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Stereocontrolled Construction of Tetrahydropyrano[2,3-*c*]pyrazole Scaffold via an Organocatalyzed Formal [3 + 3] Annulation

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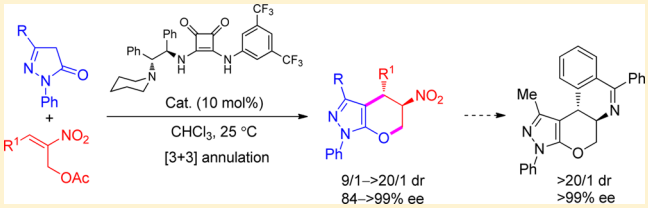
Supporting Information

ABSTRACT: A bifunctional squaramide catalyzed enantioselective formal [3 + 3] annulation reaction with pyrazolin-5-ones and nitroallylic acetates has been developed. Densely substituted tetrahydropyrano[2,3-*c*]pyrazoles with two adjacent stereogenic centers are obtained in a highly stereocontrolled manner. Representative transformation of the annulation product to a biologically important fused dihydroisoquinoline is achieved without any appreciable loss in the diastereo- and enantioselectivity.



Pyrazoles are one of the most important classes of nitrogen-containing heterocycles. Although pyrazoles are rarely found in natural products, a great number of pyrazole derivatives have been widely used as pharmaceuticals, agrochemicals, and other functional materials.[1] As an oxygen heterocycle, the tetrahydropyran (THP) skeleton is also a common structural unit found in a number of biologically active natural products such as acetogenins,[2] polyether antibiotics,[3] and ladderlike marine polycyclic ethers.[4] In the past decades, pyrazole and tetrahydropyran derivatives have intensively attracted much attention due to their diverse applications in the field of drug discovery and agricultural research. Among numerous pyrazoles and tetrahydropyran derivatives, tetrahydropyrano[2,3-*c*]pyrazoles that contain both cores of tetrahydropyran and pyrazole are especially of synthetic and pharmaceutical interest. The tetrahydropyrano[2,3-*c*]pyrazole moiety is present in many biologically important compounds (Figure 1). For example, both tetrahydropyrano[2,3-*c*]pyrazole **1**[5] and its *N*-dichlorofluoromethanesulfenyl substituted analogue **2**[6] serve as fungicides, compound **3** exhibits anti-inflammatory activity,[7] and trifluoromethyl substituted tetrahydropyrano[2,3-*c*]pyrazoles **4**[8] and **5**[9] are effective AMPA receptor agonists. Despite the importance of bioactive tetrahydropyrano[2,3-*c*]pyrazoles, the enantioselective synthesis of this type of heterocycle has rarely been explored. To the best of our knowledge, there is only one report about the enantioselective synthesis of enantiomerically enriched tetrahydropyrano[2,3-*c*]pyrazole derivatives. Enders et al. realized the synthesis of 1,4,5,6-tetrahydropyrano[2,3-*c*]-pyrazoles with high enantioselectivity via a secondary amine catalyzed asymmetric Michael/Wittig/oxa-Michael reaction sequence.[10] Therefore, the diverse biological profiles of these tetrahydropyran fused pyrazole derivatives along with our continuous efforts[11] in preparing biologically important heterocycles prompted us to develop a novel efficient catalytic method for the synthesis of structurally diverse tetrahydropyran fused pyrazoles in a highly enantioselective manner.

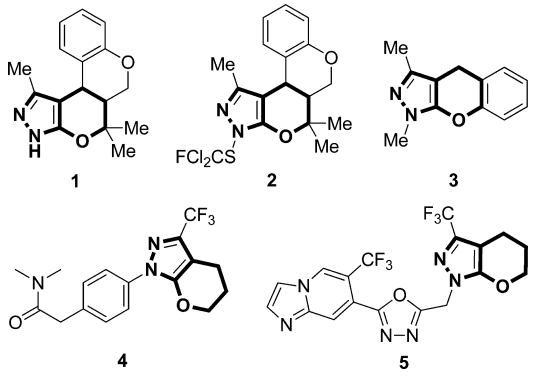


Figure 1. Some bioactive tetrahydropyrano[2,3-*c*]pyrazoles.

Due to tautomerism, pyrazolin-5-one can act either as a carbonyl compound or as a hydroxyl substituted aromatic heterocycle. This binucleophilic nature makes pyrazolin-5-one function as a versatile 1,3-dinucleophile in the synthesis of fused pyrazole derivatives.[12] We envisioned that enantiomerically enriched tetrahydropyrano[2,3-*c*]pyrazoles **8** with two adjacent stereogenic centers could be conveniently accessed through a formal annulation of 1,3-binucleophilic pyrazolin-5-ones **6** and 1,3-bielectrophilic Morita–Baylis–Hillman (MBH) acetates of nitroalkenes **7**[13] (Scheme 1). Herein, we report an organocatalytic [3 + 3] cascade reaction to access enantiomerically enriched tetrahydropyrano[2,3-*c*]pyrazoles in acceptable yields with excellent diastereo- and enantioselectivities.

Toward this endeavor, the bielectrophilic MBH acetate of nitroalkene **7a** was subjected to a domino Michael–

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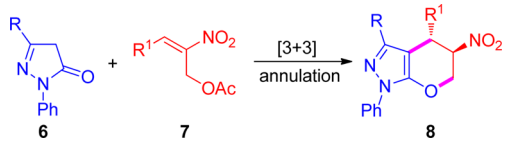
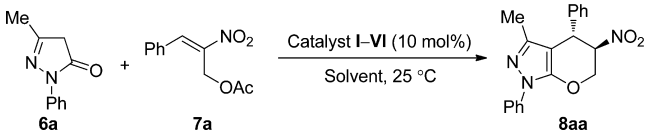
Scheme 1. Construction of Tetrahydropyrano[2,3-*c*]pyrazole Scaffold via a [3 + 3] Annulation Strategy



elimination−Michael reaction with pyrazolin-5-one **6a** in the presence of 10 mol % of Takemoto's thiourea catalyst **I** in dichloromethane at room temperature. The reaction ran smoothly to afford tetrahydropyran fused pyrazole derivative **8aa** in 58% yield with 8/1 dr and 43% ee (Table 1, entry 1). To improve the stereoselectivity of this transformation, we screened other thiourea-[14] or squaramide-based hydrogen-bonding catalysts[15] (Figure 2), the results are summarized in Table 1. Further screening revealed that squaramide catalyst **Vd** derived from L-*tert*-leucine containing a piperidinyl group afforded a significantly improved enantioselectivity of 91% ee (entry 8). The ee value of the model reaction was further slightly enhanced to 93% ee by using squaramide catalyst **VIa** bearing a piperidinyl group derived from (1*R*,2*R*)-1,2-diphenyl-ethane-1,2-diamine (entry 9). An inferior result was obtained by replacing the piperidinyl group with a pyrrolidinyl group (entry 10 vs 9).

