Tetrahydropyridines’ Stereoselective Formation, How Lockdown Assisted in the Identification of the Features of Its Mechanism

Anatoly N. Vereshchagin*, Taigib M. Iliyasov, Kirill A. Karpenko, Radmir N. Akchurin and Mikhail E. Minyaev

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Prospect, 119991 Moscow, Russia; nfsmwm5@mail.ru (T.M.I.); karpenkok_09@mail.ru (K.A.K.); akch.r@yandex.ru (R.N.A.); mminyaev@ioc.ac.ru (M.E.M.)

* Correspondence: vereshchagin@ioc.ac.ru

Abstract: The multicomponent reaction of aldehydes, cyano-containing C-H acids, esters of 3-oxocarboxylic acid and ammonium acetate led to unexpected results. The boiling of starting materials in methanol for one to two hours resulted in the formation of polysubstituted 1,4,5,6-tetrahydropyridines with two or three stereogenic centers. During the 2020 lockdown, we obtained key intermediates of this six-step domino reaction. A number of fast and slow reactions occurred during the prolonged stirring of the reaction mass at rt. Sequence: 1. Knoevenagel condensation; 2. Michael addition; 3. Mannich reaction; 4. cyclization—fast reactions and cyclization of the product polysubstituted 2-hydroxypiperidine—was isolated after 40 min stirring at rt. Further monitoring proved the slow dehydration of 2-hydroxypiperidine to obtain 3,4,5,6-tetrahydropyridine after 7 days. Then, four-month isomerization occurred with 1,4,5,6-tetrahydropyridine formation. All reactions were stereoselective. Key intermediates and products structures were verified by X-ray diffraction analysis. Additionally, we specified conditions for the selective intermediates’ preparation.

Keywords: multicomponent reactions; domino processes; stereoselectivity; aldehydes; C-H acids; 1,4,5,6-tetrahydropyridines; 3,4,5,6-tetrahydropyridines; 2-aryl-2-hydroxypiperidines; reaction monitoring

1. Introduction

Six-membered heterocycles form the main subgroup of nitrogen-containing heterocycles. These compounds are well-known frameworks (piperidine, tetrahydropyridine, 1,4-dihydropyridine and pyridine) with a wide spectrum of biological activities [1,2]. Thus, piperidine derivatives display antihypertensive [3], neuroprotective [4,5], antibacterial [6], anticonvulsant [7] and anti-inflammatory [8] abilities, and are inhibitors of farnesyl transferase [9]. Additionally, substituted piperidines are important therapeutic agents in the treatment of influenza [10–12], diabetes [13,14], viral infections including AIDS [15–17], pulmonary embolism [18] and cancer metastases [19]. Tetrahydropyridines are known as insecticides [20], analgesics [21] and antimalarial agents [22]. Among medications, 4-phenylpiperidine derivatives are of great importance, because they resemble morphine pharmacophore [23,24].

The most common synthetic approaches to produce tetrahydropyridines include imines, in which the nitrogen atom is a source to construct nitrogen-containing six-membered rings. Diels–Alder reactions [25,26], using azadienophiles or azadienes, and domino addition–cyclization reactions involving imines were reported [27,28]. The latter reactions are multicomponent. For organic compounds’ preparation, domino and multicomponent syntheses are superior to two-component reactions in high atom efficiency [29,30], time, materials, energy saving, eco-friendliness and access to greater diversity [31–36]. Several
publications describe the multicomponent synthesis of substituted tetrahydropyridines from aromatic aldehydes, C-H acids and aromatic amines [37,38], cyanoacetamide [39] or cyanothioacetamide [40].

We have carried out the multicomponent synthesis of substituted piperidines [41–45]. Ammonium acetate or aqueous ammonia were the nitrogen sources for piperidine cycles. Using this approach, we performed the stereoselective synthesis of substituted 1,4,5,6-tetrahydropyridines from electron-deficient olefins and aqueous ammonia [46] (three-component synthesis), or from alkylidenemalononitriles, 3-oxopropanecarboxylates, aldehydes and ammonium acetate [47] (four-component synthesis) as a nitrogen source for the newly formed six-membered ring. The reaction was carried out by refluxing the starting compounds in methanol for 2–12 h. We hypothesized that the formation of tetrahydropyridine occurs through the following sequence of reactions: Michael addition to obtain 2-substituted 3-aryl-4,4-dicyanobutanoic acid ester A, Mannich reaction to give 2-substituted 5-amino-3,5-diaclyl-4,4-dicyanopentanoic acid B, intramolecular cyclization yielding polysubstituted 2-hydroxypiperidine C, and dehydration (Scheme 1). Previously, Verboom et al. [48] studied the formation of close analogues of intermediate A from benzylidenemalononitriles and malononitrile, or ethyl cyanoacetate. However, the intermediates B and C have never been isolated or identified.

![Scheme 1](image)

**Scheme 1.** Presumed mechanism of the substituted 1,4,5,6-tetrahydropyridines’ formation.

Subsequently, we studied the multicomponent synthesis of cyclic [49–51] and heterocyclic [52–56] compounds from carbonyls and C-H acids. The current research is dedicated to the pseudo-five-component synthesis of 1,4,5,6-tetrahydropyridines 4,5 directly from aromatic aldehydes 1 (both with electron-withdrawing and electron-donating substituents), cyano C-H acids 2 (malononitrile or ethyl cyanoacetate), esters of 3-oxoarboxylic acids 3 and ammonium acetate (Scheme 2, Table 1). Additionally, we examine the multicomponent process mechanism.

![Scheme 2](image)

**Scheme 2.** Pseudo-five-component transformation of aldehydes 1, C-H acids 2, esters of 3-oxoarboxylic acid 3 and ammonium acetate into 1,4,5,6-tetrahydropyridines 4,5.
Table 1. Multicomponent synthesis of 1,4,5,6-tetrahydropyridines 4,5.  

| Entry | Aldehyde | C-H Acid | C-H Acid | X | Ar | R¹ | R² | Product | Yield |
|-------|----------|----------|----------|---|----|----|----|---------|-------|
| 1     | 1a       | 2a       | 3a       | CN|  C₆H₅| Me | Me | 4a      | 80    |
| 2     | 1b       | 2a       | 3a       | CN| 2-MeC₆H₄| Me | Me | 4b      | 65    |
| 3     | 1c       | 2a       | 3a       | CN| 3-MeC₆H₄| Me | Me | 4c      | 76    |
| 4     | 1d       | 2a       | 3a       | CN| 4-MeC₆H₄| Me | Me | 4d      | 72    |
| 5     | 1e       | 2a       | 3a       | CN| 3-FC₆H₄| Me | Me | 4e      | 71    |
| 6     | 1f       | 2a       | 3a       | CN| 3-CIC₆H₄| Me | Me | 4f      | 68    |
| 7     | 1g       | 2a       | 3a       | CN| 3-Py | Me | Me | 4g      | 62    |
| 8     | 1a       | 2a       | 3b       | CN|  C₆H₅| Me | Et | 4h      | 86    |
| 9     | 1b       | 2a       | 3b       | CN| 4-FC₆H₄| Me | Et | 4i      | 69    |
|10     | 1i       | 2a       | 3b       | CN| 4-NO₂C₆H₄| Me | Et | 4j      | 63    |
|11     | 1a       | 2a       | 3c       | CN|  C₆H₅| Et | Me | 4k      | 90    |
|12     | 1d       | 2a       | 3c       | CN| 4-MeC₆H₄| Et | Me | 4l      | 82    |
|13     | 1j       | 2a       | 3c       | CN| 4-BrC₆H₄| Et | Me | 4m      | 82    |
|14     | 1l       | 2a       | 3c       | CN| 4-NO₂C₆H₄| Et | Me | 4n      | 58    |
|15     | 1a       | 2a       | 3d       | CN|  C₆H₅|  C₆H₅| Me | 4o      | 76    |
|16     | 1e       | 2a       | 3d       | CN| 3-FC₆H₄|  C₆H₅| Me | 4p      | 52    |
|17     | 1a       | 2a       | 3e       | CN|  C₆H₅|  C₆H₅| Et | 4q      | 58    |
|18     | 1k       | 2a       | 3e       | CN| 4-OMeC₆H₄|  C₆H₅| Et | 4r      | 44    |
|19     | 1a       | 2a       | 3f       | CN|  C₆H₅| 4-BrC₆H₄| Me | 4s      | 62    |
|20     | 1d       | 2a       | 3f       | CN| 4-MeC₆H₄| 4-BrC₆H₄| Me | 4t      | 75    |
|21     | 1j       | 2b       | 3f       | CN| CO₂Et| 4-BrC₆H₄| Me | 5a      | 73    |
|22     | 1j       | 2b       | 3g       | CN| CO₂Et| 4-BrC₆H₄| 4-CIC₆H₄| Me | 5b      | 66    |

*a Reaction conditions: aldehyde 1 (6 mmol), cyano C-H acid 2 (3 mmol), ester of 3-oxocarboxylic acid 3 (3 mmol), NH₄OAc (6 mmol) and methanol (10 mL), refluxing for 2 h. b Isolated yields.

