JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Absolute Configuration Determination of 2,3-Dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles Using Chiroptical Methods at Different Wavelengths

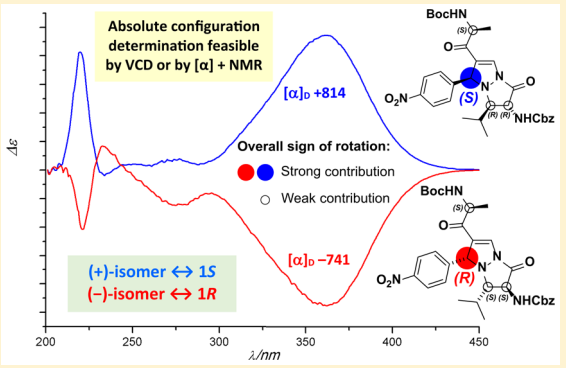
Eva Pušavec Kirar,[†] Uroš Grošelj,[†] Amalija Golobič,[†] Franc Požgan,[†] Stefan Pusch,[‡] Carina Weber,[‡] Lars Andernach,[‡] Bogdan Štefane,[†] Till Opatz,*[,‡] and Jurij Svete*[,†]

[†]Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia

[‡]Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10−14, D-55128 Mainz, Germany

Supporting Information

ABSTRACT: A correlation between the absolute configuration and chiroptical properties of nonracemic 1,6,7-trisubstituted 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles was studied. A series of 16 novel representatives were prepared by Cu-catalyzed [3 + 2] cycloadditions of racemic (*Z*)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ides to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate, and their structures were determined by NMR, VCD, ECD, and X-ray diffraction. A clear correlation between the sign of specific rotation and configuration at position C(1) allows for easy determination of the absolute configuration of 1,6,7-trisubstituted 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles by ECD and NMR. While VCD, requiring milligram quantities, allowed the determination of the correct relative and absolute configuration without additional information from other methods, the stereochemical analysis by ECD required knowledge of the relative configuration derived from NMR at a comparable computational level.



1. INTRODUCTION

The determination of the relative and absolute configuration of organic molecules is an important task for synthetic chemists. The use of chiroptical methods represents a standard approach for this purpose if X-ray crystallography is not applicable or inconclusive. While electronic circular dichroism (ECD) and especially visible light polarimetry are frequently employed, the use of vibrational circular dichroism (VCD) is still rare in the synthetic organic community.[1] Here, we present a case study on the stereochemical analysis of a series of 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles using chiroptical methods at three different wavelength ranges.

Hetero(bi)cycles represent frequently used building blocks for applications in medicinal chemistry, catalysis, and materials science.[2] For example, dipeptide motifs in a given native (or natural) peptidic substrate can be replaced with U-shaped conformationally constrained heterocyclic analogues that simulate β-turn structures.[3] An important group of such conformationally constrained dipeptide analogues are the azabicycloalkane amino acids, which comprise various saturated fused heterocycles with a bridgehead nitrogen atom.[4] In this context, pyrazolo[1,2-*a*]pyrazoles are a notable subgroup of 5,5-fused systems with Eli Lilly's γ-lactam antibiotics (Figure 1) as prototypical representatives.[5] These antibiotics are based on 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole scaffold **3**, which in turn is easily available by [3 + 2] cycloaddition of 3-oxopyrazolidin-1-ium-2-ides **1** to acetylenes **2**.[6] In this context, copper-catalyzed cycloadditions of azomethine imines to acetylenes (CuAIAC)[6b,7] provide an easy access toward 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **3** in a regio- and stereoselective manner under mild conditions that are compliant with the requirements of "click" chemistry (Figure 1).[8,9]

In the absence of a general access to the nonracemic dipoles **1** (and their pyrazolidinone precursors), [3 + 2] cycloadditions are usually performed with achiral or racemic dipoles **1**.[6,7] Since compounds **3** contain up to three stereogenic centers (cf. Figure 1), mixtures of up to 8 stereoisomers are conceivable. Although mixtures of this kind are routinely separated and characterized by HPLC-MS, unambiguous structure determination of a given isomer may not be straightforward because larger (tens of milligrams) quantities of the sample are required. However, if the absolute configuration could be determined on the basis of NMR data and chiroptical properties, this would significantly simplify and speed up structure elucidation. The same would apply for compound series, for which relations of stereochemistry with easily accessible chiroptical properties have been established using more sophisticated measurements.

Received: September 15, 2016
Published: November 1, 2016

ACS Publications © 2016 American Chemical Society

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812

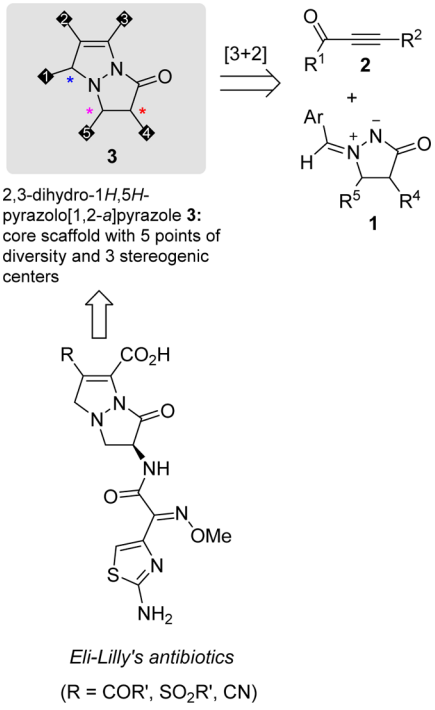


Figure 1. Examples of biologically active 2,3-dihydro-1*H*,5*H*-pyrazolo-[1,2-*a*]pyrazoles **3** and their synthetic availability.

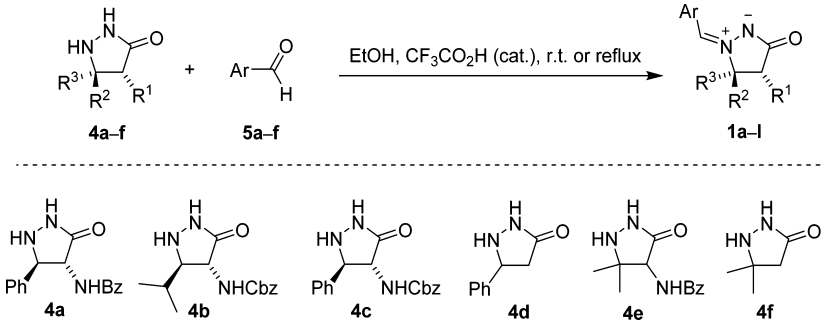
Our previous studies on CuAIAC reactions also included cycloadditions of the racemic (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-3-oxo-5-phenyltetrahydropyrazol-1-ium-2-ides **1a−d** to chiral nonracemic (*S*)-*N*-Boc-alanine-derived ynone **2**,[10] which afforded separable mixtures of diastereomeric nonracemic cycloadducts, (+)-**3a−d** and (−)-**3a−d** (cf. Table 2). Unfortunately, the absolute configurations of these nonracemic products could initially not be determined.[7e] In extension, novel analogous nonracemic cycloadducts (+)-**3e−l** and (−)-**3e−l** were synthesized, and their absolute configuration was determined by X-ray diffraction, VCD, ECD, and correlation between their sign of specific rotation and absolute configuration. This might be useful as a simple method for the determination of the absolute configuration of novel cycloadducts of this type if the dominance of one of the stereogenic centers for the chiroptical properties in compound series is clearly demonstrated.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Cycloadducts 3. First, a small library of nonracemic cycloadducts **3** with different substituents at positions 1, 6, and 7 was synthesized. Later on, this would allow us to compare the influence of a given substituent on the specific rotation. Azomethine imines **1a−l** with variable substituents at positions 4 and 5 and bearing typical aryl residues at position 1′ were prepared in good yields by condensation of racemic 3-pyrazolidinones **4a**,[11] **4b**,[12] **4c**,[13] **4d**,[14] and **4e**[15] and achiral compound **4f**,[16] with **5a−f** following general literature procedures.[11,12,17] The *Z* configuration around the C=N double bond in 3-oxopyrazolidin-1-ium-2-ides **1** and the *trans* configuration of 4,5-disubstituted pyrazolidinones **4a−c** and dipoles **1** derived thereof were established previously.[6,18,19] Selected experimental data for dipoles **1a−l** prepared from chemsets **4a−f** and **5a−f** are presented in Table 1.

The novel cycloadducts (+)-**3e−l** and (−)-**3e−l** were synthesized according to the same strategy employed for the synthesis of the nonracemic cycloadducts (+)-**3a−d** and

Table 1. Experimental Data for Azomethine Imines 1a−l and Chemsets 4a−f and 5a−f (Chiral Compounds 1a−h and 4a−e Are Racemic Mixtures)

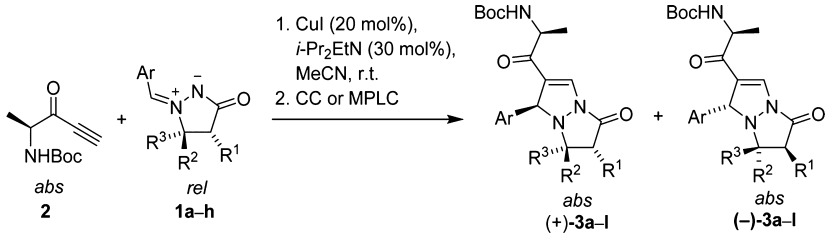


reaction	R^1	R^2	R^3	Ar	yield (%)[a]	ref
4a + **5a** → **1a**	NHBz	Ph	H	Ph	89	11
4a + **5b** → **1b**	NHBz	Ph	H	4-$O_2NC_6H_4$	76	11
4a + **5c** → **1c**	NHBz	Ph	H	4-$MeOC_6H_4$	78	11
4a + **5d** → **1d**	NHBz	Ph	H	3,4,5-$(MeO)_3C_6H_2$	92	19
4b + **5e** → **1e**	NHCbz	*i*-Pr	H	4-ClC_6H_4	56	*b*
4b + **5b** → **1f**	NHCbz	*i*-Pr	H	4-$O_2NC_6H_4$	67	*b*
4c + **5a** → **1g**	NHCbz	Ph	H	Ph	81	13
4d + **5b** → **1h**	H	Ph	H	4-$O_2NC_6H_4$	88	*b*
4e + **5b** → **1i**	NHBz	Me	Me	4-$O_2NC_6H_4$	49	*b*
4e + **5f** → **1j**	NHBz	Me	Me	2,4-$Cl_2C_6H_3$	51	*b*
4e + **5d** → **1k**	NHBz	Me	Me	3,4,5-$(MeO)_3C_6H_2$	62	*b*
4f + **5b** → **1l**	H	Me	Me	4-$O_2NC_6H_4$	93	17

[a]Isolated yields. [b]This paper.