Table 1. Screening Studies of the Model Reaction between 6a and 7a[a]



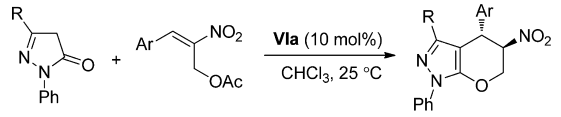
entry	catalyst	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	CH_2Cl_2	10	58	8/1	43
2	**II**	CH_2Cl_2	16	54	9/1	−53
3	**III**	CH_2Cl_2	10	66	9/1	56
4	**IV**	CH_2Cl_2	24	45	9/1	−45
5	**Va**	CH_2Cl_2	10	69	11/1	−55
6	**Vb**	CH_2Cl_2	12	79	9/1	−60
7	**Vc**	CH_2Cl_2	12	76	13/1	−76
8	**Vd**	CH_2Cl_2	16	60	9/1	−91
9	**VIa**	CH_2Cl_2	24	59	9/1	93
10	**VIb**	CH_2Cl_2	30	49	9/1	85
11	**VIa**	$CHCl_3$	30	61	>20/1	>99
12	**VIa**	EA	24	36	3/1	89
13	**VIa**	THF	24	33	2/1	89
14	**VIa**	CH_3OH	24	37	8/1	91
15	**VIa**	$PhCH_3$	24	41	8/1	86
16	**VIa**	MeCN	24	36	7/1	83
17[e]	**VIa**	$CHCl_3$	40	74	>20/1	98
18[f]	**VIa**	$CHCl_3$	70	45	>20/1	>99
19[g]	**VIa**	$CHCl_3$	12	52	>20/1	95
20[h]	**VIa**	$CHCl_3$	24	46	>20/1	99
21[i]	**VIa**	$CHCl_3$	36	55	>20/1	99

[a]Unless otherwise specified, all reactions were carried out with **6a** (0.20 mmol), **7a** (0.20 mmol) in the presence of 10 mol % of catalyst in solvent (1 mL) at 25 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis using a chiral stationary phase. [e]In the presence of 5 mol % of catalyst **VIa**. [f]The reaction was performed at 0 °C. [g]The reaction was carried out under refluxing. [h]0.5 mL of chloroform was loaded. [i]2 mL of chloroform were added.

Subsequently, with the aim of further improving the selectivity, several common solvents were screened at room temperature. The reactions were not complete and generally gave product **8aa** in low yields (31−41%) but good enantioselectivities (83−91% ee) in solvents such as ethyl acetate, tetrahydrofuran, methanol, toluene, and acetonitrile (entries 12−16). It is worth noting that a protic solvent is generally detrimental to the catalytic efficacy and the stereochemical outcome of hydrogen bonding catalysis owing to the competitive hydrogen bonding interaction. However, in this study, the model reaction proceeded with good diastereo- (8/1 dr) and excellent enantioselectivity (91% ee) in protic solvent methanol (entry 5). A considerable improvement in both the dr (>20/1) and ee value (>99%) was achieved by conducting the reaction in chloroform (entry 11). In addition, adjusting the catalyst loading to 5 mol % led to a slightly enhanced yield but a slightly decreased enantioselectivity (entry 17). Either variation of reaction temperature (entries 18 and 19) or changing the concentration (entries 20 and 21) failed to improve the yield of the reaction.

After establishing the optimized reaction conditions (Table 1, entry 11), the substrate scope and limitations of this formal [3 + 3] annulation were explored (Table 2). First, the reaction was extended to a variety of MBH acetate of nitroalkenes **7**. Generally, the reaction worked well with aromatic MBH acetates **7** bearing electron-neutral (**7a**), -withdrawing (**7b**−**h**),

Table 2. Substrate Scope and Limitations of the Organocatalyzed Formal [3 + 3] Annulations[a]



entry	**8** (R, Ar)	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**8aa** (Me, Ph)	30	61	>20/1	>99
2	**8ab** (Me, 4-FC_6H_4)	58	65	9/1	>99
3	**8ac** (Me, 4-ClC_6H_4)	60	57	>20/1	91
4	**8ad** (Me, 3-ClC_6H_4)	36	59	>20/1	>99
5	**8ae** (Me, 2-ClC_6H_4)	48	59	>20/1	98
6	**8af** (Me, 4-BrC_6H_4)	64	76	>20/1	98
7	**8ag** (Me, 3-BrC_6H_4)	54	79	>20/1	92
8	**8ah** (Me, 2-BrC_6H_4)	30	66	>20/1	97
9	**8ai** (Me, 4-$MeOC_6H_4$)	72	66	>20/1	>99
10	**8aj** (Me, 2-$MeOC_6H_4$)	48	68	>20/1	>99
11	**8ak** (Me, 2-MeC_6H_4)	73	63	>20/1	>99
12	**8al** (Me, 1-Naph)	70	78	>20/1	>99
13	**8am** (Me, 2-Furyl)	70	65	>20/1	99
14	**8an** (Me, 2-Thienyl)	67	75	>20/1	>99
15	**8ao** (Me, Cy)	72	NR[e]		
16	**8ba** (CF_3, Ph)	70	52	>20/1	>99
17	**8ca** (Pr, Ph)	64	77	9/1	88
18	**8da** (Ph, Ph)	53	81	9/1	86
19	**8ea** (4-$EtOC_6H_4$, Ph)	60	79	9/1	84

[a]All reactions were carried out with **6** (0.20 mmol), **7** (0.20 mmol) in the presence of 10 mol % of catalyst **VIa** in chloroform (1 mL) at 25 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis using a chiral stationary phase. [e]NR means no reacton occurred.