2. Results and Discussion

The refluxing of the starting compounds in MeOH led to the selective formation of esters of 2-alkyl(or aryl)-4,6-diaryl-5,5-dicyano-1,4,5,6-tetrahydropyridine-3-carboxylic acids 4 (X=CN) with two stereogenic centers, or diesters of 5-cyano-2,4,6-triaryl-1,4,5,6-tetrahydropyridine-5,5-carboxylates 5 (X=COOEt) with three stereogenic centers (Scheme 2, Table 1). This technique was developed in the study of the four-component synthesis of 1,4,5,6-tetrahydropyridines [47]. The new multicomponent reaction allows us to obtain 1,4,5,6-tetrahydropyridines 4, 5 in moderate to excellent yields in one step from cheap and available starting materials via the domino process with the formation of three C-C and two C-N bonds. All reactions were monitored via thin-layer chromatography (TLC).

Product 4 was isolated in a 44–90% yield by simple filtration after freezing the reaction mixture. Product 5 was isolated by chromatography in moderate yields of 33% and 36%.

As the NMR spectra of compounds 4, 5 showed only a single set of signals, we assumed the stereoselective formation of individual diastereoisomers. The structure of 4r is shown in Figure 1. X-ray crystal diffraction data indicated that structure 4a with two stereogenic centers should be defined as ethyl (4SR,6SR)-5,5-dicyano-2-phenyl-4,6-bis(4-methoxy)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate. The structure of 5a is shown in Figure 2. X-ray indicated that structure 5a with three stereogenic centers had the conformation 4RS,5SR,6RS. In both 4r, 5a diastereomers, we observed bulky aryl substituents in sterically least-hindered positions relative to each other.

To validate the proposed mechanism (Scheme 1), we monitored the reaction between aldehydes 1, malononitrile 2a, aryl containing esters of 3-oxocarboxylic acids 3 and ammonium acetate in methanol at room temperature (Scheme 3, Table 2). In all cases, 40–45 min stirring of the reaction mass created a dense white precipitate. After filtration and drying, single compounds (by TLC and NMR) were obtained. The ¹H and ¹³C NMR spectra of compounds 6 showed one set of signals, indicating the formation of a single diastereomer. The 6d structure is shown in Figure 3. X-ray crystal diffraction data indicated that the structure 6d with four stereogenic centers should be
defined as methyl (2SR,3RS,4SR,6RS)-5,5-dicyano-2-(4-bromo)phenyl-2-hydroxy-4,6-bis(4-methyl)phenyl-piperidine-3-carboxylate.

Figure 1. X-ray structure of the 4r 4SR,6RS configuration.

Figure 2. X-ray structure of the 5a 4RS,5SR,6RS configuration.

Scheme 3. Pseudo-five-component transformation of aldehydes 1, malonitrile 2a, esters of 3-oxocarboxylic acid 3 and ammonium acetate into the substituted (2SR,3RS,4SR,6RS)-2-hydroxypiperidines 6.
Table 2. Multicomponent synthesis of (2SR,3RS,4SR,6RS)-2-hydroxypiperidines 6 a.

| Entry | Aldehyde | C-H Acid | R   | R1  | R2  | Product | Yield b |
|-------|----------|----------|------|-----|-----|---------|---------|
| 1     | 1a       | 3e       | H    | C6H5| Et  | 6a      | 72      |
| 2     | 1d       | 3e       | 4-Me | C6H5| Et  | 6b      | 61      |
| 3     | 1l       | 3e       | 4-Cl | C6H5| Et  | 6c      | 56      |
| 4     | 1d       | 3f       | 4-Me | 4-BrC6H4| Me| 6d      | 87      |

a Reaction conditions: aldehyde 1 (6 mmol), malononitrile 2a (3 mmol), ester of 3-oxocarboxylic acid 3 (3 mmol), NH4OAc (6 mmol) and methanol (10 mL), rt, 40 min. b Isolated yields.

Figure 3. X-Ray structure of the 6d (2SR,3RS,4SR,6RS) configuration. Hydrogen bonding between the molecules of 6d and DMSO.

It should be noted that the introduction of alkyl-substituted esters of 3-oxocarboxylic acid 3 (R1 = Alk) into this reaction did not result in the formation of 2-hydroxypiperidine 6. Apparently, the aryl substituent in position 2 is a “stabilizer” of the molecule as a whole. Thus, we found that 2-hydroxypiperidines 6 are formed as a result of a “fast” domino sequence: Knoevenagel condensation, Michael addition, Mannich reaction and intramolecular cyclization. This sequence of reactions takes only 40 min at rt. Unordinary results were found when one of the reaction mixtures was left for a long time without stirring due to isolation measures in spring 2020. The TLS monitoring of the reaction mixture containing 4-methylbenzaldehyde 1d, malononitrile 2a, methyl 3-(4-bromophenyl)-3-oxopropanoate 3f and ammonium acetate in methanol after one and a half months of standing at rt showed the presence of a new substance, different (according to TLS) from 2-hydroxypiperidine 6d and the final 1,4,5,6-tetrahydropyridine 4t. We monitored this reaction for 4.5 months. Every week, we took samples of the precipitate from the reaction mixture and analyzed it with 1H NMR spectroscopy (Figure 4).

We found the complete conversion of 2-hydroxypiperidine 6d within a week. A set of signals of the unknown compound 7 and 1,4,5,6-tetrahydropyridine 4t was observed in the reaction mixture precipitate. Further, over the course of 4 months, we observed the slow transformation of 7 into 4t. To isolate compound 7, we made the following assumption. Under reaction conditions, ammonium acetate dissociated into ammonia and acetic acid. Ammonia was consumed to form a six-membered nitrogen-containing ring, while acetic acid remained in the reaction mixture. Therefore, the dehydration of 6d to 7t should be carried out under acidification. The acidity of the reaction medium should influence the course of dehydration (Scheme 4, Table 3). Indeed, 6d refluxing in methanol for 2 h in the absence of the acid produced no conversion (Table 3, entry 1). When acidified with 2 eq. of acetic acid, the compound 6d was completely consumed after 2 h refluxing (Table 3, entry...
2, TLC monitoring, eluting with hexane—ethyl acetate, 3:1). Additionally, we observed the formation of 7. The increase in the acid amount led to 4t (Table 3, entries 4–7).

**Figure 4.** $^1$H NMR monitoring of the characteristic signals of 6d, unknown compound 7 and 4t over 4.5 months.

**Scheme 4.** Dehydration of methyl (2SR,3RS,4SR,6RS)-5,5-dicyano-2-(4-bromo)phenyl-2-hydroxy-4,6-bis(4-methyl)phenyl-piperidine-3-carboxylate 6d.
Table 3. Dehydration of 6d.

| Entry | AcOH/mol.eq. | Time, h | Tetrahydropyridine | Yield (%) |
|-------|--------------|---------|--------------------|-----------|
| 1     | 0            | 2       | -                  | -         |
| 2     | 2            | 2       | 7                  | 90        |
| 3     | 4            | 2       | 7                  | 88        |
| 4     | 10           | 2       | 7/4t = 1:1         | 90 c      |
| 5     | 10           | 4       | 7/4t = 1:1.5       | 92 c      |
| 6     | 25           | 2       | 7/4t = 1:2         | 88 c      |
| 7     | 50           | 2       | 4t                 | 92        |

* 6d (1 mmol), MeOH (8 mL), refluxing. The progress of the reaction was monitored by TLC. b Isolated yields. c Total yield of tetrahydropyridines.

The structure of 7 is shown in Figure 5a. X-ray crystal diffraction data indicated that structure 7 with three stereogenic centers should be defined as methyl (3RS,4SR,6RS)-5,5-dicyano-2-(4-bromophenyl)-3-cyano-2,4-bis(4-methyl)phenyl-3,4,5,6-tetrahydropyridine-3-carboxylate. Structure 7 is the isomer of 4t. The Gibbs free energy of 4t is 15.64 kJ/mol lower than that of 7. DFT calculations were performed with the Gaussian 16 Rev C.01 quantum chemistry program [57].

Likewise, we studied the multicomponent reaction between 4-flurobenzaldehyde 1h, ethyl cyanoacetate 2b, methyl 3-(4-bromophenyl)-3-oxopropanoate 3f and ammonium acetate in methanol at rt (Scheme 5). TLC and 1H NMR monitoring allowed us to obtain the reaction intermediate 8 in 24%. The structure of 8 is shown in Figure 5b. X-ray crystal diffraction data indicated that structure 8 with four stereogenic centers should be defined as 5-ethyl 3-methyl (3SR,4RS,5SR,6SR)-6-(4-bromophenyl)-3-cyano-2,4-bis(4-fluorophenyl)-3,4,5,6-tetrahydropyridine-3,5-dicarboxylate. When ethyl cyanoacetate was introduced into the multicomponent reaction, the formation of an intermediate substituted 2-hydroxypiperidine was not observed.
Likewise, we studied the multicomponent reaction between 4-fluorobenzaldehyde and ammonium acetate in methanol at rt with ethyl cyanoacetate.

Crystal data and the structure refinement of 4r, 5a, 6d, 7 and 8 are shown in Table 4.