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812

Table 2. Synthesis and Experimental Data of Cycloadducts (+)-3a–l and (−)-3a–l



compound	R^1	R^2	R^3	Ar	yield of 3 (%)[a] (±)[a,b]	(+)[a]	(−)[a]	ref
3a	NHBz	Ph	H	Ph	91	44	5	7e
3b	NHBz	Ph	H	4-$O_2NC_6H_4$	95	39	17	7e
3c	NHBz	Ph	H	4-$MeOC_6H_4$	98	25	14	7e
3d	NHBz	Ph	H	3,4,5-$(MeO)_3C_6H_2$	66	30	14	7e
3e	NHCbz	*i*-Pr	H	4-ClC_6H_4	quant.	44	30	*c*
3f	NHCbz	*i*-Pr	H	4-$O_2NC_6H_4$	quant.	42[d]	32[d,e]	*c*
3g	NHCbz	Ph	H	Ph	96	42	21	*c*
3h	H	Ph	H	4-$O_2NC_6H_4$	97	39[e]	37[e]	*c*
3i	NHBz	Me	Me	4-$O_2NC_6H_4$	95	35	30	*c*
3j	NHBz	Me	Me	2,4-$Cl_2C_6H_3$	79	27	23	*c*
3k	NHBz	Me	Me	3,4,5-$(MeO)_3C_6H_2$	89	29	31	*c*
3l	H	Me	Me	4-$O_2NC_6H_4$	93	35	28	*c*

[a]Isolated yield. [b]Combined yield of diastereomers (+)-**3** and (−)-**3** after workup by FC and before separation of diastereomers by MPLC. [c]This paper. [d]Absolute configuration was determined by VCD. [e]Absolute configuration was determined by X-ray diffraction.

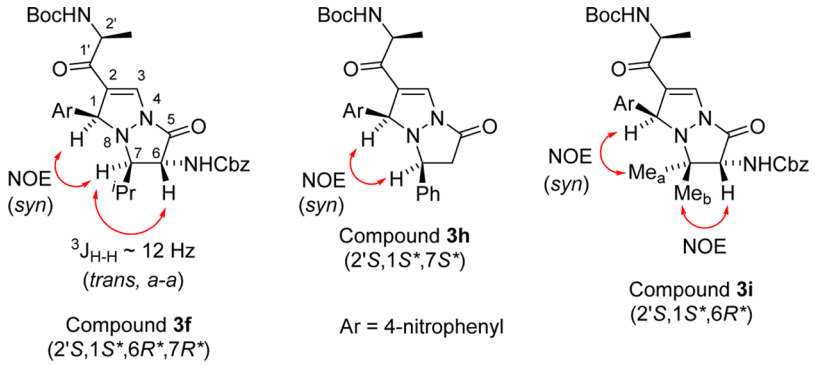


Figure 2. Determination of relative configuration of compounds **3e–l** by NMR.

(−)-**3a–d** reported previously.[7e] Briefly, cycloadditions of racemic dipoles **1e–l** to the nonracemic ynone **2** were performed in the presence of 20 mol% of CuI and 30 mol% of DIPEA in MeCN at room temperature. Subsequent workup by flash column chromatography (FC) afforded mixtures of diastereomeric nonracemic cycloadducts, (+)-**3e–l**/(−)-**3e–l** in 79–100% yields. These mixtures of isomers (+)-**3e–l**/(−)-**3e–l** were separated, either by column chromatography (CC) or by medium-pressure liquid chromatography (MPLC) to furnish diastereomerically pure nonracemic compounds (+)-**3e–l** and (−)-**3e–l** in 21–44% yield (Table 2).

2.2. Structure Elucidation. The structures of novel compounds (+)-**3e–l** and (−)-**3e–l** were determined by spectroscopic methods [IR, NMR spectroscopy (^1H and ^{13}C NMR, COSY, HSQC, HMBC, and NOESY experiments), and MS-HRMS] and by elemental analyses for C, H, and N.[20] The relative configurations of novel diastereomeric cycloaducts (+)-**3e–l** and (−)-**3e–l** were initially determined by NOESY experiments and by inspection of the vicinal coupling constant $^3J_{H(6)-H(7)}$.[7e,12,18,19] In compound **3h**, a NOE between H–C(1) and H–C(7) supported the *syn*-orientation of these two nuclei. In compound **3i**, on the other hand, the *anti*-orientation of H–C(1) and H–C(6) was established by NOE between H–C(1) and Me_a–C(7) as well as between Me_b–C(7) and H–C(6). In compounds **3e–g**, the magnitude of vicinal coupling constant, $^3J_{H(6)-H(7)}$ ~ 12 Hz, was in agreement with the *trans* configuration around the C(6)–C(7) bond (Figure 2).[18] The structure and relative configuration of compounds **3a–g** were additionally confirmed by correlation of characteristic chemical shifts δ and vicinal coupling constants ($^3J_{H(6)-H(7)}$ ~ 12 Hz).[20] These values were in very good agreement with the literature values for closely related compounds.[7e,12,18,19] Correlation also revealed a significant difference in chemical shifts, $\Delta\delta$ > 0.3 ppm, for protons H–C(3) and H–C(6) in diastereoisomeric pairs **3a–g,i–k** with a 6-acylamino substituent.[20]

The absolute configurations of nonracemic diastereomers (+)-**3f** and (−)-**3f** were investigated by VCD spectroscopy, that is, comparison of the experimental data with DFT-calculated spectra at the B3LYP/6-311G(d,p) level with IEFPCM solvation (see section 4.4 and the Supporting Information for details). The calculated IR spectra were fitted to the experimental spectra based on the wavenumber range from

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802–11812

1100 to 1650 cm^{-1}, thus excluding the problematic carbonyl region and avoiding artifacts due to solvent absorptions. Based on the optimized fitting parameters, the calculated and experimental VCD spectra were compared, generating a similarity factor *f*, using the method developed by Bringmann and co-workers.[21] For the hypothetical enantiomeric calculated VCD spectra, analogous similarity factors *f** were generated along with the differences $\Delta = f - f^*$ (also termed enantiomeric similarity index, ESI, for the absolute value). In an ideal case, the values would be $f = 1$, $f^* = 0$, and $\Delta = 1$ (or $f = 0$, $f^* = 1$, and $\Delta = -1$ for the enantiomer). The *f*, *f**, and Δ values for all eight possible diastereomers of compound **3f** are shown in Table 3 with CCl_4 as a solvent; the extremal value of each column is marked in boldface.

Table 3. Similarity Factors for the VCD Analysis of (+)-3f and (−)-3f in CCl_4

	(+)-**3f**			(−)-**3f**		
	f	*f**	Δ	*f*	*f**	Δ
(2′*S*,1*R*,6*R*,7*R*)	0.3747	0.2247	0.1500	0.3802	0.2643	0.1159
(2′*S*,1*R*,6*R*,7*S*)	0.2603	0.2895	−0.0292	0.6272	0.1015	0.5257
(2′*S*,1*R*,6*S*,7*R*)	0.3566	0.3246	0.0320	0.6868	0.0720	0.6148
(2′*S*,1*R*,6*S*,7*S*)	0.2157	0.4206	−0.2049	**0.7671**	0.0496	**0.7175**
(2′*S*,1*S*,6*R*,7*R*)	**0.5833**	0.1529	**0.4304**	0.0501	**0.6690**	−0.6189
(2′*S*,1*S*,6*R*,7*S*)	0.2463	0.3409	−0.0946	0.1071	0.5892	−0.4821
(2′*S*,1*S*,6*S*,7*R*)	0.3675	0.1528	0.2147	0.0783	0.5711	−0.4928
(2′*S*,1*S*,6*S*,7*S*)	0.1577	**0.4583**	−0.3006	0.4805	0.1823	0.2982

The two structures out of the 16 theoretically possible stereoisomers (eight diastereomers plus the corresponding enantiomers) with the highest *f* and Δ values for each of the two samples, respectively, are shown in Figure 3.

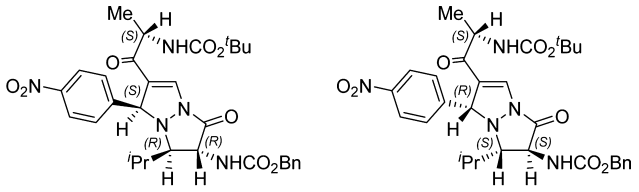


Figure 3. Assignment of absolute configurations for the diastereomers (+)-**3f** and (−)-**3f**.

Based on the known *S* configuration of amino ketone **2**, the *trans* configuration of dipole **1**, and the *syn*-orientation between the substituents at positions 1 and 7 (cf. Figure 2), the initial set of possible stereoisomers reduces to only two configurations, (2′*S*,1*R*,6*S*,7*S*) and (2′*S*,1*S*,6*R*,7*R*); the corresponding *f* values are marked in gray in Table 3. This strongly supports the assignment made in Figure 3. The predicted configuration of (+)-**3f** appears to be logical from a synthetic point of view, although the Δ value is only 43%. The deviation may be attributed to intermolecular hydrogen bonding and/or missing conformers due to the sparse conformational search algorithm required to reduce the computing time to an acceptable level. For (−)-**3f**, the Δ value is satisfactory with 72%, and the configuration could subsequently be confirmed by X-ray crystallography of a single crystal (see below). The measurements and calculations were repeated using three different solvents of higher polarity (chloroform, acetonitrile, and DMSO).[20] The results are very consistent among all four solvents, and the same absolute configurations as those shown in Figure 3 are predicted for compounds (+)-**3f** and (−)-**3f**.