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J. Org. Chem. 2016, 81, 4340−4346

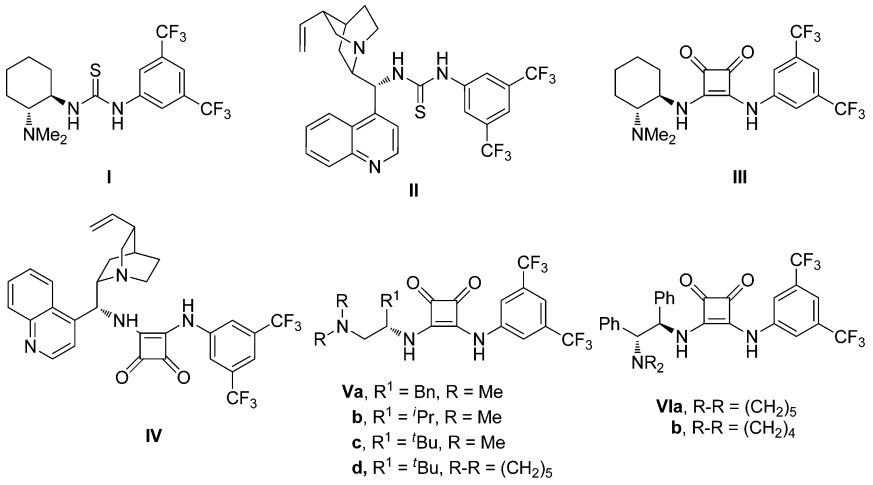
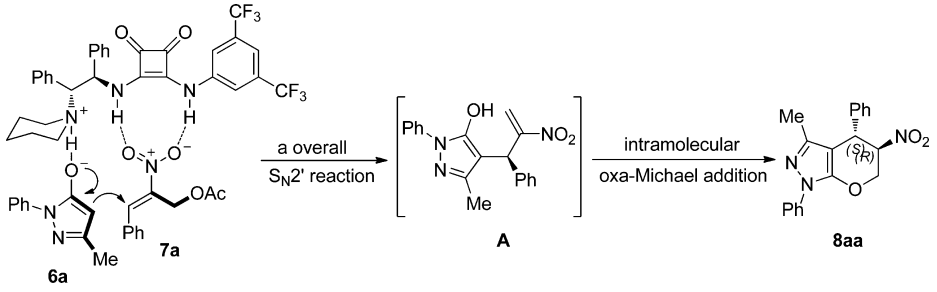
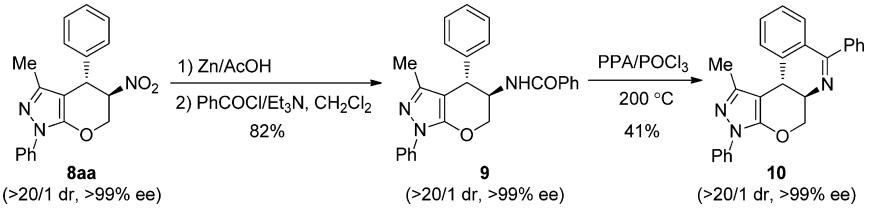


Figure 2. Screened thiourea- and squaramide-based organocatalysts.

Scheme 2. Proposed Reaction Mechanism



Scheme 3. Transformation of Tetrahydropyrano[2,3-*c*]pyrazole 8aa



and -donating (**7i**–**k**) substituents on the benzene ring, delivering the corresponding cyclization products in fine yields (57–79%) and high stereoselectivities (entries 1–11, 9/1–>20/1 dr; 91–>99% ee). The MBH acetate **7l** with a fused aromatic ring also reacted smoothly with pyrazolin-5-one **6a** to give product **8al** in good yield with high diastereo- (>20/1 dr) and enantioselectivity (>99%) (entry 12). Heteroaromatic 2-furyl and 2-thienyl substituted MBH acetates **7m** and **7n** were also good reaction partners, affording the annulation products **8am** and **8an** with uniformly high levels of diastereo- and enantioselectivity (entries 13 and 14). In addition, the reaction proved to be limited to aromatic MBH acetates. For example, the less reactive aliphatic MBH acetate **7o** bearing a cyclohexyl group failed to undertake this type of [3 + 3] formal cycloaddition reaction (entry 15).

On the other hand, the substitution patterns of pyrazolin-5-ones **6** were investigated in the reactions with the 2-nitroallylic acetate **7a** bearing a phenyl group. It is noteworthy that 3-trifluoromethyl substituted pyrazolin-5-one **6b** works well to afford fluorinated tetrahydropyrano[2,3-*c*]pyrazole **8ba** in acceptable yield with almost perfect stereoselectivity (entry 16, >20/1 dr; >99% ee). Replacing the methyl group in 3-methyl-1-phenylpyrazol-5-one **6a** with a larger propyl (**6c**), phenyl (**6d**), or 4-ethoxyphenyl group (**6e**) all led to an obvious decrease in both diastereo- and enantioselectivity (entries 17–19, 84–88% ee, 9/1 dr for all cases).

The absolute configuration and molecular structure of **8aa** were unambiguously determined by X-ray crystallography (see the Supporting Information), and the remaining configurations are assumed by analogy.[16]

To account for the observed stereochemistry of this cascade transformation, a plausible mechanism is shown in Scheme 2. An enolate is formed via the deprotonation of **6a** by the tertiary amine group. Simultaneously, nitroallylic acetate **7a** was activated via a bidentate H-bond interaction between the nitro group and the squaramide moiety. The enolate then approaches the nitroolefin from the *Re* face in a Michael fashion accompanied by the elimination of the acetate to generate nitroolefin intermediate **A**. The overall process is an S_N2'-type reaction. Finally, spontaneous intramolecular oxa-Michael addition with the aid of a bifunctional squaramide catalyst via a similar dual activation fashion gave rise to the desired tetrahydropyrano[2,3-*c*]pyrazole **8aa**. The observed high diastereoselectivity may be attributed to the preferential

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formation of the thermodynamically more stable *trans*-diastereomer by equilibration of the epimerizable stereogenic center α to the nitro group.