Table 4. Crystal data and structure refinement.

| Structure | 4r | 5a | 6d | 7 | 8 |
|-----------|----|----|----|---|---|
| Empirical formula | C₃₀H₂₇N₅O₄ | C₂₉H₂₃Br₃N₄O₄ | C₂₉H₂₈BrN₃O₃C₂H₄OS | C₂₉H₂₃BrN₃O₂ | C₂₉H₂₃BrF₂N₂O₄ |
| Formula weight | 493.54 | 703.22 | 622.56 | 526.42 | 581.40 |
| Crystal system | Monoclinic | Monoclinic | Monoclinic | Orthorhombic | Triclinic |
| Space group | P2₁/n | P2₁/c | P₂₁ | P₂₁2₁₂₁ | PT |
| Unit cell parameters | | | | | |
| a, Å | 13.5215(6) | 14.1399(5) | 9.3382(4) | 8.9278(2) | 7.9773(3) |
| b, Å | 14.4873(6) | 13.7544(4) | 17.5838(8) | 14.0848(3) | 15.5602(6) |
| c, Å | 13.6402(6) | 14.6488(5) | 10.1005(5) | 19.5522(4) | 21.8741(8) |
| α, ° | 90 | 90 | 90 | 90 | 90 |
| β, ° | 90.0602(13) | 107.0120(13) | 116.3107(12) | 90 | 91.0048(12) |
| γ, ° | 90 | 90 | 90 | 90 | 90 |
| Volume, Å³ | 2724.32(16) | 2642.06(17) | 2642.06(17) | 2642.06(17) | 2642.06(17) |
| Z | 4 | 4 | 4 | 4 | 4 |
| Density (calcld.), g/cm³ | 1.298 | 1.715 | 1.425 | 1.422 | 1.462 |
| μ, mm⁻¹ | 0.087 | 4.481 | 1.530 | 1.704 | 1.608 |
| F (000) | 1040 | 1392 | 644 | 1080 | 1184 |
| θ range, ° | 2.56–30.00 | 2.07–33.73 | 2.43–30.50 | 2.51–33.74 | 2.32–31.53 |
| Completeness to θ max | 0.999 | 1.000 | 1.000 | 0.999 | 0.999 |
| Index ranges | | | | | |
| -19 ≤ h ≤ 19, -20 ≤ k ≤ 20, -19 ≤ l ≤ 19 | -13 ≤ h ≤ 13, -21 ≤ k ≤ 22, -30 ≤ l ≤ 29 | -13 ≤ h ≤ 13, -24 ≤ k ≤ 24, -14 ≤ l ≤ 14 | -13 ≤ h ≤ 13, -21 ≤ k ≤ 22, -30 ≤ l ≤ 29 | -11 ≤ h ≤ 11, -22 ≤ k ≤ 22, 0 ≤ l ≤ 32 |
| Reflections collected | 37323 | 90656 | 42307 | 80903 | 20648 |
| Independent reflections (R(int)) | 7344 [0.0737] | 10,873 [0.0808] | 8837 [0.0539] | 9808 [0.0411] | 20,648 [-] |
| Observed reflections (I > 2σ(I)) | 4852 | 6974 | 7570 | 8717 | 11,148 |
| Data, restraints, parameters | 7344, 0, 341 | 10,873, 1, 357 | 8837, 8, 386 | 9808, 0, 321 | 20,648, 0, 691 |
| Goodness of fit on F² | 1.037 | 1.019 | 1.039 | 1.050 | 1.019 |
| Final R1, wR2 (I > 2σ(I)) | 0.0523, 0.0942 | 0.0491, 0.1042 | 0.0328, 0.0637 | 0.0295, 0.0667 | 0.0593, 0.0984 |
| Final R1, wR2 (all data) | 0.0951, 0.1171 | 0.0955, 0.1250 | 0.0454, 0.0693 | 0.0385, 0.0712 | 0.1452, 0.1219 |
| Absolute structure parameter | - | - | 0.016(6) | 0.388(6) | - |
| Largest diff. peak, hole, e/Å³ | 0.321, −0.282 | 0.993, −1.176 | 0.377, −0.488 | 0.348, −0.378 | 0.595, −0.861 |
| CCDC number | 1979309 | 2032519 | 1979186 | 2011646 | 2011600 |

Scheme 5. Stereoselective multicomponent synthesis of (3SR,4RS,5SR,6SR)-6-(4-bromophenyl)-3-cyano-2,4-bis(4-fluorophenyl)-3,4,5,6-tetrahydropyridine-3,5-dicarboxylate 8.
Thus, the multicomponent reaction between aldehyde 1, cyano C-H acids 2 (malononitrile or ethyl cyanoacetate), esters of 3-oxocarboxylic acids 3 and ammonium acetate is a six-step domino process (Scheme 6). At the first stage, the Knoevenagel condensation between aldehydes and cyano C-H acid occurs. Ammonium acetate is a catalyst for this reaction. The formation of cyano olefins A under ammonium salts catalysis is already known [58]. The second step of the process is the Michael addition of C-H acid 3 to the electron-poor styrene A to form the Michael adduct B. The formation of close analogues of intermediate B from benzylidenemalononitriles and malononitrile or ethyl cyanoacetate was studied previously by Verboom et al. [48]. The subsequent Mannich reaction of B, aldehyde 1 (second equivalent) and ammonia, which is formed from ammonium acetate, leads to intermediate C. The latter undergoes intra-molecular cyclization with the formation of close analogues of 1,4,5,6-tetrahydropyridines 6, which was identified and characterized in this work for the first time. A similar sequence of Knoevenagel condensation —Michael addition—Mannich reaction—intramolecular cyclization was described by Latypova et al. when studying the multicomponent reaction between 1,3-dicarboxyl compounds (two equiv.), formaldehyde and diamines with the formation of substituted bis-1,2,3,4-tetrahydropyridines [59]. None of the intermediates were isolated. Moreover, we tried to isolate C in the course of the work, but failed because in the reaction mass, after 10–30 min from the reaction start, there were many compounds (by TLC) that were almost impossible to isolate due to the rapid reaction rate. Polysubstituted 2-hydroxy-piperidines 6 were isolated up to 87% even after stirring at rt for 40 min (see Table 2). The fifth step of the domino process is C dehydration. We established formation of 3,4,5,6-tetrahydropyridines 7, 8. A final isomerization produces 1,4,5,6-tetrahydropyridines 4, 5.

Scheme 6. Verified mechanism of the substituted 1,4,5,6-tetrahydropyridines’ formation.

3. Experimental Procedure

3.1. General Information

All melting points were measured with a Stuart SMP30 melting point apparatus (Bibby Sterling Ltd., Granton, UK). 1H and 13C NMR spectra were recorded with a Bruker AM300 (Bruker, Bremen, Germany) and Bruker DRX 500 (Bruker BioSpin GmbH, Bremen, Germany) at ambient temperature in DMSO-d6 or CDCl3 solutions. Chemical shifts values are given in δ scale relative to Me4Si. The J values are given in hertz. Only discrete or characteristic signals for the 1H NMR are reported. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer (Bruker Corporation, Bremen, Germany) in KBr pellets. HR-ESI-MS were measured on a Bruker microTOF II instrument (Bruker Daltonik GmbH, Bremen, Germany); external or internal calibration was performed with electrospray calibrant solution (Fluka). All starting materials were obtained from commercial sources and used without purification. All reactions were monitored with thin-layer chromatography.
(TLC) and carried out with Merck precoated plates DC-AlufolienKieselgel60 F254 (Merck KGaA, Darmstadt, Germany). X-ray crystallographic analyses were performed with Bruker Quest D8 diffractometer (Bruker AXS GmbH, Bremen, Germany).

3.2. DFT Calculations

DFT calculations were performed with Gaussian 16 Rev C.01. B3LYP DFT (Gaussian Inc., Wallingford CT, USA, 2016) functional with GD3BJ empirical dispersion correction, and a Def2SVP basis set was used for geometry optimization and calculations of thermodynamics. Data from X-ray diffraction experiment for 7 were used as starting points for geometry optimizations. Cartesian coordinates are given in angstroms; absolute energies for all substances are given in hartrees. The analysis of vibrational frequencies was performed for all optimized structures. All compounds were characterized by only real vibrational frequencies. Wavefunction stability, using stable keyword, was also checked for each molecule. For more information see Supplementary Materials.

For the calculations of the optimized geometries, frequencies and thermodynamics with the following keywords were used:

```
# opt freq b3lyp nosymm def2svp empiricaldispersion = gd3bj test
```

3.3. X-ray Crystallographic Data and Refinement Details

X-ray diffraction data for all compounds were collected at 100 K on a Bruker Quest D8 diffractometer equipped with a Photon-III area detector, using graphite-monochromatized Mo Kα-radiation (0.71073 Å) and the shutterless ϕ- and ω-scan technique. Relying on the analysis of preliminary collected reflections with the Cell_Now program [60], all crystals of 8 from various batches contained over seven major domains with apparently chaotic orientations. This, along with a chiral space group, seriously impeded data analysis, resulting in six attempts to collect reflection data and to solve the structure. The intensity data were integrated by the SAINT program [61] and were semi-empirically corrected for absorption and decay, using SADABS [62] for 4r, 6d, 5a and 7 or using TWINABS [61] for 8. The structures were solved by direct methods using SHELXT [63] and refined by the full-matrix least-squares method on $F^2$ using SHELXL-2018 [64]. The crystals of 6d and 7 were refined as inversion twins, for which the absolute structure parameter (Flack) was determined by classical fit [65]. The selected specimen of 8 was refined as a non-merohedral 2-component twin.

All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The locations of atoms H1 (in 4r, 5a) and H1A, H1B (in 6d) were found from the electron density difference map; these H atoms were refined with individual isotropic displacement parameters. All other hydrogen atoms were placed in geometrically calculated positions and refined as riding atoms with relative isotropic displacement parameters. A rotating group model was applied for methyl groups. Mercury program [66] was used for molecular graphics. Crystal data, data collection and structure refinement details are summarized in Table 4.