Finally, the structure and absolute configuration of compounds (−)-**3f**, (+)-**3h**, and (−)-**3h** were determined by X-ray diffraction. The results unambiguously established the (2′*S*,1*R*,6*S*,7*S*) configuration for compound (−)-**3f**, (2′*S*,1*S*,7*S*) configuration for compound (+)-**3h**, and (2′*S*,1*R*,7*R*) configuration for compound (−)-**3h**.[20]

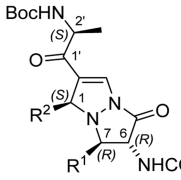
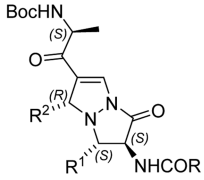
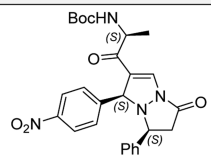
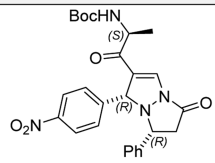
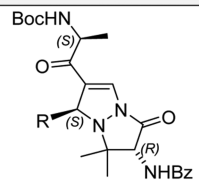
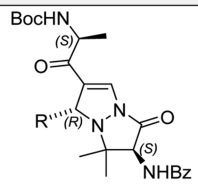
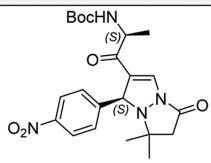
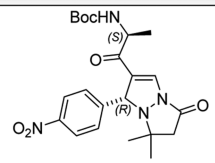
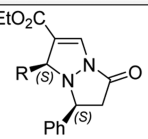
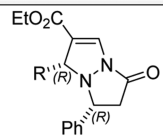
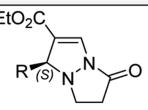
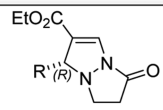
2.3. Correlation between the Absolute Configuration and Specific Rotation in Novel Compounds 3e−l and Known Analogues 3a−d,m−r (Table 4 and Figure 5). For the relevance of this correlation, it is important that all specific rotations of known compounds **3a−d**[7e] and **3m−r**[7a,b] and novel compounds **3e−l** were measured in CH_2Cl_2. First, the specific rotations of diastereomers (+)-**3e−g,h** and (−)-**3e−g,h** and enantiomers (+)-**3m−r** and (−)-**3m−r**[7a,b] were correlated with their absolute configurations that had been unambiguously determined by X-ray diffraction or by VCD (Table 4, entries 6, 8, 13, and 16).[22] This correlation revealed that all 1*S*-isomers were strongly dextrorotatory, whereas all 1*R*-isomers were strongly levorotatory. The typical specific rotation value was ∼450 regardless of the number of stereogenic centers. For example, the (1*R*)-(−)-isomers **3p**, **3m**, **3h**, and **3f** with one to four stereogenic centers exhibited specific rotation values of −442, −392, −524, and −741, respectively. Altogether, 55 literature examples,[7a−d,f] including representatives (+)-**3m−r** and (−)-**3m−r**, were in complete agreement with the above correlation.[20] This strongly suggested substantially different contributions of each stereogenic center to the overall sign and the magnitude of specific rotation of isomers (+)-**3m−r** and (−)-**3m−r**. Accordingly, the configuration at position 1 had a major impact on the specific rotation of compounds **3a−r**, whereas the configurations at stereogenic centers at positions 6, 7, and 2′ have less influence in this respect. Consequently, the (−) sign of specific rotation could be "anchored" to the 1*R* configuration in all compounds (−)-**3a−r**. In this case, assignment of the absolute configuration of compounds **3a−e,g,i−l** with multiple stereogenic centers is feasible by NMR (cf. Figure 2).

The above hypothesis on the key role of the configuration at position C(1) on the sign of specific rotation is exemplified in Figure 4. Similar specific rotation values of compounds **3a**, **3h**, **3m**, and **3p** with the same C(1)-substituent (Ph) are in agreement with the hypothesis that strong specific rotation is most probably due to the stereogenic center C(1).

To additionally confirm the proposed correlation between the specific rotation and configuration at position C(1), ECD spectra of diastereomers (+)-**3e−l** and (−)-**3e−l** were recorded. Spectra of all diastereomeric pairs behaved almost like mirror images, with the strongest absorption bands located around 350 nm. These results were in agreement with the proposed correlation between the specific rotation and absolute configuration of bicyclic pyrazolidinones **3**. The ECD spectra of diastereomeric pairs (+)-**3e−l** and (−)-**3e−l** are given in the Supporting Information, while the representative spectra of the

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812

Table 4. Correlation of Configuration of Compounds 3a–r[a]

Entry	Cpd.	(+)-Isomer	$[\alpha]_D$	(–)-Isomer	$[\alpha]_D$	Ref.
1	**3a**		+260		–532	7e
2	**3b**		+686		–769	7e
3	**3c**		+509		–607	7e
4	**3d**		+117		–194	7e
5	**3e**		+584		–718	b
6	**3f**	2′*S*,1*S*,6*R*,7*R* (+)-**3a–g**	+814[d]	2′*S*,1*R*,6*S*,7*S* (–)-**3a–g**	–741[c,d]	b
7	**3g**		+331		–259	b
8	**3h**	 2′*S*,1*S*,7*S* (+)-**3h**	+464[c]	 2′*S*,1*R*,7*R* (–)-**3h**	–524[c]	b
9	**3i**	 2′*S*,1*S*,6*R* (+)-**3i–k**	+751	 2′*S*,1*R*,6*S* (–)-**3i–k**	–611	b
10	**3j**		+572		–592	b
11	**3k**		+591		–533	b
12	**3l**	 2′*S*,1*S* (+)-**3l**	+758	 2′*S*,1*R* (–)-**3l**	–520	b
13	**3m**[e]	 1*S*,7*S* (+)-**3m–o**	+400[f]	 1*R*,7*R* (–)-**3m–o**	–392[c]	7b
14	**3n**[e]		+315[f]		–315	7b
15	**3o**[e]		+220[f]		–220	7b
16	**3p**[e]	 1*S* (+)-**3p–r**	+440[f]	 1*R* (–)-**3p–r**	–442[c,g]	7a
17	**3q**[e]		+410[f]		–410[c,g]	7a
18	**3r**[e]		+240[f]		–242[c,g]	7a

[a]Unless otherwise stated, specific rotations were measured in CH_2Cl_2. [b]This work. [c]Determined by X-ray diffraction. [d]Determined by VCD. [e]R = Ph (**3m**, **3p**), 2-furyl (**3n**), *c*-C_6H_{11} (**3o**), 4-$F_3CC_6H_4$ (**3q**), 4-FC_6H_4 (**3r**). [f]Estimated value, only [α] for the other enantiomer is given. [g]Measured in $CHCl_3$.

diastereomeric pairs (+)-**3e**/(–)-**3e** and (+)-**3f**/(–)-**3f** are shown in Figure 5.

On the other hand, comparison of the experimental ECD spectra with computational data at the TD-B3LYP/def2-TZVPP level with COSMO solvation (see section 4.4 for details) did only allow for a unique assignment of the absolute configuration of (+)-**3f** and (–)-**3f** if additional information on the absolute configuration of the amino-acid-derived stereogenic center C(2′) and on the relative configuration of H(1)/H(7) as well as H(6)/H(7) determined by NMR was used as

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802–11812

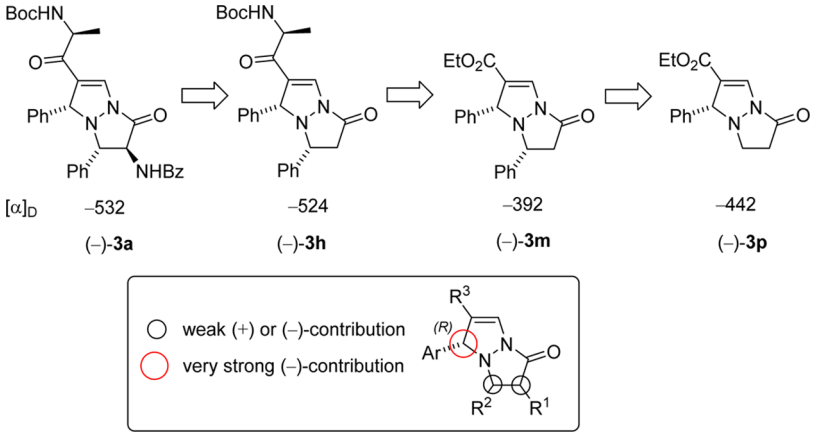


Figure 4. Deconvolutive estimation of participation of the three stereogenic centers in 6-acyl-5-phenyl-2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-ones **3a**,**h**,**m**,**p** to overall specific rotation.

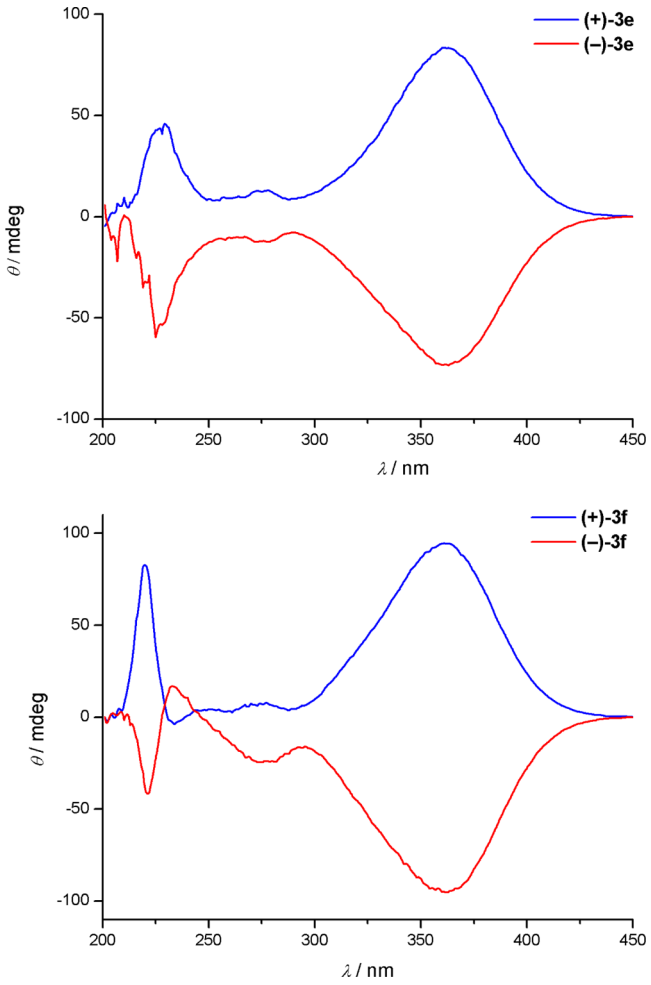


Figure 5. ECD spectra of diastereomeric pairs (+)-**3e**,**f** (blue) and (–)-**3e**,**f** (red).

an input (see the Supporting Information for details). The same phenomenon has already been observed by us in another compound series.[23] However, if these strongly restrictive assumptions are taken into account, the ECD data support our previously made VCD assignments with satisfying Δ values of approximately 89% for (+)-**3f** and 64% for (–)-**3f**.