The multifunctional products obtained in these formal [3 + 3] annulations would find more application in organic synthesis and medicinal chemistry. For example, as outlined in Scheme 3, the nitro group of tetrahydropyrano[2,3-*c*]pyrazole **8aa** was transformed to the amino group using the Zn/AcOH reduction system. Subsequent treatment of the amine with benzoyl chloride in the presence of triethylamine afforded the corresponding benzamide **9**. Ring closure of **9** upon treatment with PPA/$POCl_3$ at 200 °C afforded biologically important polycyclic dihydroisoquinoline derivative **10**. It is worth noting that all these transformations proceeded without any appreciable loss in the diastereo- and enantioselectivity.

In conclusion, we developed an organocatalytic asymmetric formal [3 + 3] annulation of pyrazolin-5-ones and MBH acetates of nitroolefins. Under the catalysis of a (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine derived tertiary amine-squaramide catalyst, the reactions ran smoothly to provide a series of densely functionalized tetrahydropyrano[2,3-*c*]pyrazoles in good yields, high *anti*-selectivities, and excellent enantioselectivities. This method serves as a useful tool for the stereocontrolled construction of tetrahydropyrano[2,3-*c*]-pyrazole scaffolds with two adjacent tertiary stereogenic centers. Moreover, multifunctional tetrahydropyrano[2,3-*c*]pyrazoles could be transformed into biologically important fused dihydroisoquinoline derivatives via a sequence of nitro group reduction, benzoylation, and intromolecular dehydration without any appreciable loss in the diastereo- and enantioselectivities.

EXPERIMENTAL SECTION

General Information. Materials were obtained from commercial suppliers and were used without further purification. NMR spectra were obtained with a 400 MHz spectrometer (^{1}H 400 MHz, ^{13}C 100.6 MHz) in $CDCl_3$. The chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. HRMS spectra were recorded with a Q-TOF mass spectrometer, equipped with an ESI source. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at 20 °C. Enantiomeric excesses were determined by HPLC analysis with a chiral stationary phase.

General Procedure for VIa Catalyzed Asymmetric Formal [3 + 3] Annulation of Pyrazolin-5-one 6 and MBH Acetate of Nitroolefins 7. A solution of squaramide catalyst **VIa** (10 mol %), pyrazolin-5-ones (**6**, 0.20 mmol), and MBH acetate of nitroolefins (**7**, 0.20 mmol) in chloroform (1 mL) was stirred at 25 °C. Upon completion of the reaction (monitored by TLC), the product was directly purified by column chromatography on silica gel (200−300 mesh, PE/EtOAc = 12/1) to afford the desired tetrahydropyrano[2,3-*c*]pyrazoles **8**. The title compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and specific rotation data. The enantiomeric excess of the pure products was determined by HPLC analysis using a chiral stationary phase.

*(4S,5R)-3-Methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano-[2,3-c]pyrazole (**8aa**).* White solid, mp 160−162 °C, 41 mg, 61% yield, $[\alpha]_D^{20}$ +85.3 (*c* 1.27, $CHCl_3$), >20/1 dr, >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3 H), 4.41 (d, *J* = 11.2 Hz, 1 H), 4.77 (s, 1 H), 4.91 (s, 1 H), 4.93 (d, *J* = 14.0 Hz, 1 H), 7.26−7.45 (m, 8 H), 7.75 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.9, 39.5, 65.8, 84.8, 95.0, 120.4, 125.9, 128.0, 128.2, 129.0, 129.3, 138.1, 139.3, 146.7, 149.0. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}N_3O_3$ [M + H]$^+$: 336.1343, found 336.1340. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 88:12, flow rate = 0.4 mL/min, wavelength = 254 nm): R_t = 29.80 (major) and 33.39 min (minor).

*(4S,5R)-4-(4-Fluorophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ab**).* White solid, mp 120−122 °C, 46 mg, 65% yield, $[\alpha]_D^{20}$ +122.2 (*c* 1.10, $CHCl_3$), 90/10 dr, >99% ee for the *trans* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 2.70 H, *trans* diastereomer), 1.96 (s, 0.3 H, *cis* diastereomer), 4.41 (dd, *J* = 12.0, 2.0 Hz, 0.90 H, *trans* diastereomer), 4.52 (t, *J* = 11.2 Hz, 0.10 H, *cis* diatereomer), 4.63 (dd, *J* = 11.6, 3.2 Hz, 0.10 H, *cis* diastereomer), 4.72−4.76 (m, 0.90 H, *trans* diastereomer), 4.88−4.94 (m, 1.90 H, major diastereomer), 5.22−5.27 (m, 0.10 H, *cis* diastereomer), 7.03 (t, *J* = 8.4 Hz, 0.20 H, *cis* diastereomer), 7.08 (t, *J* = 8.4 Hz, 1.80 H, *trans* diastereomer), 7.24−7.27 (m, 3 H), 7.44 (t, *J* = 7.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): *trans* diastereomer: δ 12.9, 39.0, 65.8, 84.8, 95.0, 116.2 (d, *J* = 21.6 Hz), 120.4, 126.0, 129.1, 129.7 (d, *J* = 8.1 Hz), 134.9 (*J* = 3.1 Hz), 138.0, 146.8, 149.0, 162.4 (d, *J* = 247.7 Hz); *cis* diastereomer: δ 12.5, 39.3, 62.9, 81.3, 95.0, 115.8 (d, *J* = 21.2 Hz), 120.3, 126.1, 129.1, 130.5 (d, *J* = 8.5 Hz), 134.9 (*J* = 3.1 Hz), 138.0, 146.8, 149.7, 165.5 (d, *J* = 252.0 Hz). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}FN_3O_3$ [M + H]$^+$: 354.1248, found 354.1255. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 80:20, flow rate = 0.5 mL/min, wavelength = 254 nm): R_t = 19.17 (major, *trans* diastereomer), 20.83 (major, *cis* diastereomer), and 31.93 min (minor, *trans* diastereomer).