3.4. Synthesis of 4–5

A mixture of aldehydes 1 (6 mmol), cyano C-H acid 2 (3 mmol), ester of 3-oxocarboxylic acids 3 (3 mmol) and ammonium acetate (6 mmol) was refluxed in methanol (10 mL) for 2 h. After the reaction completion, the mixture was maintained at −10 °C for 30 min for the complete precipitation of the product, the precipitate was collected by filtration and dried to obtain pure tetrahydropyridine 4. Compound 5 was purified by column chromatography.

Methyl (4SR,6RS)-5,5-dicyano-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4a) Yield: 0.86 g (80%); white solid; m.p. 218–219 °C. (lit. [46] m.p. 218–219 °C); 1H-NMR (DMSO-d6, 300.13 MHz): δ = 7.63–7.7 (m, 2H, Ar), 7.52 (dd, 4 H, Ar, J1 = 5.9 Hz, J2 = 1.6 Hz), 7.34–7.28 (m, 4H, Ar + NH), 5.27 (s, 1H, CH), 4.83 (s, 1H, CH), 3.11 (s, 3H, OCH3), 2.32 (s, 3H, CH3).
Methyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-bis(2-methylphenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (4b) Yield: 0.75 g (65%); white solid; m.p. 233–235 °C; 1H-NMR (CDCl3, 300.13 MHz): δ = 7.92–7.86 (m, 1H, Ar), 7.51–7.18 (m, 7H, Ar), 5.22 (s, 1H, CH), 5.09 (s, 1H, CH), 4.35 (s, 1H, NH), 3.26 (s, 3H, OCH3), 2.59 (s, 3H, CH3), 2.56 (s, 3H, CH3), 2.48 (s, 3H, CH3); 13C-NMR (CDCl3, 75.47 MHz): δ = 166.67, 151.99, 137.24, 136.92, 135.95, 131.95, 131.47, 130.69, 130.20, 128.03, 127.29, 126.49, 126.34, 126.22, 113.82, 112.61, 99.28, 57.54, 50.44, 46.09, 45.63, 20.04, 19.89; IR (KBr): 3343, 2249, 1686, 1460, 1247 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C24H24N3O2+: 386.1863; found: 386.1857.

Methyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-bis(3-methylphenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (4c) Yield: 0.88 g (76%); white solid; m.p. 191–193 °C; 1H-NMR (CDCl3, 300.13 MHz): δ = 7.85 (d, J = 8.0 Hz, 2H, Ar), 7.44 (s, 1H, NH), 7.32 (d, J = 8.0 Hz, 2H, Ar), 7.21–7.14 (m, 4H, Ar), 5.19 (s, 1H, CH), 4.75 (s, 1H, CH), 3.13 (s, 3H, OCH3), 2.36 (s, 3H, CH3), 2.30 (s, 6H, 2CH3).

Methyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-bis-(3-fluoro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4d) Yield: 0.83 g (72%); white solid; m.p. 208–210 °C; 1H-NMR (DMSO-d6, 300.13 MHz): δ = 7.57 (d, J = 7.7–7.3 Hz, 5H, 2H, Ar + NH), 7.06 (d, J = 10.11 Hz, 1H, Ar), 5.32 (s, 1H, CH), 4.87 (s, 1H, CH), 3.17 (s, 3H, CH3), 2.34 (s, 3H, CH3). IR(KBr): 3041, 2191, 1617, 1354, 1248 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C22H18Cl2N2O2+: 426.0740; found: 426.0771.

Methyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-bis(3-chlorophenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (4e) Yield: 0.87 g (68%); white solid; m.p. 210–213 °C; 1H-NMR (DMSO-d6, 300.13 MHz): δ = 7.68 (d, J = 10.15 Hz, 2H, Ar), 7.63–7.25 (m, 7H, Ar + NH), 5.31 (s, H, CH), 4.86 (s, H, CH), 3.18 (s, 3H, OCH3), 2.34 (s, 3H, CH3); 13C-NMR (CDCl3, 75.47 MHz): δ = 166.39, 152.75, 139.74, 135.36, 135.19, 134.46, 131.06, 130.68, 129.9, 128.8, 128.07 (s, 2C), 126.27, 125.86, 113.22, 111.36, 97, 19, 61.22, 50.68, 50.46, 47, 48, 20.35; IR(KBr): 3411, 2240, 1712, 1458, 1247, 711 cm⁻¹; HRMS (ESI) m/z [M + H]+ (for 35Cl) 426.0760; calcd for C22H18Cl2N2O2+: 426.0771, (for 35Cl and 37Cl) 428.0736; calcd for C22H18Cl2N2O2+: 428.0742.

Methyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-(3-pyridine)-1,4,5,6-tetrahydropyridine-3-carboxylate (4g) Yield: 0.67 g (62%); white solid; m.p. 200–203 °C; 1H-NMR (DMSO-d6, 300.13 MHz): δ = 8.81 (d, J = 8 Hz, 1H, Ar), 8.72 (dd, J = 4.8 Hz, J1 = 1.5 Hz, 1H, Ar), 8.56–8.53 (m, 2H, Ar), 8.03 (dt, J = 8 Hz, J1 = 1.7 Hz, 1H, Ar), 7.8 (s, 1H, NH), 7.68 (dt, J = 8 Hz, J1 = 1.6 Hz, 1H, Ar), 7.6 (dd, J = 8 Hz, J1 = 4.8 Hz, 1H, Ar), 7.43 (dd, J = 8 Hz, J1 = 4.8 Hz, 1H, Ar), 5.42 (s, 1H, CH), 4.95 (s, 1H, CH), 3.16 (s, 3H, OCH3), 2.36 (s, 3H, CH3); 13C-NMR (DMSO-d6, 125.76 MHz): δ = 166.01, 153.02, 152.28, 149.94, 149.60, 149.48, 135.23 (s, 2C), 133.51, 129.12, 124.2, 123.55, 112.85, 113.30, 96.97, 59.70, 50.82, 48.51, 47.55, 20.58; IR (KBr): 3204, 2248, 1651, 1459, 1263 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C20H18N5O2+: 360.1455; found: 360.1456.

Ethyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4h) Yield: 1.00 g (90%); white solid; m.p. 200–202 °C; 1H-NMR (DMSO-d6, 500.13 MHz): δ = 7.72–7.31 (m, 11H, Ar + NH), 5.31 (s, 1H, CH), 4.86 (s, 1HCH), 3.79–3.55 (m, 2H, CH2), 2.36 (s, 3H, CH3), 0.57 (t, J = 7.12Hz, 3H, CH3); 13C-NMR (DMSO-d6, 75.47 MHz): δ = 166.25, 154.33, 139.71, 134.84, 130.43, 129.06 (s, 2C), 128.82 (s, 2C), 128.63 (s, 2C), 128.33 (s, 3C), 114.44, 113.36, 94.9, 60.01, 58.61, 49.64, 48.2, 19.43, 13.79; IR (KBr): 3312, 2225, 1644, 1470, 1456, 1247 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C32H22N3O2+: 372.1707; found: 372.1700.

Ethyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-bis(4-fluorophenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (4i) Yield: 0.84 g (69%); white solid; m.p. 154–156 °C; 1H-NMR (DMSO-
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Methyl (4SR,6RS)-5,5-dicyano-2-ethyl-4,6-bis(4-bromo)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4j) Yield: 0.98 g (82%); white solid; m.p. 191–193 ºC; IR (KBr): 3387, 2250, 1670, 1570, 1496, 1463, 1256 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C23H20N5O6: 462.1408; found: 462.1402.

Methyl (4SR,6RS)-5,5-dicyano-2-ethyl-4,6-bis(4-fluoro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4k) Yield: 1.30 g (82%); white solid; m.p. 1685, 1484, 1349, 1256 cm⁻¹; 1H-NMR (CDCl3 300.13 MHz): δ = 7.96–7.33 (m, 15H, Ar), 4.98 (s, 1H, CH), 4.78 (s, 1H, CH), 4.61 (s, 1H, NH), 3.33 (s, 3H, OCH3) 2.93–2.65 (m, 2H, CH2), 1.32 (t, J = 7.5 Hz, 3H, CH3).

Methyl (4SR,6RS)-5,5-dicyano-2-ethyl-4,6-bis(4-nitro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4l) Yield: 0.80 g (58%); white solid; m.p. 243–248 ºC; IR (KBr): 3387, 2250, 1685, 1484, 1349, 1256 cm⁻¹; IR (KBr): 3387, 2250, 1685, 1484, 1349, 1256 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C23H20N5O6: 462.1408; found: 462.1402.

Methyl (4SR,6RS)-5,5-dicyano-2-methyl-4,6-bis(4-nitro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4m) Yield: 0.95 g (76%); white solid; m.p. 191–193 ºC; 1H-NMR (CDCl3 300.13 MHz): δ = 7.96–7.33 (m, 15H, Ar), 4.98 (s, 1H, CH), 4.78 (s, 1H, CH), 4.61 (s, 1H, NH), 3.33 (s, 3H, OCH3) 2.93–2.65 (m, 2H, CH2), 1.32 (t, J = 7.5 Hz, 3H, CH3).