3. CONCLUSIONS

A series of nonracemic 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazol-1-ones (+)-**3a–l** and (–)-**3a–l** were prepared from racemic azomethine imines **1** and nonracemic ynone **2** followed by chromatographic separation. The structure and absolute configuration of compounds (+)/(–)-**3f** and (+)/(–)-**3h** were unambiguously determined by X-ray diffraction or by VCD and ECD spectroscopy. The structures of the remaining compounds in the 6,7-disubstituted series, (+)/(–)-**3a–e**,**g**,**i–l**, were determined by correlation of their specific rotations, taking also known derivatives **3m–r** with unambiguously determined absolute configurations into account. Correlation between the absolute configuration of compounds **3e–h** and **3m–r** and their sign of specific rotation revealed that all dextrorotatory isomers had 1*S* configuration and all levorotatory isomers had 1*R* configuration. In contrast, the configuration at positions 6 and 7 did not affect the overall sign of the specific rotation. If proven reliable, this correlation could be a useful and simple analytical tool that would enable easy absolute configuration determination of novel 2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-ones. The method might be particularly useful in high-throughput synthesis of libraries of title compounds because HPLC-MS coupled with the determination of the optical rotation at wavelength(s)[24] above 350 nm would provide configuration at position C(1) along with the basic characterization data. This type of analysis can be used wherever the configuration of a single stereogenic center is solely responsible for the shape of an ECD curve (or a charcteristic band) or the sign of specific rotation. As shown in our case, the predominance of one of the stereogenic centers for the chiroptical properties and clear correlations are also required for the analysis of other compound classes.

4. EXPERIMENTAL SECTION

4.1. General Methods. Melting points were determined on a Kofler micro hot stage and on an automated melting point system. The NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as the internal standard on a 300 or 500 MHz instrument at 300 and 500 MHz for ^{1}H and at 75.5 and 126 MHz for ^{13}C nucleus, respectively. Mass spectra were recorded on TOF LC/MS spectrometer and IR spectra on a FTIR ATR spectrophotometer. Microanalyses were performed by combustion analysis on a CHN analyzer. Flash column chromatography and column chromatography were performed on silica gel (particle size = 0.035–0.070 mm). Medium-pressure liquid chromatography was performed on silica gel

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802–11812

(particle size = 15−25 μm, wet-filled column dimensions = 22 × 460 mm) using an automated chromatography system equipped with UV−vis detector and fraction collector (back pressure = 15 bar, detection wavelength = 254 nm). The VCD spectra were recorded using an FTIR spectrometer equipped with one photoelastic modulator optimized for 1400 cm^{-1}. An accumulation time of 360 min, a spectral range of 1800−800 cm^{-1}, a resolution of 4 cm^{-1}, and a 100 μm path length BaF_2 sample cell were used for all measurements. All spectra were baseline-corrected by subtraction of a solvent spectrum recorded with the same parameters. The sample concentrations amounted to 76−79 mM. The CD spectra were recorded using a CD spectropolarimeter equipped with a thermoelectric temperature controller at 25 °C, spectral range = 200−450 nm, averaging time of 3 s, 1 nm bandwidth, acetonitrile as solvent, and sample concentration of 1 mg mL^{-1}.

Aromatic aldehehydes **5a−f**, trifluoroacetic acid, CuI, and DIPEA are commercially available. Azomethine imines **1a−c**,[11] **1d**,[19] **1g**,[13] and **1l**,[17] *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**2**),[7e,10] 3-pyrazolidinones **4a**,[11] **4b**,[12] **4c**,[13] **4d**,[14] **4e**,[15] and **4f**,[16] and the nonracemic cycloadducts (+)-**3a−d** and (−)-**3a−d**[7e] were prepared following the literature procedures.

4.2. General Procedure for the Synthesis of Novel Azomethine Imines 1e,f,h−k. Compounds **1e,f,h−k** were prepared following a general procedure for the synthesis of closely analogous compounds.[11,13] A mixture of pyrazolidinone **4** (1 mmol), aromatic aldehyde **5** (1.2 mmol), and anhydrous EtOH (4 mL) was stirred at rt for 5 min. Then, trifluoroacetic acid (2 drops) was added, and the mixture was stirred at rt for 12 h. The precipitate was collected by filtration and washed with EtOH and Et_2O to give **1**.

4.2.1. (3R,4R*)-4-Benzyloxycarbonylamino-2-((Z)-4-chlorobenzylidene)-3-isopropyl-5-oxopyrazolidin-2-ium-1-ide (**1e**):* Prepared from pyrazolidinone **4b** (2.722 g, 9.2 mmol) and aldehyde **5e** (1.505 g, 10.7 mmol); yield 2.182 g (56%) of white solid; mp 206−210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 and 1.04 (6H, 2d, 1:1, *J* = 6.7 Hz); 2.50−2.59 (1H, m); 4.10 (1H, dd, *J* = 4.2, 7.6 Hz); 4.49 (1H, t, *J* = 4.4 Hz); 5.05 (2H, s); 7.25−7.40 (5H, m); 7.64 and 8.37 (4H, 2d, 1:1, *J* = 8.7, 8.4 Hz); 7.81 (1H, s); 7.88−7.92 (1H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.1, 17.9, 30.5, 51.0, 65.6, 78.2, 127.7, 127.9, 128.3, 128.5, 128.9, 131.7, 133.0, 136.1, 136.8, 155.7, 180.4; HRMS found for $C_{21}H_{23}ClN_3O_3$ *m*/*z* 400.1421 (MH^+), requires *m*/*z* = 400.1422 (found C, 62.78; H, 5.28; N, 10.46; $C_{21}H_{22}ClN_3O_3$ requires C, 63.08; H, 5.55; N, 10.51); ν_{max} (ATR) 3030, 1713 (C═O), 1659 (C═O), 1587, 1250, 1089, 1042, 748, 671 cm^{-1}.

4.2.2. (3R,4R*)-4-Benzyloxycarbonylamino-3-isopropyl-2-((Z)-4-nitrobenzylidene)-5-oxopyrazolidin-2-ium-1-ide (**1f**):* Prepared from pyrazolidinone **4b** (824 mg, 3.0 mmol) and aldehyde **5b** (458 mg, 3.1 mmol); yield 814 mg (67%) of yellow solid; mp 188−191 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 and 1.06 (6H, 2d, 1:1, *J* = 6.7 Hz); 2.59 (1H, br septet, *J* = 6.8 Hz); 4.13 (1H, dd, *J* = 4.2, 7.9 Hz); 4.59 (1H, t, *J* = 4.1 Hz); 5.05 (2H, s); 7.29−7.40 (5H, m); 7.94−7.97 (2H, m); 8.38 and 8.58 (4H, 2d, 1:1, *J* = 8.6, 8.8 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.0, 17.9, 30.6, 50.7, 65.7, 78.9, 123.8, 127.7, 127.9, 128.3, 130.1, 132.1, 135.2, 136.8, 147.8, 155.7, 181.1; HRMS found for $C_{21}H_{23}N_4O_5$ *m*/*z* 411.1654 (MH^+), requires *m*/*z* = 411.1663 (found C, 61.12; H, 5.19; N, 13.71; $C_{21}H_{22}N_4O_5$ requires C, 61.46; H, 5.40; N, 13.65); ν_{max} (ATR) 3036, 1713 (C═O), 1667 (C═O), 1569, 1519, 1272, 1100, 731, 679 cm^{-1}.

*4.2.3. (Z)-2-(4-Nitrobenzylidene)-5-oxo-3-phenylpyrazolidin-2-ium-1-ide (**1h**):* Prepared from pyrazolidinone **4d** (486 mg, 3 mmol) and aldehyde **5b** (458 mg, 3.1 mmol); yield 0.778 g (88%) of yellowish solid; mp 181−185 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.59 (1H, dd, *J* = 16.6, 4.3 Hz); 3.26 (1H, dd, *J* = 16.7, 9.7 Hz); 5.98 (1H, dd, *J* = 9.8, 4.2 Hz); 7.38−7.47 (5H, m); 7.56 (1H, s); 8.31−8.34 (2H, m); 8.51−8.54 (2H, m); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.4, 73.8, 123.8, 126.7, 129.1, 129.5, 129.6, 131.8, 135.3, 139.1, 147.6, 183.4; HRMS found for $C_{16}H_{14}N_3O_3$ *m*/*z* 296.103 (MH^+), requires *m*/*z* = 296.103; ν_{max} (ATR) 3107, 1688 (C═O), 1569, 1508, 1336, 1262, 1091, 681 cm^{-1}.

*4.2.4. (Z)-4-Benzoylamino-3,3-dimethyl-2-(4-nitrobenzylidene)-5-oxopyrazolidin-2-ium-1-ide (**1i**):* Prepared from pyrazolidinone **4f** (699 mg, 3 mmol) and aldehyde **5b** (756 mg, 5 mmol); yield 0.540 g (49%) of yellow solid; mp 246−248 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.55 and 1.87 (6H, 2s, 1:1); 4.90 (1H, d, *J* = 5.1 Hz); 7.48−7.52 (2H, m); 7.56−7.59 (1H, m); 7.93−7.95 (2H, m); 8.10 (1H, s); 8.41−8.43 (2H, m); 8.63−8.66 (2H, m); 8.97 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.3, 27.6, 57.9, 76.7, 123.8, 127.5, 128.4, 128.9, 131.6, 132.2, 133.5, 135.6, 147.8, 167.2, 179.7; HRMS found for $C_{19}H_{19}N_4O_4$ *m*/*z* 367.1406 (MH^+), requires *m*/*z* = 367.1411; ν_{max} (ATR) 3325, 1686 (C═O), 1672 (C═O), 1655 (C═O), 1600, 1517, 1308, 1082 cm^{-1}.

*4.2.5. (Z)-4-Benzoylamino-2-(2,4-dichlorobenzylidene)-3,3-dimethyl-5-oxopyrazolidin-2-ium-1-ide (**1j**):* Prepared from pyrazolidinone **4f** (1.398 g, 6 mmol) and aldehyde **5f** (1.750 g, 10 mmol); yield 1.190 g (51%) of white solid; mp 204−205 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.55 and 1.86 (6H, 2s, 1:1); 4.87 (1H, d, *J* = 8.4 Hz); 7.46−7.60 (3H, m); 7.67 (1H, dd, *J* = 8.8, 2.2 Hz); 7.70 (1H, s); 7.78 (1H, d, *J* = 2.2 Hz); 7.92−7.95 (2H, m); 8.93 (1H, d, *J* = 8.2 Hz); 9.00 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.3, 27.5, 58.0, 76.8, 125.3, 126.3, 127.5, 127.7, 128.4, 129.5, 131.7, 132.9, 133.5, 135.0, 136.2, 167.3, 179.4; HRMS found for $C_{19}H_{18}Cl_2N_3O_2$ *m*/*z* 390.077 (MH^+), requires *m*/*z* = 390.0771 (found C, 58.55; H, 4.52; N, 10.51; $C_{19}H_{17}Cl_2N_3O_2$ requires C, 58.47; H, 4.39; N, 10.77); ν_{max} (ATR) 3264, 1673 (C═O), 1650 (C═O), 1582, 1537 cm^{-1}.