*(4S,5R)-4-(4-Chlorophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ac**).* White solid, mp 140−142 °C, 42 mg, 57% yield, $[\alpha]_D^{20}$ +99.2 (*c* 1.37, $CHCl_3$), >20/1 dr, 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 4.71 (s, 1 H), 4.86 (d, *J* = 3.2 Hz, 1 H), 4.90 (dd, *J* = 11.6, 4.4 Hz, 1 H), 7.19−7.26 (m, 3 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.9, 39.0, 65.7, 84.5, 94.7, 120.3, 126.0, 129.0, 129.3, 129.4, 134.1, 137.6, 137.9, 146.7, 149.0. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}ClN_3O_3$ [M + H]$^+$: 370.0953, found 370.0957. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 75:25, flow rate = 0.3 mL/min, wavelength = 254 nm): R_t = 19.09 (minor, *trans* diastereomer), 22.57 (major, *trans* diastereomer), and 24.07 min (major, *cis* diastereomer).

*(4S,5R)-4-(3-Chlorophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ad**).* White solid, mp 148−150 °C, 44 mg, 59% yield, $[\alpha]_D^{20}$ +146.5 (*c* 1.20, $CHCl_3$), >20/1 dr, >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (s, 3 H), 4.42 (dd, *J* = 12.0, 2.4 Hz, 1 H), 4.75−4.78 (m, 1 H), 4.91 (d, *J* = 3.2 Hz, 1 H), 4.96 (dd, *J* = 12.0, 4.4 Hz, 1 H), 7.18−7.20 (m, 1 H), 7.28 (s, 1 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 7.34−7.35 (m, 2 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.76 (d, *J* = 7.60 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.0, 39.2, 65.8, 84.4, 94.4, 120.4, 126.1, 126.3, 128.2, 128.5, 129.1, 130.6, 135.3, 138.0, 141.4, 146.8, 149.1. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}ClN_3O_3$ [M + H]$^+$: 370.0953, found 370.0961. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 12.30 (major) and 15.30 min (minor).

*(4R,5R)-4-(2-Chlorophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ae**).* White solid, mp 158−160 °C, 44 mg, 59% yield, $[\alpha]_D^{20}$ +157.8 (*c* 0.70, $CHCl_3$), >20/1 dr, >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3 H), 4.23 (dd, *J* = 12.4, 2.0 Hz, 1 H), 4.81 (d, *J* = 2.4 Hz, 1 H), 5.06 (ddd, *J* = 12.0, 2.8, 1.6 Hz, 1 H), 5.35 (s, 1 H), 7.10 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.24−7.30 (m, 2 H), 7.30 (dt, *J* = 7.6, 1.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.49 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.7, 35.7, 65.4, 81.6, 93.9, 120.4, 126.0, 127.5, 129.1, 129.6, 130.2, 130.3, 133.6, 136.5, 138.1, 146.9, 149.4. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}ClN_3O_3$ [M + H]$^+$: 370.0953, found 370.0961. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 13.84 (major) and 20.39 min (minor).

*(4S,5R)-4-(4-Bromophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8af**).* White solid, mp 130−132 °C, 63 mg, 76% yield, $[\alpha]_D^{20}$ +84.5 (*c* 2.00, $CHCl_3$), >20/1 dr, >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3 H), 4.39 (dd, *J* = 12.0, 1.6 Hz, 1 H), 4.72 (d, *J* = 1.6 Hz, 1 H), 4.86 (d, *J* = 3.6 Hz, 1 H), 4.92 (dd, *J* = 12.0, 4.4 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.0, 39.2, 65.8,

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J. Org. Chem. 2016, 81, 4340−4346

84.5, 94.6, 120.4, 122.3, 126.1, 129.1, 129.7, 132.4, 138.0, 138.3, 146.8, 149.0. HRMS (ESI) m/z calcd for $C_{19}H_{17}BrN_3O_3$ $[M + H]^+$: 414.0448, found 414.0450. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 85:15, flow rate = 0.5 mL/min, wavelength = 254 nm): R_t = 15.67 (minor, *trans* diastereomer), 19.35 min (major, *trans* diastereomer), and 21.08 (major, *cis* diastereomer).

*(4S,5R)-4-(3-Bromophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ag**).* White solid, mp 140−142 °C, 47 mg, 57% yield, $[\alpha]_D^{20}$ +59.3 (c 0.97, $CHCl_3$), >20/1 dr, 92% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3 H), 4.41 (dd, J = 12.0, 2.4 Hz, 1 H), 4.76 (dt, J = 3.6, 2.4 Hz, 1 H), 4.91 (d, J = 3.6 Hz, 1 H), 4.98 (ddd, J = 12.0, 4.4, 0.8 Hz, 1 H), 7.22−7.31 (m, 3 H), 7.44−7.51 (m, 4 H), 7.77 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.0, 39.1, 65.7, 84.4, 94.3, 120.4, 123.4, 126.1, 126.7, 129.1, 130.8, 131.0, 131.4, 138.0, 141.6, 146.7, 149.0. HRMS (ESI) m/z calcd for $C_{19}H_{17}BrN_3O_3$ $[M + H]^+$: 414.0448, found 414.0446. HPLC analysis (Chiralpak OD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 32.23 (major) and 43.56 min (minor).

*(4R,5R)-4-(2-Bromophenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ah**).* White solid, mp 138−140 °C, 55 mg, 66% yield, $[\alpha]_D^{20}$ +49.4 (c 1.60, $CHCl_3$), >20/1 dr, 97% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3 H), 4.23 (dd, J = 12.4, 0.8 Hz, 1 H), 4.81 (s, 1 H), 5.06 (dd, J = 12.0, 0.8 Hz, 1 H), 5.31 (s, 1 H), 7.10 (dd, J = 7.6, 1.2 Hz, 1 H), 7.22 (dt, J = 7.6, 1.2 Hz, 1 H), 7.25 (t, J = 7.6 Hz, 1 H), 7.31 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 8.0 Hz, 2 H), 7.67 (d, J = 8.0, 1.2 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.7, 38.0, 65.4, 81.9, 94.2, 120.3, 124.1, 126.0, 128.1, 129.0, 129.8, 130.5, 133.7, 138.0, 146.9, 149.4. HRMS (ESI) m/z calcd for $C_{19}H_{17}BrN_3O_3$ $[M + H]^+$: 414.0448, found 414.0453. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 15.44 (major) and 21.50 min (minor).