Methyl (4SR,6RS)-5,5-dicyano-2-ethyl-4,6-bis(4-nitro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4n) Yield: 0.69 g (52%); white solid; m.p. 191–193 ºC; 1H-NMR (CDCl3 300.13 MHz): δ = 7.96–7.33 (m, 15H, Ar), 4.98 (s, 1H, CH), 4.78 (s, 1H, CH), 4.61 (s, 1H, NH), 3.33 (s, 3H, OCH3) 2.93–2.65 (m, 2H, CH2), 1.32 (t, J = 7.5 Hz, 3H, CH3).

Methyl (4SR,6RS)-5,5-dicyano-2-4,6-triphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4o) Yield: 0.95 g (76%); white solid; m.p. 223–225 ºC; IR (KBr): 3387, 2250, 1685, 1484, 1349, 1256 cm⁻¹; IR (KBr): 3387, 2250, 1685, 1484, 1349, 1256 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for C23H20N5O6: 462.1408; found: 462.1402.

Methyl (4SR,6RS)-5,5-dicyano-2-4,6-triphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4p) Yield: 0.69 g (52%); white solid; m.p. 191–193 ºC; 1H-NMR (CDCl3 300.13 MHz): δ = 7.72–7.61 (m, 2H, Ar), 7.55 (s, 1H, NH), 7.44–7.3 (m, 4H, Ar), 7.29–7.16 (m, 2H, Ar), 5.31 (s, 1H, CH), 4.85 (s, 1H, CH), 3.77–3.54 (m, 2H, CH2), 2.32 (s, 3H, CH3), 0.61 (t, J = 7.19 Hz, 3H, CH3); 13C-NMR (DMSO-d6, 300.13 MHz): δ = 166.09, 163.44 (s, 1C, 13C-NMR (DMSO-d6, 300.13 MHz): 3C-F, 124.29 (s, 4C), 124.07 (s, 2C), 114.28, 113.23, 94.81, 59.16, 58.69, 48.74, 48.31, 19.47, 13.87; IR (KBr): 3352, 2253, 1688, 1458, 1250, 1158 cm⁻¹; HRMS (ESI) m/z [M + H]+ calcd for 408.1518; found: 408.1512.
Ethyl (4SR,6RS)-5,5-dicyano-2-phenyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4q) Yield: 0.75 g (58%); white solid; m.p. 118–121 °C; IR(KBr): 3385, 2240, 1699, 1466, 1260 cm\(^{-1}\); 1H-NMR (CDCl\(_3\) 300.13 MHz): \(\delta = 7.72–7.34\) (m, 15H, Ar), 4.98 (s, 1H, CH), 4.79 (s, 1H, CH), 4.6 (s, 1H, NH), 3.75–3.56 (m, 2H, CH\(_2\)), 0.6 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)); 13C-NMR (CDCl\(_3\), 75.47 MHz): \(\delta = 165.37, 153.91, 153.74, 153.69, 153.69, 129.54, 129.42\) (s, 2C), 128.68 (s, 2C), 128.63, 128.51 (s, 2C), 128.24 (s, 4C), 127.93 (s, 2C), 113.66, 111.85, 99.18, 62.32, 59.53, 51.31, 48.17, 13.3; HRMS (ESI) \(m/z [M + H]^+\) calcld for C\(_{28}\)H\(_{24}\)N\(_3\)O\(_2^+\): 434.1863; found: 434.1850.

Ethyl (4SR,6RS)-5,5-dicyano-2-phenyl-4,6-bis(4-methoxy)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4r) Yield: 0.92 g (62%); white solid; m.p. 167–170 °C; 1H-NMR (CDCl\(_3\) 300.13 MHz): \(\delta = 7.69–7.33\) (m, 14H, Ar), 4.96 (s, 1H, CH), 4.75 (s, 1H, CH), 4.57 (s, 1H, NH), 3.17 (s, 3H, OCH\(_3\)).

Methyl (4SR,6RS)-5,5-dicyano-2-(4-bromo)phenyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4s) Yield: 1.18 g (75%); white solid; m.p. 131–134 °C; 1H-NMR (CDCl\(_3\) 300.13 MHz): \(\delta = 7.79\) (d, \(J = 8.2\) Hz, 2H, Ar), 7.53 (d, \(J = 7.9\) Hz, 2H, Ar), 7.42 (d, \(J = 6.3\) Hz, 2H, Ar), 7.39 (d, \(J = 6.6\) Hz, 2H, Ar), 7.3 (d, \(J = 9\) Hz, 2H, Ar), 7.22 (d, \(J = 7.8\) Hz, 2H, Ar), 4.90 (s, 1H, CH), 4.70 (s, 1H, CH), 4.54 (s, 1H, NH), 3.18 (s, 3H, OCH\(_3\)), 2.41 (s, 3H, CH\(_3\)), 2.38 (s, 3H, CH\(_3\)); 13C-NMR (CDCl\(_3\), DMSO-d\(_6\), 75.47 MHz): \(\delta = 165.99, 154.72, 135.77, 136.24, 137.72, 139.86, 131.48\) (s, 2C), 129.4 (s, 2C), 129.34 (s, 2C), 128.83 (c, 2C), 128.13 (c, 3C), 122.64, 114.51, 113.34, 97.06, 60.43, 50.46, 49.47, 48.82, 21.26, 21.2; IR (KBr): 3494, 2255, 1690, 1433, 1262, 726 cm\(^{-1}\); HRMS (ESI) \(m/z [M + H]^+\) calcd for C\(_{29}\)H\(_{24}\)Br\(_2\)ClN\(_2\)O\(_4^+\): 700.9276; found: 700.9281.

5-ethyl 3-methyl (4SR,5SR,6RS)-5-cyano-2-(4-bromophenyl)4,6-bis(4-methoxy)phenyl-1,4,5,6-tetrahydropyridine-5-carboxylate (5a) Yield: 0.77 g (36%); white solid; m.p. 221–223 °C; 1H-NMR (CDCl\(_3\) 300.13 MHz): \(\delta = 7.62–7.18\) (m, 12H, Ar), 4.87 (s, 1H, CH), 4.82 (s, 1H, CH), 4.5 (s, 1H, NH), 3.93 (q, \(J = 7\) Hz, 2H, CH\(_2\)), 3.17 (s, 3H, OCH\(_3\)), 0.89 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)); 13C-NMR (CDCl\(_3\), 75.47 MHz): \(\delta = 166.14, 166.09, 152.55, 137.52, 135.69, 133.13, 132.33\) (s, 2C), 131.71, 131.59 (s, 2C), 131.44 (s, 2C), 130.14 (s, 2C), 129.46 (s, 2C), 129.34, 129.35, 129.86, 121.8, 114.87, 100.12, 63.14, 61.31, 57.65, 50.63, 49.16, 13.61; IR(KBr): 3334, 2247, 1737, 1259, 501 cm\(^{-1}\); HRMS (ESI) \(m/z [M + H]^+\) (for 79Br) 700.9281 calcd for C\(_{29}\)H\(_{24}\)Br\(_2\)CIN\(_2\)O\(_4^+\): 700.9276.

5-ethyl 3-methyl (4SR,5SR,6RS)-5-cyano-2-(4-chlorophenyl)4,6-bis(4-methoxy)phenyl-1,4,5,6-tetrahydropyridine-5-carboxylate (5b) Yield: 0.61 g (33%); white solid; m.p. 205–208 °C; IR (KBr): 3333, 2247, 1739, 1259, 810, 500 cm\(^{-1}\); 1H-NMR (CDCl\(_3\) 300.13MHz): \(\delta = 7.59–7.21\) (m, 12H, Ar), 4.87 (s, 1H, CH), 4.83 (s, 1H, CH), 4.48 (s, 1H, NH), 3.93 (q, \(J = 7\) Hz, 2H, CH\(_2\)), 3.17 (s, 3H, OCH\(_3\)), 0.89 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)); 13C-NMR (CDCl\(_3\), 75.47 MHz): \(\delta = 166.17, 166.12, 152.56, 137.55, 135.65, 135.18, 133.14, 132.34\) (s, 2C), 131.6 (s, 2C), 129.91 (s, 2C), 129.47 (s, 2C), 129.33 (s, 2C), 128.48 (s, 2C), 124.35, 121.8, 114.89, 100.1, 63.15, 61.30, 57.67, 50.63, 49.15, 13.61; IR(KBr): 3333, 2247, 1739, 1259, 810, 500 cm\(^{-1}\); HRMS (ESI) \(m/z [M + H]^+\) (for 35Cl and 79Br) 656.9786 calcd for C\(_{29}\)H\(_{24}\)Br\(_2\)CIN\(_2\)O\(_4^+\): 656.9776.
3.5. Synthesis of 6

A mixture of aldehyde 1 (6 mmol), malononitril 2a (3 mmol), ester of 3-oxocarboxylic acid 3 (3 mmol) and ammonium acetate (6 mmol) was stirred in methanol (7 mL) at rt for 40 min. The precipitate was collected by filtration and dried to obtain piperidine 6.