*4.2.6. (Z)-4-Benzoylamino-2-(3,4,5-trimethoxybenzylidene)-3,3-dimethyl-5-oxopyrazolidin-2-ium-1-ide (**1k**):* Prepared from pyrazolidinone **4f** (233 mg, 1 mmol) and aldehyde **5d** (235 mg, 1.2 mmol); yield 255 mg (62%) of white solid; mp 215−219 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.49 and 1.81 (6H, 2s, 1:1); 3.78 and 3.84 (9H, 2s, 1:2); 4.80 (1H, d, *J* = 8.3 Hz); 7.47−7.51 (2H, m); 7.54−7.58 (1H, m); 7.86 (1H, s); 7.90 (2H, s); 7.92−7.95 (2H, m); 8.91 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1, 27.8, 56.1, 58.3, 60.3, 75.1, 109.5, 125.3, 127.5, 128.4, 131.6, 132.1, 133.6, 140.6, 152.6, 167.3, 178.6; HRMS found for $C_{22}H_{26}N_3O_5$ *m*/*z* 412.1869 (MH^+), requires *m*/*z* = 412.1867; ν_{max} (ATR) 3246, 1656 (C═O), 1638 (C═O), 1596, 1327, 1237, 1131, 999 cm^{-1}.

4.3. General Procedure for the Synthesis of of Cycloadducts (+)-3e−l and (−)-3e−l. These compounds were prepared following the literature procedure for the synthesis of closely related compounds (+)-**3a−d** and (−)-**3a−d**.[7e] CuI (117 mg, 0.6 mmol) and DIPEA (156 μL, 0.9 mmol) were added to a stirred suspension of **1a−l** (3 mmol) and *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**2**) (651 mg, 3.3 mmol) in anhydrous acetonitrile (20 mL), and stirring at rt was continued until complete dissolution of the starting dipole **1** (1−72 h). Volatile components were evaporated in vacuo (35 °C, 10 mbar), and the residue was purified by FC (EtOAc−hexanes). Fractions containing the product were combined and evaporated in vacuo (40 °C, 10 mbar) to give a mixture of diastereomers (+)-**3a−l**/(−)-**3a−l**, which were separated by CC or MPLC. Fractions containing the products were evaporated in vacuo to give two diastereomeric nonracemic compounds (+)-**3a−l** and (−)-**3a−l**.

*4.3.1. tert-Butyl ((S)-1-((1S,6R,7R)-6-Benzyloxycarbonylamino-1-(4-chlorophenyl)-7-isopropyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3e**) and Its (S)-(1R,6S,7S)-Diastereomer (−)-**3e**:* Prepared from **1e** (798 mg, 2 mmol), **2** (433 mg, 2.2 mmol), CuI (76 mg, 0.4 mmol), DIPEA (105 μL, 0.60 mmol), FC (EtOAc), and MPLC (EtOAc/hexanes, 1:2).

*4.3.1.1. tert-Butyl ((S)-1-((1S,6R,7R)-6-Benzyloxycarbonylamino-1-(4-chlorophenyl)-7-isopropyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3e**):* Yield 524 mg (44%) of yellowish solid; mp 173−177 °C; $[\alpha]_{589}^{23}$ +584 (*c* = 0.24, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 and 0.85 (6H, 2d, 1:1, *J* = 7.0 Hz); 1.11 (3H, d, *J* = 7.1 Hz); 1.35 (9H, s); 1.76 (1H, br septet of d, *J* = 7.0, 2.5 Hz); 3.19 (1H, dd, *J* = 2.8, 11.7 Hz); 4.77 (1H, p, *J* = 7.3 Hz); 4.97 (1H, dd, *J* = 9.7, 11.7 Hz); 5.08 and 5.13 (2H, 2d, 1:1, *J* = 12.3 Hz); 5.17 (1H, s); 5.24 (1H, d, *J* = 8.6 Hz); 6.85 (1H, d, *J* = 9.8 Hz); 7.28−7.31 (7H, m); 7.41 (2H, d, *J* = 8.4 Hz); 8.38 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.0, 18.1, 20.4, 27.4, 28.4, 52.0, 55.9, 67.2, 73.2, 78.3, 80.3, 124.2, 128.1, 128.2, 128.5, 128.6, 129.5, 130.2, 133.8, 136.3, 138.9, 155.7, 156.5, 166.4, 194.8; HRMS

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812

found for $C_{31}H_{38}ClN_4O_6$ m/z 597.2467 (MH^+), requires m/z = 597.2474; ν_{max} (ATR) 2965, 1711 (C═O), 1696 (C═O), 1659 (C═O), 1487, 1436, 1244, 1160, 1035 cm^{-1}.

*4.3.1.2. tert-Butyl ((S)-1-((1R,6S,7S)-6-Benzyloxycarbonylamino-1-(4-chlorophenyl)-7-isopropyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo-[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3e**):* Yield 358 mg (30%) of yellowish solid; mp 107−110 °C; $[\alpha]_{589}^{23}$ −718 (c = 0.23, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 and 0.84 (6H, 2d, 1:1, J = 7.0 Hz); 1.23 (3H, d, J = 7.0 Hz); 1.37 (9H, s); 1.78 (1H, br septet of d, J = 7.0, 2.8 Hz); 3.31 (1H, dd, J = 2.7, 11.5 Hz); 4.61 (1H, p, J = 7.5 Hz); 4.72 (1H, dd, J = 8.8, 11.7 Hz); 4.99 (1H, d, J = 8.6 Hz); 5.11 and 5.14 (2H, 2d, 1:1, J = 12.5 Hz); 5.21 (1H, s); 5.43 (1H, d, J = 9.1 Hz); 7.29−7.40 (9H, m); 7.76 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.3, 17.8, 19.1, 27.5, 28.4, 51.4, 56.2, 67.7, 73.1, 77.5, 80.2, 123.7, 128.3, 128.49, 128.53, 128.7, 129.3, 129.7, 133.8, 135.9, 139.0, 155.0, 156.0, 165.4, 194.6; HRMS found for $C_{31}H_{38}ClN_4O_6$ m/z 597.2464 (MH^+), requires m/z = 597.2474 (found C, 62.06; H, 6.39; N, 9.13; $C_{31}H_{37}ClN_4O_6$ requires C, 62.36; H, 6.25; N, 9.38); ν_{max} (ATR) 2978, 1741 (C═O), 1697 (C═O), 1675 (C═O), 1509, 1245, 1160, 1040, 698 cm^{-1}.

*4.3.2. tert-Butyl ((S)-1-((1S,6R,7R)-6-Benzyloxycarbonylamino-7-isopropyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3f**) and Its (S)-(1R,6S,7S)-Diastereomer (−)-**3f**:* Prepared from **1f** (646 mg, 1.57 mmol), **2** (318 mg, 1.61 mmol), CuI (32 mg, 0.17 mmol), DIPEA (84 μL, 0.48 mmol), FC (EtOAc), and CC (EtOAc/hexanes, 1:2).

*4.3.2.1. tert-Butyl ((S)-1-((1S,6R,7R)-6-Benzyloxycarbonylamino-7-isopropyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo-[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3f**):* Yield 401 mg (42%) of yellow solid; mp 183−185 °C; $[\alpha]_{589}^{23}$ +814 (c = 0.25, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 and 0.86 (6H, 2d, 1:1, J = 6.8, 7.1 Hz); 1.09 (3H, d, J = 7.1 Hz); 1.35 (9H, s); 1.70−1.77 (1H, m); 3.23 (1H, dd, J = 2.6, 11.5 Hz); 4.77 (1H, p, J = 7.5 Hz); 4.99−5.03 (1H, m); 5.06−5.15 (2H, m); 5.22 (1H, d, J = 8.7 Hz); 5.32 (1H, s); 6.89−6.94 (1H, m); 7.29−7.34 (5H, m); 7.70 and 8.21 (4H, 2d, 1:1, J = 8.6 Hz); 8.48 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.1, 18.1, 20.4, 27.5, 28.4, 51.9, 55.8, 67.3, 73.1, 78.2, 80.4, 123.5, 123.7, 128.1, 128.3, 128.5, 129.2, 130.8, 136.2, 147.5, 147.7, 155.7, 156.5, 166.6, 194.8; HRMS found for $C_{31}H_{38}N_5O_8$ m/z 608.2712 (MH^+), requires m/z = 608.2715 (found C, 61.13; H, 6.18; N, 11.45; $C_{31}H_{37}N_5O_8$ requires C, 61.27; H, 6.14; N, 11.53); ν_{max} (ATR) 3438, 2970, 1710 (C═O), 1700 (C═O), 1655 (C═O), 1346, 1244, 1158, 1030, 752 cm^{-1}.

*4.3.2.2. tert-Butyl ((S)-1-((1R,6S,7S)-6-Benzyloxycarbonylamino-7-isopropyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo-[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3f**):* Yield 308 mg (32%) of yellow solid; mp 128−130 °C; $[\alpha]_{589}^{23}$ −741 (c = 0.23, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 and 0.84 (6H, 2d, 1:1, J = 6.9, 7.1 Hz); 1.25 (3H, d, J = 7.0 Hz); 1.35 (9H, s); 1.71−1.79 (1H, m); 3.38 (1H, dd, J = 2.7, 11.5 Hz); 4.61 (1H, p, J = 7.3 Hz); 4.69−4.73 (1H, m); 4.91 (1H, d, J = 8.3 Hz); 5.11−5.16 (2H, m); 5.34−5.40 (2H, m); 7.31−7.38 (5H, m); 7.66 and 8.19 (4H, 2d, 1:1, J = 8.3 Hz); 7.80 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.4, 17.9, 18.8, 27.6, 28.4, 51.4, 56.1, 67.7, 73.1, 77.3, 80.3, 123.0, 123.6, 128.3, 128.6, 128.8, 129.4, 129.7, 135.9, 147.7, 155.0, 155.9, 165.6, 194.6; HRMS found for $C_{31}H_{38}N_5O_8$ m/z 608.2713 (MH^+), requires m/z = 608.2715; ν_{max} (ATR) 3377, 2975, 1747 (C═O), 1697 (C═O), 1674 (C═O), 1518, 1246, 1040, 754, 698 cm^{-1}.