*(4S,5R)-4-(4-Methoxyphenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ai**).* White solid, mp 84−86 °C, 48 mg, 66% yield, $[\alpha]_D^{20}$ +126.6 (c 1.37, $CHCl_3$), >20/1 dr, >99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 3 H), 3.81 (s, 3 H), 4.40 (dd, J = 12.0, 2.4 Hz, 1 H), 4.71−4.74 (m, 1 H), 4.83 (d, J = 3.6 Hz, 1 H), 4.90 (dd, J = 12.0, 4.4 Hz, 1 H), 6.90 (d, J = 8.4 Hz, 2 H), 7.17 (d, J = 8.8 Hz, 2 H), 7.25 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.74 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.9, 38.9, 55.3, 65.8, 85.0, 95.4, 114.6, 120.3, 125.9, 129.0, 129.1, 131.1, 138.1, 147.0, 148.9, 159.4. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_4$ $[M + H]^+$: 366.1448, found 366.1453. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 18.91 (minor) and 22.92 min (major).

*(4S,5R)-4-(2-Methoxyphenyl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8aj**).* White solid, mp 158−160 °C, 50 mg, 68% yield, $[\alpha]_D^{20}$ +37.0 (c 1.40, $CHCl_3$), >20/1 dr, >99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 3 H), 3.93 (s, 3 H), 4.20 (dd, J = 12.0, 2.0 Hz, 1 H), 4.85 (d, J = 4.4, 2.0 Hz, 1 H), 4.99 (ddd, J = 12.0, 2.8, 1.6 Hz, 1 H), 5.22 (s, 1 H), 6.92 (dt, J = 7.6, 0.8 Hz, 1 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.97 (dt, J = 7.6, 2.0 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.32 (dt, J = 7.6, 1.6 Hz, 1 H), 7.42 (t, J = 8.0 Hz, 2 H), 7.75 (dd, J = 8.4, 1.2 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.8, 32.9, 55.5, 65.7, 81.8, 94.3, 110.4, 120.3, 120.9, 125.8, 127.1, 129.0, 129.3, 129.5, 138.3, 147.1, 149.4, 156.4. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_4$ $[M + H]^+$: 366.1448, found 366.1456. HPLC analysis (Chiralpak OD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 23.79 (major, *trans* diastereomer) and 29.94 min (major, *cis* diastereomer).

*(4S,5R)-3-Methyl-4-(2-methylphenyl)-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ak**).* White solid, mp 128−130 °C, 44 mg, 63% yield, $[\alpha]_D^{20}$ +109.8 (c 1.00, $CHCl_3$), >20/1 dr, >99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3 H), 2.54 (s, 3 H), 4.36 (dd, J = 12.4, 2.0 Hz, 1 H), 4.61 (d, J = 4.8, 2.0 Hz, 1 H), 4.99 (ddd, J = 12.4, 3.2, 0.8 Hz, 1 H), 5.12 (s, 1 H), 7.02 (d, J = 7.2 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.21−7.28 (m, 3 H), 7.44 (t, J = 8.0 Hz, 2 H), 7.76 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.7, 19.3, 36.8, 65.2, 82.8, 95.0, 120.3, 125.9, 126.8, 128.0, 128.3, 129.1, 131.3, 135.8, 137.4, 138.2, 146.8, 149.3. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_3$ $[M + H]^+$: 350.1499, found 350.1502. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 11.66 (major) and 14.98 min (minor).

*(4S,5R)-3-Methyl-4-(naphthalen-1-yl)-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8al**).* Yellow solid, mp 70−72 °C, 60 mg, 78% yield, $[\alpha]_D^{20}$ −3.2 (c 1.20, $CHCl_3$), >20/1 dr, >99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3 H), 4.25 (dd, J = 12.4, 1.2 Hz, 1 H), 4.83 (s, 1H), 5.04 (ddd, J = 12.4, 2.4, 1.6 Hz, 1 H), 5.79 (s, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 8.4 Hz, 2 H), 7.61 (t, J = 8.0 Hz, 1 H), 7.70 (t, J = 8.0 Hz, 1 H), 7.80 (dd, J = 8.4, 1.2 Hz, 2 H), 7.85 (d, J = 8.4 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.34 (d, J = 8.8 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.7, 35.1, 64.6, 82.2, 93.9, 120.4, 121.8, 125.4, 125.9, 126.4, 127.0, 127.6, 129.0, 129.1, 129.6, 130.3, 134.2, 135.0, 138.2, 147.1, 149.5. HRMS (ESI) m/z calcd for $C_{23}H_{20}N_3O_3$ $[M + H]^+$: 386.1499, found 386.1505. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 16.25 (major, *trans* diastereomer) and 25.09 min (major, *cis* diastereomer).

*(4S,5R)-4-(Furan-2-yl)-3-methyl-5-nitro-1-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8am**).* White solid, mp 138−140 °C, 42 mg, 65% yield, $[\alpha]_D^{20}$ +91.7 (c 1.40, $CHCl_3$), >20/1 dr, 99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3 H), 4.42 (dd, J = 12.0, 2.0 Hz, 1 H), 4.96 (dd, J = 5.2, 2.4 Hz, 1 H), 4.99 (s, 1 H), 5.06 (ddd, J = 12.0, 3.2, 1.2 Hz, 1 H), 6.13 (d, J = 3.2 Hz, 1 H), 6.34 (dd, J = 7.2, 1.6 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.42 (t, J = 8.0 Hz, 3 H), 7.71 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.7, 33.1, 65.9, 80.6, 93.3, 109.3, 110.7, 120.4, 126.0, 129.0, 138.0, 143.1, 146.7, 148.7, 151.8. HRMS (ESI) m/z calcd for $C_{17}H_{16}N_3O_4$ $[M + H]^+$: 326.1135, found 326.1141. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 8.29 (major) and 11.46 min (minor).