Ethyl (2SR,3RS,4SR,6RS)-5,5-dicyano-2-phenyl-2-hydroxy-4,6-diphenyl-piperidine-3-carboxylate (6a) Yield: 0.97 g (72%); white solid; m.p. 135–137 °C; 1H-NMR (DMSO-d6, 300.13 MHz): 7.72 (d, J = 7.2 Hz, 4H, Ar), 7.5–7.3 (m, 11H, Ar), 6.01 (s, OH), 5.14 (s, H, CH), 4.39 (d, J = 12.4 Hz, H, CH), 3.58 (s, NH), 3.52 (q, J = 7.1 Hz, 2H, CH2), 3.45 (d, J = 12.4 Hz, H, CH), 0.56 (t, J = 7.1 Hz, 3H, CH3) 13C-NMR (DMSO-d6, 75.47MHz): 168.2, 144.7, 136.9, 136.2, 130.06, 129.3, 129.04 (s, 4C), 128.9 (s, 4C), 128.4, 128.3 (s, 2C), 126.5 (s, 2C), 114.1, 113.5, 84.4, 60.12, 59.5, 54.7, 49.2, 46.7, 13.7; IR (umax) (KBr), ν/cm−1: 3503, 3317, 1711, 703 cm−1; HRMS (ESI) m/z [M + H]+ 452.1977.

Ethyl (2SR,3RS,4SR,6RS)-5,5-dicyano-2-phenyl-2-hydroxy-4,6-bis(4-methyl)phenyl-piperidine-3-carboxylate (6b) Yield: 0.88 g (61%); white solid; m.p. 130–132 °C; 1H-NMR (DMSO-d6, 300.13 MHz): 7.71 (d, J = 7.1 Hz, 2H, Ar), 7.59 (d, J = 8.1 Hz, 2H, Ar), 7.45–7.24 (m, 7H, Ar), 7.19 (d, J = 8.1 Hz, 2H, Ar), 6 (s, OH), 5.06 (s, H, CH), 4.31 (d, J = 12.4 Hz, H, CH), 3.51 (q, J = 7.1 Hz, 2H, CH2), 3.47 (s, NH), 3.41 (d, J = 12.4 Hz, H, CH), 2.3 (s, 3H, CH3), 2.28 (s, 3H, CH3), 0.58 (t, J = 7.1 Hz, 3H, CH3); 13C-NMR (DMSO-d6, 75.47MHz): 168.2, 144.8, 139.5, 138.6, 134, 133.3, 129.6 (s, 2C), 129.4 (s, 2C), 128.9 (s, 2C), 128.7 (s, 2C), 128.4, 128.3 (s, 2C), 126.5 (s, 2C), 114.2, 113.5, 84.4, 60.1, 59.2, 54.7, 49.5, 46.3, 21.3, 21.1, 13.7; IR (umax) (KBr), ν/cm−1: 3498, 3320, 2224, 1713, 702 cm−1; HRMS (ESI) m/z [M + H]+ 480.2293 calcd for C30H30N3O3+: 480.2282.

Ethyl (2SR,3RS,4SR,6RS)-5,5-dicyano-2-phenyl-2-hydroxy-4,6-bis(4-chloro)phenyl-piperidine-3-carboxylate (6c) Yield: 0.87 g (56%); white solid; m.p. 126–128 °C; 1H-NMR (DMSO-d6, 300.13 MHz): δ = 7.72 (d, J = 8.6 Hz, 2H, Ar), 7.73–7.69 (m, 2H, Ar), 7.56 (d, J = 8.5 Hz, 2H, Ar), 7.48 (d, J = 2.4 Hz, 3H, Ar), 7.52–7.31 (m, 4H, Ar), 6.07 (s, OH), 5.17 (s, H, CH), 4.46 (d, J = 12.4 Hz, H, CH), 3.75 (s, NH), 3.54 (q, J = 7.1 Hz, 2H, CH2), 3.42 (d, J = 12.3 Hz, H, CH), 0.59 (t, J = 7.1 Hz, 3H, CH3); 13C-NMR (DMSO-d6, 75.47MHz): δ = 168, 144.5, 135.75, 135.27, 134.7, 134.1, 131.95 (s, 2C), 130.7 (s, 2C), 129.2 (s, 2C), 128.96 (s, 2C), 128.4, 128.3 (s, 2C), 126.6 (s, 2C), 113.8, 113.2, 84.5, 60.3, 58.7, 54.6, 48.98, 45.75, 13.7; IR (umax) (KBr), ν/cm−1: 3501, 3317, 1711, 1494, 705 cm−1; HRMS (ESI) m/z [M + H]+ 520.1189 calcd for C28H26N3O3+: 520.1177.

Methyl (2SR,3RS,4SR,6RS)-5,5-dicyano-2-(4-bromo)phenyl-2-hydroxy-4,6-bis(4-methyl)phenyl-piperidine-3-carboxylate (6d) Yield: 1.42 g (87%); white solid; m.p. 144–146 °C; 1H-NMR (DMSO-d6, 300.13 MHz): δ = 7.56–7.77 (m, 4H, Ar), 7.58 (d, J = 8.1 Hz, 2H, Ar), 7.33–7.24 (m, 4H, Ar), 7.19 (d, J = 7.9 Hz, 2H, Ar), 6.15 (s, OH), 5.04 (s, H, CH), 4.32 (d, J = 12.4 Hz, 1H, CH), 3.63 (s, NH), 3.4 (d, J = 12.4Hz, H, CH), 3.09 (s, 3H, OCH3), 2.33 (s, 3H, CH3), 2.28 (s, 3H, CH3); 13C-NMR (DMSO-d6, 75.47MHz): δ = 168.59, 144.36, 139.5, 138.67, 133.88, 133.22, 131.21 (s, 2C), 129.67 (s, 2C), 129.4 (s, 2C), 128.0 (s, 4C), 128.67 (s, 2C), 121.75, 114.15, 113.44, 84.20, 59.1, 54.6, 51.56, 49.4, 46.2, 21.26, 21.1; IR (umax) (KBr), ν/cm−1: 3490, 3316, 2250, 1715, 512 cm−1; HRMS (ESI) m/z [M + H]+ (for 79Br) 544.1230 calcd for C29H27BrN3O3+: 544.1217.

3.6. Synthesis of 7

(2SR,3RS,4SR,6RS)-5,5-dicyano-2-(4-bromo)phenyl-2-hydroxy-4,6-bis(4-methyl)phenyl-piperidine-3-carboxylate 6d (1 mmol) and acetic acid (2 mmol) were refluxed in methanol (8 mL) for 2 h. The mixture was maintained at −10 °C for 30 min for the complete precipitation of the product. The precipitate was collected by filtration and dried to obtain pure 7.

Methyl (3RS,4SR,6RS)-5,5-dicyano-2-(4-bromo)phenyl-4,6-bis(4-methyl)phenyl-tetrahydropridine-3-carboxylate (7) Yield: 0.18 g (90%); white solid; m.p. 235–237 °C; 1H-NMR (DMSO-d6, 300.13 MHz): δ = 7.86 (d, J = 8.6 Hz, 2H, Ar), 7.69 (d, J = 8.6 Hz, 2H, Ar), 7.54 (d, J = 8.1 Hz, 2H, Ar), 7.35–7.25 (m, 6H, Ar), 6.03 (d, J = 3 Hz, H, CH), 5 (dd, J1 = 11.2 Hz, J2 = 3 Hz, H, CH), 4.4 (d, J = 11.2 Hz, H, CH), 3.32 (s, 3H, OCH3), 2.35 (s, 6H,
1,4,5,6-tetrahydropyridine was found to be more stable than the isomeric intermediate 115.49 (d, \( J = 130.61 \) (d, \( J = 162.84, 162.67 \) (d, \( J = 183–185 \) °C, 131.96 (s, 2C), 131.93, 130.03 (s, 2C), 129.5 (s, 2C), 129.37 (s, 2C), 129.04 (s, 2C), 128.72 (s, 2C), 125.20, 113.91, 112.69, 65.78, 53.25, 48.18, 47.16, 45.37, 21.22 (s, 2C); IR (umax) (KBr), \( \nu / \text{cm}^{-1} \): 2952, 2252, 1742, 1636, 1259, 500; HRMS (ESI) \( m/z \) [M + H]+ (for 79Br) 526.1125 calcd for C29H27BrN3O3+: 526.1118.

3.7. Synthesis of 8

4-fluorobenzaldehyde 1h (6 mmol), ethyl cyanoacetate 2b (3 mmol), methyl 3-(4-bromophenyl)-3-oxopropanoate 3f (3 mmol) and ammonium acetate (6 mmol) in methanol (10 mL) were stirred at rt for 3 days. The solvent was evaporated under reduced pressure. Compound 8 was purified by column chromatography (eluent hexane/ethyl acetate = 3/1).