*4.3.3. tert-Butyl ((S)-1-((1S,6R,7R)-6-Benzyloxycarbonylamino-1,7-diphenyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3g**) and Its (S)-(1R,6S,7S)-Diastereomer (−)-**3g**:* Prepared from **1g** (798 mg, 2 mmol), **2** (433 mg, 2 mmol), CuI (76 mg, 0.4 mmol), DIPEA (105 μL, 0.60 mmol), FC (EtOAc), and MPLC (EtOAc/hexanes, 1:1).

*4.3.3.1. tert-Butyl ((S)-1-((1S,6R,7R)-6-Benzyloxycarbonylamino-1,7-diphenyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3g**):* Yield 500 mg (42%) of yellow solid; mp 167−170 °C; $[\alpha]_{589}^{23}$ +331 (c = 0.28, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (3H, br d, J = 7.0 Hz); 1.40 (9H, s); 4.26 (1H, d, J = 11.5 Hz); 4.81 (1H, br p, J = 7.3 Hz); 4.89 (1H, br t, J = 10.4 Hz); 4.99 and 5.03 (2H, 2d, 1:1, J = 12.4 Hz); 5.24 (1H, s); 5.30 (1H, d, J = 8.2 Hz); 6.63 (1H, br d, J = 8.3 Hz); 6.99−7.36 (15H, m); 8.37 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4, 28.5, 52.2, 62.7, 67.2, 73.4, 76.8, 80.2, 123.7, 127.7, 127.9, 128.0, 128.1, 128.17, 128.22, 128.51, 128.54, 129.0, 130.8, 133.7, 136.2, 140.0, 155.7, 156.3, 165.8, 194.7; HRMS found for $C_{34}H_{37}N_4O_6$ m/z 597.2703 (MH^+), requires m/z = 597.2708 (found C, 68.61; H, 5.83; N, 9.36; $C_{34}H_{36}N_4O_6$ requires C, 68.44; H, 6.08; N, 9.39); ν_{max} (ATR) 2979, 1722 (C═O), 1711 (C═O), 1661 (C═O), 1490, 1245, 1044, 696, 660, 639, 617 cm^{-1}.

*4.3.3.2. tert-Butyl ((S)-1-((1R,6S,7S)-6-Benzyloxycarbonylamino-1,7-diphenyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3g**):* Yield 250 mg (21%) of yellow solid; mp 94−98 °C; $[\alpha]_{589}^{23}$ −259 (c = 0.23, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (3H, br d, J = 6.6 Hz); 1.40 (9H, s); 4.49 (1H, br s); 4.67 (1H, br p, J = 7.4 Hz); 5.00−5.12 (3H, m); 5.24 (1H, br s); 5.44 (1H, br s); 6.95−7.40 (16H, m); 7.88 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.1, 28.4, 51.4, 63.2, 67.6, 73.2, 75.1, 80.1, 123.1, 127.88, 127.90, 128.0, 128.16, 128.19, 128.4, 128.6, 128.7, 129.0, 130.5, 134.0, 135.9, 140.1, 155.1, 155.7, 164.6, 194.6; HRMS found for $C_{34}H_{37}N_4O_6$ m/z 597.2705 (MH^+), requires m/z = 597.2708; ν_{max} (ATR) 3032, 1705 (C═O), 1656 (C═O), 1496, 1232, 1162, 695 cm^{-1}.

*4.3.4. tert-Butyl ((S)-1-((1S,7S)-1-(4-Nitrophenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)-carbamate ((+)-**3h**) and Its ((S)-(1R,7R)-Diastereomer (−)-**3h**:* Prepared from **1h** (414 mg, 1.40 mmol), **2** (287 mg, 1.45 mmol), CuI (29 mg, 0.15 mmol), DIPEA (49 μL, 0.28 mmol), and CC (EtOAc/hexanes, 2:3).

*4.3.4.1. tert-Butyl ((S)-1-((1S,7S)-1-(4-Nitrophenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3h**):* Yield 272 mg (39%) of yellow solid; mp 196−199 °C; $[\alpha]_{589}^{23}$ +464 (c = 0.35, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (3H, d, J = 7.2 Hz); 1.42 (9H, s); 2.94 (1H, dd, J = 6.8, 16.6 Hz); 3.03 (1H, dd, J = 12.1, 16.5 Hz); 4.44 (1H, dd, J = 6.9, 12.0 Hz); 4.69 (1H, p, J = 7.3 Hz); 5.09 (1H, d, J = 7.9 Hz); 5.41 (1H, d, J = 1.0 Hz); 7.16−7.23 (5H, m); 7.33−7.35 (2H, m); 7.83 (1H, s); 8.01−8.03 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.2, 28.4, 44.2, 51.9, 71.6, 72.3, 80.1, 122.1, 123.4, 127.5, 128.6, 128.9, 129.2, 130.3, 135.1, 147.4, 147.5, 155.3, 166.6, 194.9; HRMS found for $C_{26}H_{29}N_4O_6$ m/z 493.2082 (MH^+), requires m/z = 493.2082 (found C, 63.11; H, 5.69; N, 11.15; $C_{26}H_{28}N_4O_6$ requires C, 63.40; H, 5.73; N, 11.38); ν_{max} (ATR) 3087, 1736 (C═O), 1718 (C═O), 1653 (C═O), 1597, 1342, 1152, 1013, 834 cm^{-1}.

*4.3.4.2. tert-Butyl ((S)-1-((1R,7R)-1-(4-Nitrophenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3h**):* Yield 258 mg (37%) of yellow solid; mp 177−180 °C; $[\alpha]_{589}^{23}$ −524 (c = 0.35, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 7.0 Hz); 1.39 (9H, s); 2.97 (1H, dd, J = 6.7, 16.6 Hz); 3.03 (1H, dd, J = 12.2, 16.5 Hz); 4.44 (1H, dd, J = 6.7, 12.2 Hz); 4.68 (1H, p, J = 7.2 Hz); 5.01 (1H, d, J = 8.3 Hz); 5.36 (1H, s); 7.18−7.24 (5H, m); 7.28 (2H, d, J = 9.2 Hz); 7.86 (1H, s); 7.99 (2H, d, J = 8.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.0, 28.4, 44.2, 51.4, 71.7, 72.1, 80.2, 121.8, 123.4, 127.6, 128.8, 128.9, 129.2, 130.7, 135.1, 147.3, 147.6, 155.1, 166.7, 194.8; HRMS found for $C_{26}H_{29}N_4O_6$ m/z 493.2079 (MH^+), requires m/z = 493.2082 (found C, 63.17; H, 5.77; N, 11.16; $C_{26}H_{28}N_4O_6$ requires C, 63.40; H, 5.73; N, 11.38); ν_{max} (ATR) 3081, 1735 (C═O), 1709 (C═O), 1659 (C═O), 1595, 1342, 1225, 1146, 1015, 836 cm^{-1}.

*4.3.5. tert-Butyl ((S)-1-((1S,6R)-6-Benzamido-7,7-dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (+)-**3i** and Its (S)-1-((1R,6S)-Diastereomer (−)-**3i**:* Prepared from **1i** (275 mg, 0.75 mmol), **2** (148 mg, 0.75 mmol), CuI (29 mg, 0.15 mmol), DIPEA (39 μL, 0.22 mmol), and CC (EtOAc/hexanes, 1:1).

*4.3.5.1. tert-Butyl ((S)-1-((1S,6R)-6-Benzamido-7,7-dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3i**):* Yield 148 mg (35%) of yellow solid; mp 132−135 °C; $[\alpha]_{589}^{23}$ +751 (c = 0.23, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (3H, d, J = 7.0 Hz); 1.17 (3H, s); 1.25 (3H, s); 1.31 (9H, s); 4.90 (1H, p, J = 7.3 Hz); 5.34 (1H, d, J = 8.2 Hz); 5.48 (1H, d, J = 8.3 Hz); 5.72 (1H, s); 7.42 (2H, t, J = 7.6 Hz); 7.50−

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812

7.54 (1H, m); 7.50−7.55 (1H, m); 7.73 (2H, d, J = 8.6 Hz); 7.85 (2H, d, J = 8.1 Hz); 8.23 (2H, d, J = 8.7 Hz); 8.36 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 20.3, 24.0, 28.4, 51.8, 62.8, 64.5, 70.7, 80.3, 123.4, 123.9, 127.6, 128.7, 128.9, 130.6, 132.3, 133.3, 147.8, 148.3, 155.6, 166.0, 168.4, 195.0; HRMS found for $C_{29}H_{34}N_5O_7$ m/z 564.2443 (MH^+), requires m/z = 564.2453 (found C, 61.07; H, 5.59; N, 12.03; $C_{29}H_{33}N_5O_7 \cdot {}^1/_3H_2O$ requires C, 61.15; H, 5.96; N, 12.30); ν_{max} (ATR) 2977, 1720 (C═O), 1656 (C═O), 1521, 1346, 1153, 831, 694 cm^{-1}.

*4.3.5.2. tert-Butyl ((S)-1-((1R,6S)-6-Benzamido-7,7-dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3i**):* Yield 126 mg (30%) of yellow solid; mp 127−130 °C; $[\alpha]_{589}^{23}$ −611 (c = 0.23, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (3H, s); 1.27 (3H, d, J = 7.0 Hz); 1.29 (3H, s); 1.38 (9H, s); 4.66 (1H, p, J = 7.2 Hz); 4.93 (1H, d, J = 7.9 Hz); 5.31 (1H, d, J = 7.5 Hz); 5.64 (1H, s); 6.64−6.67 (1H, m); 7.47 (2H, t, J = 7.7 Hz); 7.54−7.58 (1H, m); 7.67 (2H, d, J = 8.3 Hz); 7.81−7.83 (2H, m); 7.88 (1H, s); 8.20−8.22 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.4, 18.7, 23.9, 28.4, 51.4, 62.7, 64.4, 71.3, 80.5, 123.1, 123.8, 127.4, 128.9, 129.0, 130.4, 132.5, 133.1, 147.8, 148.5, 155.1, 166.5, 168.0, 194.7; HRMS found for $C_{29}H_{34}N_5O_7$ m/z 564.2447 (MH^+), requires m/z = 564.2453 (found C, 60.75; H, 5.87; N, 12.02; $C_{29}H_{33}N_5O_7 \cdot {}^1/_2H_2O$ requires C, 60.83; H, 5.99; N, 12.23); ν_{max} (ATR) 2978, 1708 (C═O), 1656 (C═O), 1580, 1520, 1346, 1237, 1154, 711 cm^{-1}.