*(4S,5R)-3-Methyl-5-nitro-1-phenyl-4-(thiophen-2-yl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8an**).* White solid, mp 178−180 °C, 51 mg, 75% yield, $[\alpha]_D^{20}$ +134.2 (c 0.80, $CHCl_3$), >20/1 dr, >99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3 H), 4.50 (dd, J = 12.0, 2.0 Hz, 1 H), 4.80−4.82 (m, 1 H), 5.02 (ddd, J = 12.0, 4.0, 1.2 Hz, 1 H), 5.17 (d, J = 2.8 Hz, 1 H), 6.96 (d, J = 3.6 Hz, 1 H), 7.01 (dd, J = 5.2, 3.6 Hz, 1 H), 7.25 (t, J = 7.6 Hz, 1 H), 7.29 (dd, J = 4.8, 1.2 Hz, 1 H), 7.43 (t, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.4, 1.2 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.8, 34.4, 65.6, 84.3, 95.7, 120.4, 125.9, 126.0, 126.4, 127.5, 129.0, 138.0, 143.6, 146.8, 148.4. HRMS (ESI) m/z calcd for $C_{17}H_{16}N_3O_3S$ $[M + H]^+$: 342.0907, found 342.0914. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 6.40 (minor) and 6.98 min (major).

*(4S,5R)-5-Nitro-1,4-diphenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ba**).* White solid, mp 96−98 °C, 40 mg, 52% yield, $[\alpha]_D^{20}$ +79.7 (c 0.70, $CHCl_3$), >20/1 dr, >99% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 4.32 (d, J = 12.4 Hz, 1 H), 4.65 (s, 1 H), 4.99 (d, J = 13.2 Hz, 1 H), 5.09 (s, 1 H), 7.13−7.16 (m, 2 H), 7.23−7.32 (m, 4 H), 7.39 (t, J = 8.0 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.5, 65.2, 83.4, 94.6, 120.8 (q, J = 269.8 Hz), 121.4, 127.6, 127.8, 128.3, 129.2, 129.3, 137.2, 139.3 (q, J = 38.6 Hz), 139.4, 149.2. HRMS (ESI) m/z calcd for $C_{19}H_{15}F_3N_3O_3$ $[M + H]^+$: 390.1060, found 390.1056. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 92:8, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 53.84 (minor) and 56.59 min (major).

*(4S,5R)-5-Nitro-1,4-diphenyl-3-propyl-1,4,5,6-tetrahydropyrano-[2,3-c]pyrazole (**8ca**).* Pale red solid, mp 139−141 °C, 56 mg, 77% yield, $[\alpha]_D^{20}$ +68.3 (c 1.03, $CHCl_3$), 9/1 dr, 88% ee for the *trans* diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J = 6.8 Hz, 3 H), 1.49 (s, 2 H), 2.11−2.35 (m, 2 H), 3.71 (d, J = 6.8 Hz, 0.10 H, *cis* diastereomer), 4.41 (d, J = 11.6 Hz, 0.90 H, *trans* diastereomer), 4.60 (s, 0.20 H, *cis* diastereomer), 4.74 (s, 0.90 H, *trans* diastereomer), 4.94 (s, 1.80 H, *trans* diastereomer), 5.25 (s, 0.10 H, *cis* diastereomer), 7.17−7.44 (m, 8 H), 7.75 (d, J = 7.2 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9, 21.5, 29.7, 39.6, 65.6, 84.7, 94.5, 120.5, 125.9, 128.1 (2

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J. Org. Chem. 2016, 81, 4340−4346

C), 129.0, 129.2, 138.2, 139.5, 148.7, 150.8. HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_3$ $[M + H]^+$: 364.1656, found 364.1661. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 90:10, flow rate = 0.3 mL/min, wavelength = 254 nm): R_t = 24.37 (minor, *cis* diastereomer), 27.66 (major, *trans* diastereomer), 28.81 (major, *cis* diastereomer), and 29.74 min (minor, *trans* diastereomer).

*(4S,5R)-5-Nitro-1,3,4-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]-pyrazole (**8da**).* White solid, mp 118−120 °C, 64 mg, 81% yield, $[\alpha]_D^{20}$ +99.0 (c 1.07, $CHCl_3$), 9/1 dr, 86% ee for the *trans* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (d, J = 12.4 Hz, 0.90, *trans* diastereomer), 4.66 (d, J = 6.8 Hz, 0.20 Hz, *cis* diastereomer), 4.74 (s, 0.90 H, *trans* diastereomer), 5.01 (d, J = 5.2 Hz, 0.10 H, *cis* diastereomer), 5.06 (d, J = 12.8 Hz, 0.90 H, *trans* diastereomer), 5.21 (d, J = 12.4 Hz, 0.10 H, *cis* diastereomer), 5.26 (s, 0.90 H, *trans* diastereomer), 7.20−7.26 (m, 4 H), 7.28−7.36 (m, 5 H), 7.43−7.51 (m, 4 H), 7.86 (d, J = 8.4 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.9, 64.2, 83.8, 93.1, 120.9, 126.4, 126.6, 128.0, 128.2, 128.3, 129.1, 129.5, 132.7, 138.2, 140.4, 148.3, 149.3. HRMS (ESI) m/z calcd for $C_{24}H_{20}N_3O_3$ $[M + H]^+$: 398.1499, found 398.1508. HPLC analysis (Chiralpak AS-H column, Hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 15.57 (minor, *cis* diastereomer), 22.71 (major, *cis* diastereomer), 25.80 (major, *trans* diastereomer), and 32.10 min (minor, *trans* diastereomer).