5-ethyl 3-methyl (3SR,4RS,5SR,6SR)-6-(4-bromophenyl)-3,4,5,6-tetrahydropyridine-3,5-dicarboxylate (8) Yield: 0.42 \( \Gamma \) (24%); white solid; m.p. 183–185 °C; \(^1\)H-NMR (DMSO-d_6, 300.13 MHz): \( \delta = 7.78 \) (d, \( J = 8.6 \) Hz, 2H, Ar), 7.67 (d, \( J = 8.6 \) Hz, 2H, Ar), 7.45–7.18 (m, 8H, Ar), 5.92 (d, \( J = 2.8 \) Hz, H, CH), 4.85 (dd, \( J_1 = 11.2 \) Hz, \( J_2 = 2.8 \) Hz, H, CH), 4.2 (d, \( J = 11.2 \) Hz, H, CH), 3.9 (q, \( J = 7.2 \) Hz, 2H, CH2), 3.32 (s, 3H, OCH3), 0.88 (t, \( J = 7.1 \) Hz, 3H, CH3); \(^{13}\)C-NMR (DMSO-d_6, 75.47 MHz): \( \delta = 170.88, 165.02, 162.84, 162.67 \) (d, \( f_{CF} = 245.5 \) Hz, 2C), 162.38 (d, \( f_{CF} = 245.5 \) Hz, 2C), 137.35, 134.77 (d, \( f_{CF} = 2.9 \) Hz, 2C), 132.16 (d, \( f_{CF} = 2.9 \) Hz, 2C), 131.96 (s, 2C), 131.23 (d, \( f_{CF} = 8.5 \) Hz, 2C), 130.61 (d, \( f_{CF} = 8.5 \) Hz, 2C), 129.15 (s, 2C), 124.65, 117.61, 116.3 (d, \( f_{CF} = 21.5 \) Hz, 2C), 115.49 (d, \( f_{CF} = 21.5 \) Hz, 2C), 65.85, 63.12, 54.01, 53.01, 48.26, 47.13, 13.81; IR (umax) (KBr), \( \nu / \text{cm}^{-1} \): 2250, 1734, 1230, 1009, 517 cm\(^{-1}\); HRMS (ESI) \( m/z \) [M + H]+ (for 79Br) 581.0884 calcd for C29H27BrF2N3O3+: 581.0882.

4. Conclusions

We developed a one-pot pseudo-five-component stereoselective synthesis of substituted 1,4,5,6-tetrahydropyridine, utilizing aldehydes (both with electron-withdrawing and electron-donating substituents), malononitrile or ethylcyanoacetate, esters of 3-oxocarboxylic acids and ammonium acetate, which played a dual role, acting as a base and as a nitrogen source for six-membered nitrogen-containing rings. Five bonds were formed as a result of the multicomponent process. Our method allows to obtain 2-substituted alkyl (4R,5R,6R)-1,4,5,6-tetrahydropyridine was found to be more stable than the isomeric intermediate (3R,4S,5S)-3,4,5,6-tetrahydropyridine. The conditions of all intermediates selective preparations were specified.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/molecules27144367/s1, Pages S2–S28: \(^1\)H and \(^{13}\)C NMR spectra of compounds 4–8; Pages S29–S32: 2D spectra of compounds 6d, 7; Pages S33–S37: DFT calculations.

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References
1. Vardanyan, R. Chapter 1—Introduction. In Piperidine-Based Drug Discovery; Vardanyan, R., Ed.; Elsevier: Amsterdam, The Netherlands, 2017; pp. 1–82. [CrossRef] [PubMed]
2. Wang, W.; Hu, Y. Small molecule agents targeting the p53-MDM2 pathway for cancer therapy. Med. Res. Rev. 2012, 32, 1159–1196. [CrossRef] [PubMed]
3. Petit, S.; Nallet, J.P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmes, M.; et al. Synthèses et activités psychotropes de 3,4-diarylpipéridines. Corrélation structure-activité et recherche d’une activité antihypertensive. Eur. J. Med. Chem. 1991, 26, 19–32.
4. Borza, I.; Domany, G. NR2B Selective NMDA Antagonists: The Evolution of the Ifenprodil-Type Pharmacophore. Curr. Top. Med. Chem. 2006, 6, 687–695. [CrossRef] [PubMed]
5. Mony, L.; Lew, W.; Williams, M.A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M.S.; Mendel, D.B.; Tai, C.Y.; et al. Influenza Neuraminidase Inhibitors Possessing a Novel Hydrophobic Interaction in the Enzyme Active Site: Design, Synthesis, and Structure of 3,5-diamino-piperidine derivatives: Novel antibacterial translation inhibitors as aminoglycoside mimetics. Bioorg. Med. Chem. Lett. 2007, 17, 1206–1210. [CrossRef] [PubMed]
6. Zhou, Y.; Gregor, V.E.; Ayida, B.K.; Winters, G.C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J.M.; Fish, S.; et al. Synthesis and SAR of 3,5-diamino-piperidine derivatives: Novel antibacterial translation inhibitors as aminoglycoside mimetics. Bioorg. Med. Chem. 2008, 3, 1539–1548. [CrossRef] [PubMed]
7. Treadway, J.L.; Mendys, P.; Hoover, D.J. Glycogen phosphorylase inhibitors for treatment of type 2 diabetes mellitus. Expert Opin. Investig. Drugs 2001, 10, 439–454. [CrossRef] [PubMed]
8. Karlsson, G.B.; Butters, T.D.; Platt, F.M.; McPherson, D.; Blumberg, B.S.; Dwek, R.A.; Block, T.M. Iminosugars inhibit the formation and secretion of bovine viral diarrhea virus, a pestivirus model of hepatitis C virus: Implications for the development of broad spectrum anti-hepatitis C virus. Proc. Natl. Acad. Sci. USA 1999, 96, 11878–11882. [CrossRef] [PubMed]
9. Mochizuki, A.; Nakamoto, Y.; Naito, H.; Uoto, K.; Ohta, T. Design, synthesis, and biological activity of piperidine diaminederivatives as factor Xa inhibitor. Bioorg. Med. Chem. Lett. 2008, 18, 782–787. [CrossRef] [PubMed]
10. Sun, C.-W.; Wang, J.; Wu, Y.; Nan, S.-B.; Zhang, W.-G. Novel nitenpyram analogues with tetrahydropyridone-fixed cis-configuration: Synthesis, insecticidal activities, and molecular docking studies. Heterocycles 2013, 87, 1865–1880. [CrossRef] [PubMed]
11. Brown, B.S.; Keddy, R.; Zheng, G.Z.; Schmidt, R.G.; Koening, J.R.; McDonald, H.A.; Bianchi, B.R.; Honore, P.; Jarvis, M.E.; Suvory, C.S.; et al. Tetrahydropyridine-4-carboxamides as novel, potent transient receptor potential vanilloid 1 (TPRV1) antagonists. Bioorg. Med. Chem. 2008, 16, 8516–8525. [CrossRef]
22. Misra, M.; Pandey, S.K.; Pandey, V.P.; Pandey, J.; Tripathi, R.; Tripathi, R.P. Organocatalyzed highly atom economic one pot synthesis of tetrahydropyridines as antimalarias. *Bioorg. Med. Chem. 2009, 17, 625–633.* [CrossRef] [PubMed]

23. Kozikowski, A.P.; Johnson, K.M.; Deschaux, O.; Bandopadhyay, B.C.; Araldi, G.L.; Carmona, G.; Munzar, P.; Smith, M.P.; Balster, R.L.; Beardsley, P.M.; et al. Mixed Cocaine Agonist/Antagonist Properties of (+)-Methyl 4-(4-Chlorophenyl)-1-methylpipеридине-3-carboxylate, a Piperidine-Based Analog of Cocaine. *J. Pharmacol. Exp. Ther. 2003, 305, 143–150.* [CrossRef] [PubMed]

24. Peters, T.H.A.; Benenker, F.B.G.; Hoorn, H.J.; Picha, F. Process for Producing 4-arylpyridine-3-carboxils and Related Compounds. Patent WO200026187, 11 May 2000.

25. Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. Organocatalytic Asymmetric Inverse-Electron-Demand Aza-Diels–Alder Reaction of N-Sulfonyl-1-aza-1,3-butadienes and Aldehydes. *Angew. Chem. Int. Ed. 2008, 47, 9971–9974.* [CrossRef] [PubMed]

26. Rueping, M.; Antonchick, A.P. A Highly Enantioselective Brønsted Acid Catalyzed Reaction Cascade. *Angew. Chem. Int. Ed. 2008, 47, 5836–5838.* [CrossRef]

27. Zhang, J.; Yang, W.-J.; Sun, J.; Yan, C.-G. Convenient Synthesis of Functionalized 6-Styryl-1,4,5,6-tetrahydropyridines through a Domino $[2 + 2 + 2]$ Cycloaddition Reaction. *Eur. J. Org. Chem. 2015, 2015, 7571–7582.* [CrossRef]

28. Han, R.-G.; Wang, Y.; Li, Y.-Y.; Xu, P.-F. Proline-Mediated Enantioselective Construction of Tetrahydropyridines via a Cascade Mannich-Type/Intramolecular Cyclization Reaction. *Adv. Synth. Catal. 2008, 350, 1474–1478.* [CrossRef]

29. Clarke, P.A.; Santos, S.; Martin, W.H.C. Combining pot, atom and step economy (PASE) in organic synthesis. Synthesis of tetrahydropyran-4-ones. *Green Chem. 2007, 9, 438–440.* [CrossRef]

30. Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci. 2016, 7, 866–880.* [CrossRef]

31. Tietze, L.F.; Brasche, G.; Gerike, K. *Domino Reactions in Organic Chemistry*; Wiley: Weinheim, Germany, 2006.

32. Tietze, L.F. *Domino Reactions: Concepts for Efficient Organic Synthesis*; Wiley: Weinheim, Germany, 2014.

33. Zhu, J.P.; Bienayme, H. *Multicomponent Reactions*; Wiley: Weinheim, Germany, 2004.

34. Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev. 2006, 106, 17–89.* [CrossRef]

35. Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chemie Int. Ed. 2000, 39, 3168–3210.* [CrossRef]

36. Nair, V.; Rajesh, C.; Vinod, A.U.; Bindu, S.; Sreekanth, A.R.; Mathen, J.S.; Balagopal, L. Strategies for heterocyclic construction via novel multicomponent reactions based on isocyanides and nucleophilic carbones. *Acc. Chem. Res. 2003, 36, 899–907.* [CrossRef] [PubMed]