*4.3.6. tert-Butyl ((S)-1-((1R,6R)-6-Benzamido-1-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3j**) and Its (S)-((1S,6S)-Diastereomer (−)-**3j**:* Prepared from **1j** (387 mg, 0.99 mmol), **2** (195 mg, 0.99 mmol), CuI (38 mg, 0.2 mmol), DIPEA (52 μL, 0.30 mmol), and CC (EtOAc/hexanes, 1:1).

*4.3.6.1. tert-Butyl ((S)-1-((1R,6R)-6-Benzamido-1-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3j**):* Yield 163 mg (27%) of yellow solid; mp 132−135 °C; $[\alpha]_{589}^{23}$ +572 (c = 0.32, CH_2Cl_2). 1.23−1.26 (9H, m); 1.28 (9H, s); 4.97 (1H, p, J = 7.0 Hz); 5.42−5.44 (2H, m); 6.13 (1H, s); 7.29 (1H, dd, J = 8.4, 2.1 Hz); 7.40 (1H, d, J = 2.0 Hz); 7.42 (2H, d, J = 7.6 Hz); 7.48−7.52 (2H, m); 7.68 (1H, d, J = 8.5 Hz); 7.85 (2H, d, J = 7.4 Hz); 8.53 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 20.8, 23.9, 28.4, 51.6, 61.3, 63.0, 70.3, 80.1, 124.1, 127.7, 128.0, 128.6, 129.4, 130.7, 130.9, 132.1, 133.4, 134.0, 134.5, 137.4, 155.7, 165.3, 168.5, 194.7; HRMS found for $C_{29}H_{33}Cl_2N_4O_5$ m/z 587.182 (MH^+), requires m/z = 587.1823 (found C, 58.88; H, 5.68; N, 9.15; $C_{29}H_{32}Cl_2N_4O_5 \cdot {}^1/_3H_2O$ requires C, 58.69; H, 5.55; N, 9.44); ν_{max} (ATR) 2977, 1721 (C═O), 1657 (C═O), 1583, 1435, 1372, 1244, 1153, 852 cm^{-1}.

*4.3.6.2. tert-Butyl ((S)-1-((1S,6S)-6-Benzamido-1-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3j**):* Yield 131 mg (23%) of yellow solid; mp 123−127 °C; $[\alpha]_{589}^{23}$ −592 (c = 0.30, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, s); 1.26−1.29 (6H, m); 1.41 (9H, s); 4.68 (1H, p, J = 7.2 Hz); 4.96 (1H, d, J = 8.5 Hz); 5.23 (1H, d, J = 7.6 Hz); 6.06 (1H, s); 6.52 (1H, d, J = 7.6 Hz); 7.25−7.27 (1H, m); 7.37−7.42 (2H, m); 7.46 (2H, t, J = 7.7 Hz); 7.53−7.58 (1H, m); 7.80−7.83 (2H, m); 7.85 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 18.9, 23.8, 28.4, 51.3, 61.2, 62.8, 70.9, 80.3, 123.8, 127.4, 128.0, 128.9, 129.3, 130.0, 131.0, 132.5, 133.2, 133.7, 134.4, 137.7, 155.1, 165.6, 167.9, 194.2; HRMS found for $C_{29}H_{33}Cl_2N_4O_5$ m/z 587.1816 (MH^+), requires m/z = 587.1823 (found C, 58.98; H, 5.51; N, 9.29; $C_{29}H_{32}Cl_2N_4O_5$ requires C, 59.29; H, 5.49; N, 9.54); ν_{max} (ATR) 2977, 1711 (C═O), 1656 (C═O), 1583, 1438, 1239, 1154, 850 cm^{-1}.

*4.3.7. tert-Butyl ((S)-1-((1S,6R)-6-Benzamido-7,7-dimethyl-5-oxo-1-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3k**) and Its (S)-1-((1R,6S)-Diastereomer (−)-**3k**:* Prepared from **1k** (304 mg, 0.74 mmol), **2** (150 mg, 0.76 mmol), CuI (29 mg, 0.15 mmol), DIPEA (39 μL, 0.22 mmol), and MPLC (EtOAc/hexanes, 1:2).

*4.3.7.1. tert-Butyl ((S)-1-((1S,6R)-6-Benzamido-7,7-dimethyl-5-oxo-1-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3k**):* Yield 130 mg (29%) of yellow solid; mp 128−131 °C; $[\alpha]_{589}^{23}$ +591 (c = 0.24, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s); 1.23 (3H, d, J = 7.0 Hz); 1.31 (9H, s); 1.34 (3H, s); 3.86 (3H, s); 3.88 (6H, s); 4.94 (1H, p, J = 6.8 Hz); 5.43−5.45 (1H, m); 5.49 (1H, d, J = 8.4 Hz); 5.57 (1H, s); 6.70 (2H, s); 7.42 (2H, t, J = 7.6 Hz); 7.52 (1H, t, J = 7.5 Hz); 7.55−7.59 (1H, m); 7.87 (2H, d, J = 7.4 Hz); 8.36−8.39 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 20.7, 24.1, 28.4, 52.0, 56.3, 61.0, 62.9, 65.3, 70.7, 80.0, 104.7, 124.3, 127.7, 128.6, 130.3, 132.2, 133.4, 136.8, 137.6, 153.3, 155.6, 166.1, 168.4, 195.2; HRMS found for $C_{32}H_{41}N_4O_8$ m/z 609.2911 (MH^+), requires m/z = 609.2919 (found C, 63.03; H, 6.85; N, 9.00; $C_{32}H_{40}N_4O_8$ requires C, 63.14; H, 6.62; N, 9.20); ν_{max} (ATR) 2975, 1712 (C═O), 1655 (C═O), 1582, 1423, 1235, 1125, 1011 cm^{-1}.

*4.3.7.2. tert-Butyl ((S)-1-((1R,6S)-6-Benzamido-7,7-dimethyl-5-oxo-1-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3k**):* Yield 139 mg (31%) of yellow solid; mp 113−116 °C; $[\alpha]_{589}^{23}$ −533 (c = 0.26, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, s); 1.26 (3H, d, J = 6.9 Hz); 1.37 (3H, s); 1.40 (9H, s); 3.85 (3H, s); 3.89 (6H, s); 4.68 (1H, p, J = 7.2 Hz); 5.02 (1H, d, J = 8.6 Hz); 5.32 (1H, d, J = 7.6 Hz); 5.49 (1H, s); 6.65 (2H, s); 6.69 (1H, d, J = 7.7 Hz); 7.46 (2H, t, J = 7.7 Hz); 7.54−7.57 (1H, m); 7.81−7.83 (3H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.3, 18.8, 23.9, 28.4, 51.4, 56.2, 60.9, 62.7, 65.1, 71.4, 80.2, 104.7, 123.7, 127.4, 128.9, 130.1, 132.4, 133.2, 137.0, 137.6, 153.3, 155.1, 166.8, 167.9, 194.8; HRMS found for $C_{32}H_{41}N_4O_8$ m/z 609.2914 (MH^+), requires m/z = 609.2919 (found C, 62.43; H, 6.81; N, 8.94; $C_{32}H_{40}N_4O_8 \cdot {}^1/_3H_2O$ requires C, 62.53; H, 6.67; N, 9.11); ν_{max} (ATR) 2932, 1706 (C═O), 1658 (C═O), 1581, 1422, 1233, 1152, 1125, 1009 cm^{-1}.

*4.3.8. tert-Butyl ((S)-1-((1S)-7,7-Dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3l**) and Its (S)-(1R)-Diastereomer (−)-**3l**:* Prepared from **1l** (182 mg, 0.74 mmol), **2** (145 mg, 0.74 mmol), CuI (28 mg, 0.15 mmol), DIPEA (39 μL, 0.22 mmol), and CC (EtOAc/hexanes, 1:1).

*4.3.8.1. tert-Butyl ((S)-1-((1S)-7,7-Dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((+)-**3l**):* Yield 115 mg (35%) of yellow solid; mp 193−195 °C; $[\alpha]_{589}^{23}$ +758 (c = 0.25, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (6H, s and d (overlapping), J = 6.7 Hz); 1.24 (3H, s); 1.42 (9H, s); 2.49 (1H, d, J = 15.9 Hz); 2.90 (1H, d, J = 15.9 Hz); 4.65 (1H, p, J = 7.4 Hz); 5.14 (1H, d, J = 7.5 Hz); 5.68 (1H, s); 7.68 (2H, d, J = 8.3 Hz); 7.73 (1H, s); 8.20 (2H, d, J = 8.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.1, 19.5, 25.1, 28.4, 49.2, 51.8, 64.1, 64.6, 80.0, 122.1, 123.8, 128.8, 129.9, 147.6, 149.1, 155.2, 167.0, 194.9; HRMS found for $C_{22}H_{29}N_4O_6$ m/z 445.2077 (MH^+), requires m/z = 445.2082 (found C, 58.72; H, 6.21; N, 12.32; $C_{22}H_{28}N_4O_6 \cdot {}^1/_3H_2O$ requires C, 58.66; H, 6.41; N, 12.44); ν_{max} (ATR) 2971, 1725 (C═O), 1700 (C═O), 1652 (C═O), 1589, 1522, 1344, 1239, 1016, 829 cm^{-1}.

*4.3.8.2. tert-Butyl ((S)-1-((1R)-7,7-Dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate ((−)-**3l**):* Yield 91 mg (28%) of yellow solid; mp 74−78 °C; $[\alpha]_{589}^{23}$ −520 (c = 0.21, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, s); 1.23 (3H, s); 1.28 (3H, d, J = 6.6 Hz); 1.37 (9H, s); 2.47 (1H, d, J = 15.9 Hz); 2.90 (1H, d, J = 15.8 Hz); 4.62 (1H, p, J = 7.4 Hz); 4.96 (1H, d, J = 7.5 Hz); 5.61 (1H, s); 7.65 (2H, d, J = 8.3 Hz); 7.77 (1H, s); 8.19 (2H, d, J = 8.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.0, 19.2, 25.1, 28.4, 49.2, 51.3, 64.1, 64.7, 80.2, 121.9, 123.8, 129.0, 130.6, 147.6, 149.3, 155.1, 167.3, 194.8; HRMS found for $C_{22}H_{29}N_4O_6$ m/z 445.2077 (MH^+), requires m/z = 445.2082; ν_{max} (ATR) 2978, 1704 (C═O), 1697 (C═O), 1675 (C═O), 1519, 1344, 1233, 1156, 853, 729 cm^{-1}.

