delta\varepsilon_{255} = +12.0$; $\Delta\varepsilon_{228} = -6.0$). Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.40; H, 4.60; N, 15.56.

4.2.7. (*S*)-(+)-Methyl 6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridazine-5-carboxylate 17

Mp 142–143 °C; R_f 0.54 (eluent: ethyl acetate–light petroleum 1:1). IR ($CDCl_3$): 3350.2, 1701.6, 1650.2, 1613.8, 1530.3, 1490.1, 1461.8, 1437.0, 1351.9, 1255.2, 1098.7, 908.7, 731.6 cm^{-1}; ^1H NMR δ 8.09 (m, 2H, ArH), 7.58 (br d, 1H, ArH), 7.48 (br d, 1H, ArH), 7.42 (br s, 1H, NH), 6.95 (d, *J* 4.4, 1H, H-3), 4.69 (d, *J* 4.4, 1H, H-4), 3.67 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR δ 167.1 (s), 148.6 (s), 147.0 (s), 144.7 (s), 140.3 (d), 133.8 (d), 129.6 (d), 122.6 (d), 122.2 (d), 94.2 (s), 51.2 (q), 38.9 (d), 18.3 (q); MS *m*/*z* 274 ($M^{+\cdot}-1$, 7), 260 (33), 258 (100), 216 (32), 202 (10), 169 (10), 153 (32), 121 (12). 78% ee; $[\alpha]_D^{20} = +419.9$ (*c* 0.18, MeOH); CD (0.0006 M, MeOH): $\Delta\varepsilon_{314} = +8.2$; $\Delta\varepsilon_{270} = +0.7$; $\Delta\varepsilon_{247} = +6.6$; $\Delta\varepsilon_{225} = +2.4$). Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.22; H, 4.15; N, 15.53.

4.2.8. Ethyl 3-methyl-5-phenyl-1,4-dihydropyridazine-4-carboxylate 27

On standing in chloroform solution for 48 h, compound **5** was partially transformed into its isomer **27** and the oxidation product **28**. Although not isolated, its signals are given separately, for the sake of clarity. ^1H NMR 7.03 (d, 1H, H-6), 4.32 (s, 1H, H-4), 4.17 (dq, 2H, OCH_2), 2.15 (s, 3H, CH_3), 1.24 (t, 3H, OCH_2CH_3); ^{13}C NMR δ 170.4 (s), 137.9 (s), 136.8 (s), 128.5 (2d), 126.0 (d), 124.9 (d), 124.0 (2d), 102.1 (s, C-5), 61.4 (t), 45.1 (d, C-4), 22.4 (q), 13.7 (q). Aromatic and NH protons are hidden under the signals of compounds **5** and **28**.

4.2.9. Ethyl 3-methyl-5-phenyl-pyridazine-4-carboxylate 28

^1H NMR δ 9.17 (s, 1H, H-6), 7.49 (m, 3H, Ph), 7.41 (m, 2H, Ph), 4.22 (dq, 2H, OCH_2), 2.80 (s, 3H, CH_3), 1.08 (t, 3H, OCH_2CH_3); ^{13}C NMR δ 166.6 δ (s), 155.5 (s), 150.0 (d), 136.0 (s), 134.0 (s), 129.8 (s), 129.6 (d), 129.0 (2d), 127.9 (2d), 62.2 (t), 20.3 (q), 14.1 (q). After 10 days, conversion of the two isomers **5** and **27** into compound **28** was complete.

4.2.10. Crystal data for compound 12

$C_{13}H_{14}N_2O_2$, *M* = 230.26, orthorhombic, space group $P\,2_12_12_1$, *a* = 7.337(2), *b* = 9.362(3), *c* = 17.081(4) Å, *V* = 1173.3(6) $Å^3$, *Z* = 4, ρ_{calcd} = 1.304 g/cm^3, μ(Mo Kα) = 0.727 mm^{-1}, *F*(0 0 0) = 488. Final *R* = 0.0429, wR_2 = 0.1182, *S* = 1.093 for 156 parameters and 9238 reflections, 1757 unique [*R*(int) = 0.0620], of which 1617 with $I > 2\sigma(I)$, max positive and negative peaks in ΔF map 0.118, −0.115 e $Å^{-3}$. Absolute structure parameter 0.5(3).[22]

Diffraction data were collected at room temperature by using a Brucker Kappa CCD imaging plate mounted on a Nonius FR591 rotating anode (Cu Kα radiation, λ = 1.54178 Å). Cell refinement, indexing and scaling of the data sets were carried out using DENZO and SCALEPACK.[23] The structure was solved by direct methods and Fourier analyses and refined by the full-matrix least-squares method based on F^2.[24] All the calculations were performed using the WINGX System, Ver 1.80.05.[25]

Crystallographic data (excluding structure factors) for the structure reported have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 764970. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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