37. Wang, H.-J.; Mo, L.-P.; Zhang, Z.-H. Cerium Ammonium Nitrate-Catalyzed Multicomponent Reaction for Efficient Synthesis of Functionalized Tetrahydropyridines. *ACS Comb. Sci. 2011, 13, 181–185.* [CrossRef] [PubMed]

38. Agrawal, N.R.; Bahekar, S.P.; Sarode, P.B.; Zade, S.S.; Chandak, H.S. L-Proline nitrate: A recyclable and green catalyst for the synthesis of highly functionalized piperidines. *RSC Adv. 2015, 5, 47053–47059.* [CrossRef]

39. Ismail, M.M.F.; Farrag, A.M.; Abou-El-Ela, D. Synthesis, anticancer screening, and in silico ADME prediction of novel 2-pyridones as Pim inhibitors. *J. Heterocycl. Comp. 2020, 57, 3442–3460.*

40. Dyachenko, I.V.; Dyachenko, V.D.; Dorovatovskii, P.V.; Khrustalev, V.N.; Nenajdenko, V.G. Synthesis of functionalized tetrahydropyridines by the tandem Knoevenagel—Michael—intramolecular ammonolysis—alkylation reaction. *Russ. Chem. Bull. 2021, 70, 2145–2155.* [CrossRef]

41. Vereshchagin, A.N.; Karpenko, K.A.; Elinson, M.N.; Dorofeeva, E.O.; Goloveshkin, A.S.; Egorov, M.P. Pseudo six-component stereoselective synthesis of 2,4,6-triaryl-3,3,5,5-tetracyanopiperidines. *Mendelev Commun. 2018, 28, 384–386.* [CrossRef]

42. Vereshchagin, A.N.; Karpenko, K.A.; Elinson, M.N.; Gorbunov, S.V.; Anisina, Y.E.; Egorov, M.P. Stereoselective multicomponent synthesis of (2R,6S)-2,6-diaryl-3,3,5,5-tetracyanopiperidines. *Russ. Chem. Bull. 2018, 67, 1534–1537.* [CrossRef]

43. Vereshchagin, A.N.; Karpenko, K.A.; Elinson, M.N.; Goloveshkin, A.S.; Ushakov, I.E.; Egorov, M.P. Four-component stereoselective synthesis of tetracyano-substituted piperidines. *Res. Chem. Intermed. 2018, 44, 5623–5634.* [CrossRef]

44. Vereshchagin, A.N.; Karpenko, K.A.; Elinson, M.N.; Goloveshkin, A.S.; Dorofeeva, E.O.; Egorov, M.P. Highly diastereoselective four-component synthesis of polysubstituted 2-piperidines with three and four stereogenic centers. *Res. Chem. Intermed. 2020, 46, 1183–1199.* [CrossRef]

45. Vereshchagin, A.N.; Karpenko, K.A.; Elinson, M.N.; Minaeva, A.P.; Goloveshkin, A.S.; Hansford, K.A.; Egorov, M.P. One-pot five-component high diastereoselective synthesis of polysubstituted 2-piperidines from aromatic aldehydes, nitriles, dialkyl malonates and ammonia acetate. *Mol. Divers. 2020, 24, 1327–1342.* [CrossRef]

46. Vereshchagin, A.N.; Karpenko, K.A.; Iliyasov, T.M.; Elinson, M.N.; Dorofeeva, E.O.; Fakhrutdinov, A.N.; Egorov, M.P. Diastereoselective multicomponent synthesis of (4RS,6SR)-4,6-diaryl-5,5-dicyano-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylates. *Russ. Chem. Bull. 2018, 67, 2049–2053.* [CrossRef]

47. Vereshchagin, A.N.; Iliyasov, T.M.; Karpenko, K.A.; Smirnov, V.A.; Ushakov, I.E.; Elinson, M.N. High diastereoselective four-component synthesis of polysubstituted 1,4,6-tetrahydropyridines. *Chem. Heterocycl. Compd. 2021, 57, 929–933.* [CrossRef]

48. Nikishkin, N.I.; Huskens, J.; Verboom, W. Study on the Pd/C-Catalyzed (Retro-)Michael Addition Reaction of Activated Methylene Compounds to Electron-Poor Styrenes. *Eur. J. Org. Chem. 2010, 2010, 6820–6823.* [CrossRef]

49. Elinson, M.N.; Vereshchagin, A.N.; Feducovich, S.K.; Zaimovskaya, T.A.; Starikova, Z.A.; Belyakov, P.A.; Nikishin, G.I. Unexpected stereoselective sodium acetate catalyzed multicomponent cyclization of aryl aldehydes, malononitrile and acetone into cis-4-dicyanomethylene-2,6-diairclyclohexane-1,1-dicarbonitriles. *Tetrahedron Lett. 2007, 48, 6614–6619.* [CrossRef]
50. Vereshchagin, A.N.; Elinson, M.N.; Egorov, M.P. The first electrocatalytic stereoselective multicomponent synthesis of cyclopropanecarboxylic acid derivatives. *RSC Adv.* **2015**, *5*, 98522–98526. [CrossRef]

51. Elinson, M.N.; Vereshchagin, A.N.; Ryzhkov, F.V. Catalysis of Cascade and Multicomponent Reactions of Carbonyl Compounds and C-H Acids by Electricity. *Chem. Rec.* **2016**, *16*, 1950–1964. [CrossRef]

52. Elinson, M.N.; Feduncovich, K.; Zaimovskaya, T.A.; Vereshchagin, A.N.; Nikishin, G.I. Stereoselective electrocatalytic transformations of malononitrile and aromatic aldehydes into (1R,3S,6R)-4,4-dialkoxy-2-amino-6-aryl-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-enes. *Russ. Chem. Bull.* **2005**, *54*, 673–677. [CrossRef]

53. Elinson, N.M.; Vereshchagin, N.A.; Ryzkov, V.F. Electrochemical Synthesis of Heterocycles via Cascade Reactions. *Curr. Org. Chem.* **2017**, *21*, 1427–1439. [CrossRef]

54. Elinson, M.N.; Vereshchagin, A.N.; Nasybullin, R.F.; Bobrovsky, S.I.; Ilovaisky, A.I.; Merkulova, V.M.; Bushmarinov, I.S.; Egorov, M.P. General approach to a spiro indole-3,1′-naphthalene tetracyclic system: Stereoselective pseudo four-component reaction of isatins and cyclic ketones with two molecules of malononitrile. *RSC Adv.* **2015**, *5*, 50421–50424. [CrossRef]

55. Vereshchagin, A.N.; Elinson, M.N.; Anisina, Y.E.; Ryzhkov, F.V.; Novikov, R.A.; Egorov, M.P. PASE Pseudo-Four-Component Synthesis and Docking Studies of New 5-C-Substituted 2,4-Diamino-5H-Chromeno[2,3-b]pyridine-3-Carbonitriles. *ChemistrySelect* **2017**, *2*, 4593–4597. [CrossRef]

56. Elinson, M.N.; Ryzhkov, F.V.; Vereshchagin, A.N.; Korshunov, A.D.; Novikov, R.A.; Egorov, M.P. ‘On-solvent’ new domino reaction of salicylaldehyde, malononitrile and 4-hydroxy-6-methylpyridin-2(1H)-one: Fast and efficient approach to medicinally relevant 4-pyridinyl-2-amino-4H-chromene scaffold. *Mendeleev Commun.* **2017**, *27*, 559–561. [CrossRef]

57. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Petersson, G.A.; Nakatsuji, H.; et al. Gaussian, Inc.: Wallingford, CT, USA. 2016. Available online: https://gaussian.com/citation/ (accessed on 16 May 2022).

58. Zhou, Z.; Yuan, J.; Yang, R. Efficient Knoevenagel Condensation Catalyzed by 2-Hydroxyethylammonium Acetate Under Solvent-Free Conditions at Room Temperature. *Synth. Commun.* **2009**, *39*, 2001–2007. [CrossRef]

59. Gibadullina, N.N.; Latypova, D.R.; Nugumanov, T.R.; Spirikhin, L.V.; Dokichev, V.A. Synthesis of polyfunctionalized 1,1′-(α,ω-alkanediy)bis(1,2,3,4-tetrahydropyridines). *Chem. Heterocycl. Compd.* **2017**, *53*, 1098–1102. [CrossRef]

60. Sheldrick, G.M. CELL_NOW. Version 2008/4; Georg-August-Universität: Göttingen, Germany, 2008.

61. Bruker. APEX-III; Bruker AXS Inc.: Madison, WI, USA, 2019.

62. Krause, L.; Herbst-Irmer, R.; Sheldrick, G.M.; Stalke, D. Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *J. Appl. Cryst.* **2015**, *48*, 3–10. [CrossRef] [PubMed]

63. Sheldrick, G.M. SHELXT—Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3–8. [CrossRef]

64. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3–8. [CrossRef]

65. Flack, H.D. On enantiomorph-polarity estimation. *Acta Cryst.* **1983**, *A39*, 876–881. [CrossRef]

66. Macrae, C.F.; Sovago, I.; Cottrell, S.J.; Gale, P.T.A.; McCabe, P.; Platings, M.; Shields, G.P.; Stevens, J.S.; Towler, M.; et al. Mercury 4.0: From visualization to analysis, design and prediction. *J. Appl. Cryst.* **2020**, *53*, 226–235. [CrossRef]