*(4S,5R)-3-(4-Ethoxyphenyl)-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**8ea**).* White solid, mp 122−124 °C, 70 mg, 79% yield, $[\alpha]_D^{20}$ +74.8 (c 1.97, $CHCl_3$), 9/1 dr, 84% ee for the *trans* diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 2.70 H, *trans* diastereomer), 1.43 (t, J = 7.2 Hz, 0.30 H, *cis* diastereomer), 3.97 (q, J = 7.2 Hz, 1.80 H, *trans* diastereomer), 4.07 (q, J = 7.2 Hz, 0.20 H, *cis* diastereomer), 4.38 (dd, J = 12.4, 2.0 Hz, 1 H), 4.74 (d, J = 2.0 Hz, 1 H), 5.06 (d, J = 12.4 Hz, 1 H), 5.24 (s, 1 H), 6.74 (d, J = 8.8 Hz, 1.80 H, *trans* diastereomer), 6.96 (d, J = 8.4 Hz, 0.20 H, *cis* diastereomer), 7.25−7.40 (m, 6 H), 7.42−7.48 (m, 4 H), 7.69 (d, J = 8.8 Hz, 0.20 H, *cis* diastereomer), 7.87 (d, J = 8.4 Hz, 1.80 H, *trans* diastereomer). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8, 39.9, 63.3, 64.2, 83.8, 92.6, 120.8, 125.2, 126.2, 127.9, 128.1, 128.3, 129.0, 129.4, 138.2, 140.4, 148.2, 149.2, 158.8. HRMS (ESI) m/z calcd for $C_{26}H_{24}N_3O_4$ $[M + H]^+$: 442.1761, found 442.1763. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 10.96 (major, *trans* diastereomer), 12.99 (minor, *trans* diastereomer), 15.91 (minor, *cis* diastereomer), and 21.35 min (major, *cis* diastereomer).

*Synthesis of (5aR,11bS)-1-Methyl-3,7-diphenyl-3,5,5a,11b-tetrahydropyrazolo[4′,3′:5,6]pyrano[3,4-c]isoquinoline (**10**).* To a stirred solution of **8aa** (50.3 mg, 0.15 mmol) in 1.5 mL of acetic acid was added zinc powder (196 mg, 3 mmol) in one portion at 0 °C. Then, the resulting mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in aqueous sodium carbonate (5 mL) and extracted twice (2 × 5 mL) with ethyl acetate. The combined organic phase was dried over anhydrous magnesium sulfate and filtered. Removal of solvent under reduced pressure afforded the crude amine as a pale yellow viscous oil, which was used directly in the next step without further purification.

To a solution of the crude amine and triethylamine (25.3 mg, 0.25 mmol) in 1 mL of dichloromethane was added benzoyl chloride (35.1 mg, 0.25 mmol) at 0 °C. The resulting mixture was stirred at the same temperature until the reaction was complete (monitored by TLC). The reaction mixture was purified directly by column chromatography on silica gel (200−300 mesh, petroleum ether/ethyl acetate = 8/1) to afford (4*S*,5*R*)-5-benzamido-3-methyl-1,4-diphenyl- 1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole (**9**). White solid, 50 mg, mp 180−182 °C, 82% yield, $[\alpha]_D^{20}$ +6 (c 0.75, $CHCl_3$), >20/1 dr, >99% ee for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3 H), 4.19 (s, 1 H), 4.22 (d, J = 12.0 Hz, 1 H), 4.38 (dd, J = 11.2, 2.0 Hz, 1 H), 4.56 (d, J = 7.6 Hz, 1 H), 6.86 (d, J = 7.6 Hz, 1 H), 7.24−7.31 (m, 2 H), 7.37 (d, J = 8.4 Hz, 4 H), 7.43 (d, J = 7.2 Hz, 2 H), 7.46 (d, J = 7.2 Hz, 2 H), 7.52 (t, J = 7.2 Hz, 1 H), 7.78 (d, J = 7.6 Hz, 2 H), 7.85 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.8, 41.2, 50.8, 67.5, 95.8, 120.0, 125.7, 127.1, 127.2, 128.3, 128.6, 128.8, 129.0, 130.9, 133.7, 138.5, 141.5, 148.2, 149.6, 167.3. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm): R_t = 5.29 (minor) and 8.27 min (major).

A mixture of compound **9** (40.9 mg, 0.1 mmol), PPA (200 mg), and phosphorus oxychloride (0.4 mL) was stirred at 200 °C for 6 h. After being cooled to room temperature, the reaction mixture was neutralized with aqueous sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified through column chromatography on silca gel (200−300 mesh, petroleum ether/ethyl acetate = 8/1) to afford (5a*R*,11b*S*)-1-methyl-3,7-diphenyl-3,5,5a,11b-tetrahydropyrazolo[4′,3′:5,6]pyrano[3,4-*c*]-isoquinoline (**10**): White solid, 16 mg, mp 116−118 °C, 41% yield, $[\alpha]_D^{20}$ −138.0 (c 0.40, $CHCl_3$), >20/1 dr, >99% ee for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (dt, J = 12.0, 4.0 Hz, 1 H), 3.83 (d, J = 13.2 Hz, 1 H), 4.44 (t, J = 11.2 Hz, 1 H), 4.90 (dd, J = 10.0, 4.0 Hz, 1 H), 7.23−7.27 (m, 1 H), 7.33−7.37 (m, 2 H), 7.42−7.53 (m, 6 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.76 (t, J = 8.4 Hz, 4 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.7, 35.8, 59.7, 73.4, 96.8, 120.7, 123.7, 125.9, 126.8, 128.4, 128.6, 128.9, 129.0, 130.1, 130.2, 131.0, 138.3, 141.5, 146.5, 151.5, 168.9. HRMS (ESI) m/z calcd for $C_{26}H_{22}N_3O$ $[M + H]^+$: 392.1757, found 392.1761. HPLC analysis (Chiralpak OD-H column, Hexane/2-propanol = 80:20, flow rate = 0.2 mL/min, wavelength = 254 nm): R_t = 25.23 (minor) and 28.12 min (major).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00196.

Crystallographic data for **8aa** (CIF)

X-ray structure data of compound **8aa**, copies of NMR and HRMS spectra, HPLC analysis (PDF)

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Notes

The authors declare no competing financial interest.

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