4.4. Computational Chemistry. Spartan'10 (force-field conformational search),[25] Gaussian09 Rev. D.01 (semiempirical and DFT),[26] Orca 3.0.3 (TD-DFT),[27] and SpecDis 1.64 (spectra averaging and fitting)[21] were used as programs.

A total of 7684 MMFF conformational candidates for all eight possible diastereomers of **3f** were generated with a sparse search algorithm. The candidates were optimized, and vibrational frequencies were calculated using the semiempirical PM6 method;[28] duplicates

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812

were removed based on comparison of the Gibbs free energies and dipole moments, yielding 6034 survivors. DFT reoptimization at the B3LYP/6-31G level[29] with tight geometry convergence criteria yielded 5412 molecules after removal of duplicates based on comparison of the electronic energies and dipole moments. For each diastereomer, the molecules within a relative electronic energy range up to 4 kcal/mol were selected from this set, amounting to 371 survivors overall. The geometries were reoptimized, and vibrational frequencies were calculated at the B3LYP/6-31G(d,p)/IEFPCM level[30] with tight geometry convergence criteria and an ultrafine integration grid using four different solvents of different polarity (carbon tetrachloride, chloroform, acetonitrile, and dimethyl sulfoxide). Duplicates were removed based on comparison of the electronic energies and dipole moments as well as the Gibbs free energies and dipole moments (survivors: 267 for CCl_4, 259 for $CHCl_3$, 255 for MeCN, and 262 for DMSO). Finally, the geometries were reoptimized, and vibrational frequencies were calculated at the B3LYP/6-311G(d,p)/IEFPCM level with tight geometry convergence criteria and an ultrafine integration grid. An identical duplicate removal procedure was performed (survivors: 236 for CCl_4, 236 for $CHCl_3$, 239 for MeCN, and 238 for DMSO). The structures were confirmed as local minima (no imaginary frequencies) and enthalpy-Boltzmann-averaged IR and VCD spectra were generated.

The experimental and calculated IR spectra were fitted in the range from 1100 to 1650 cm^{-1} using screening values of 2 to 10 cm^{-1} for the line broadening γ as well as 0.9 to 1.1 for the scaling factor s; the experimental and calculated VCD spectra were then compared using these optimized parameters.

ECD spectra (solvent: acetonitrile) were calculated via TD-DFT (with TDA, number of roots: 50, size of the expansion space: 300) using the previously optimized geometries for the molecules within a relative electronic energy range up to 2 kcal/mol for each diastereomer, respectively, employing the B3LYP functional, the def2-TZVPP basis set,[31] the RIJCOSX approximation[32] together with the def2-TZVPP/J basis set, tight SCF criteria, enhanced grid settings (Grid5 FinalGrid6) and COSMO solvation.[33] Enthalpy-Boltzmann-averaged UV and ECD spectra were then generated.

The experimental and calculated UV spectra were fitted in the range from 250 nm to 450 nm using screening values of 0.1 to 0.4 eV for the line broadening σ/γ as well as −30 nm to +30 nm for the shift value s; the experimental and calculated ECD spectra were then compared using these optimized parameters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02270.

X-ray data (CIF)

Computational chemistry, VCD spectra, crystal structures, specific rotation data, ECD spectra, and NMR spectra (PDF)

Boltzmann weightings, xyz files, and IR/VCD comparisons (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

*Tel: +49(0)6131-39-22272/-24443. Fax: +49(0)6131-39-22338. E-mail: opatz@uni-mainz.de.

*Tel: +386 1 4798 562. Fax: +386 1 2419 144. E-mail: jurij.svete@fkkt.uni-lj.si.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The financial support from the Slovenian Research Agency through Grant P1-0179 and of the Carl Zeiss foundation through the project ChemBioMed is gratefully acknowledged. We also thank to EN-FIST Centre of Excellence (Ljubljana, Slovenia) for using the SuperNova diffractometer. We thank the Zentrum für Datenverarbeitung (Mainz, Germany) for access to the MOGON supercomputer. We thank Prof. Jurij Lah, University of Ljubljana, for his help by recording ECD spectra.

■ REFERENCES

(1) (a) Nafie, L. A. *Vibrational Optical Activity: Principles and Applications*; Wiley, 2011. (b) Berova, N.; Polavarapu, P. L.; Nakanishi, K.; Woody, R. W. *Comprehensive Chiroptical Spectroscopy*; John Wiley & Sons, 2012. (c) Freedman, T. B.; Cao, X.; Dukor, R. K.; Nafie, L. A. *Chirality* **2003**, *15*, 743−758. (d) Sherer, E. C.; Lee, C. H.; Shpungin, J.; Cuff, J. F.; Da, C.; Ball, R.; Bach, R.; Crespo, A.; Gong, X.; Welch, C. J. *J. Med. Chem.* **2014**, *57*, 477−494.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell, 2010. (b) Patrick, G. L. *An Introduction to Medicinal Chemistry*, 4th ed.; Oxford University Press, 2009. (c) Pernerstorfer, J. In *Molecular Design and Combinatorial Compound Libraries in Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH Verlag GmbH, 2002; Vol. 2, pp 725−742. (d) Dolle, R. E. Solid-phase Synthesis of Heterocyclic Systems (Heterocycles Containing One Heteroatom. In *Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH Verlag GmbH, 2002; Vol. 2, pp 643−684.

(3) (a) Vagner, J.; Qu, H.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292−296. (b) Robinson, J. A.; DeMarco, S.; Gombert, F.; Moehle, K.; Obrecht, D. *Drug Discovery Today* **2008**, *13*, 944−951. (c) Robinson, J. A. *Acc. Chem. Res.* **2008**, *41*, 1278−1288. (d) Hanessian, S.; Auzzas, L. *Acc. Chem. Res.* **2008**, *41*, 1241−1251. (e) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001−1009.

(4) (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (b) Halab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers* **2000**, *55*, 101−122. (c) Cluzeau, J.; Lubell, W. D. *Biopolymers* **2005**, *80*, 98−150.

(5) (a) Ternansky, R. J.; Draheim, S. E. *Tetrahedron* **1992**, *48*, 777−796. (b) Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007−4013. (c) Holmes, R. E.; Neel, D. A. *Tetrahedron Lett.* **1990**, *31*, 5567−5570;(d) Jungheim, L. N.; Sigmund, S. K.; Holmes, R. E.; Barnett, C. J.; Ternansky, R. J. Eur. Pat. Appl. EP 202046 A1 19861120, 1986. *Chem. Abstr.* **1987**, *106*, 119880.

(6) For reviews on azomethine imines, see: (a) Grashey, R. Azomethine Imines. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons, Inc., 1984; Vol. *1*, pp 733−814. (b) Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2015**, *13*, 8596−8636.

(7) (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778−10779. (b) Suarez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244−11245. (c) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049−20052. (d) Arai, T.; Ogino, Y. *Molecules* **2012**, *17*, 6170−6178. (e) Pušavec, E.; Mirnik, J.; Šenica, L.; Grošelj, U.; Stanovnik, B.; Svete, J. *Z. Naturforsch., B: J. Chem. Sci.* **2014**, *69b*, 615−626. (f) Hori, M.; Sakakura, A.; Ishihara, K. *J. Am. Chem. Soc.* **2014**, *136*, 13198−13201. (g) Pušavec Kirar, E.; Grošelj, U.; Mirri, G.; Požgan, F.; Strle, G.; Štefane, B.; Jovanovski, V.; Svete, J. *J. Org. Chem.* **2016**, *81*, 5988−5997 and references cited therein.

(8) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(9) (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952−3015. (b) Fokin, V. V.; Matyjaszewski, K. CuAAC: The Quintessential Click Reaction. In *Organic Chemistry − Breakthroughs and Perspectives*, 1st ed.; Ding, K., Dai, L.-X., Eds.; Wiley-VCH, 2012; pp 247−277. (c) Berg, R.; Straub, B. F. *Beilstein J. Org. Chem.* **2013**, *9*, 2715−2750.

(d) Haldón, E.; Nicasio, M. C.; Pérez, P. J. *Org. Biomol. Chem.* **2015**, *13*, 9528−9550.
(10) Šenica, L.; Grošelj, U.; Kasunič, M.; Kočar, D.; Stanovnik, B.; Svete, J. *Eur. J. Org. Chem.* **2014**, *2014*, 3067−3071.
(11) Svete, J.; Prešeren, A.; Stanovnik, B.; Golič, L.; Golič Grdadolnik, S. *J. Heterocycl. Chem.* **1997**, *34*, 1323−1328.
(12) Novak, A.; Testen, A.; Bezenšek, J.; Grošelj, U.; Hrast, M.; Kasunič, M.; Gobec, S.; Stanovnik, B.; Svete, J. *Tetrahedron* **2013**, *69*, 6648−6665.
(13) Novak, A.; Bezenšek, J.; Grošelj, U.; Golobič, A.; Stanovnik, B.; Svete, J. *ARKIVOC* **2011**, 18−28.
(14) (a) Shintani, R.; Soh, Y.-T.; Hayashi, T. *Org. Lett.* **2010**, *12*, 4106−4109. (b) Gould, E.; Lebl, T.; Slawin, A. M. Z.; Reid, M.; Smith, A. D. *Tetrahedron* **2010**, *66*, 8992−9008. (c) Bren, V. A.; Popova, O. S.; Tolpygin, I. E.; Chernoivanov, V. A.; Revinskii, Yu. V.; Dubonosov, A. D. *Russ. Chem. Bull.* **2015**, *64*, 668−671.
(15) (a) Nalepa, K. *Acta Universitatis Palackianae Olomucensis, Facultas Rerum Naturalium* **1984**, *79*, 47−55. (b) Budovskii, E. I.; Chang, C.-P.; Kochetkov, N. K. *Zh. Obshch. Khim.* **1961**, *31*, 1297−1303. (c) Clarke, H. T. Oxazoles and Oxazolones. *Chemistry of Penicillin*; Princeton University Press, 1949; pp 688−848.
(16) (a) Lieser, T.; Kemmner, K. *Chem. Ber.* **1951**, *84*, 4−12. (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718−719. (c) Nakano, H.; Tsugawa, N.; Takahashi, K.; Okuyama, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 10879−10887. (d) Gould, E.; Lebl, T.; Slawin, A. M. Z.; Reid, M.; Davies, T.; Smith, A. D. *Org. Biomol. Chem.* **2013**, *11*, 7877−7892.
(17) Turk, C.; Svete, J.; Stanovnik, B.; Golič, L.; Golič-Grdadolnik, S.; Golobič, A.; Selič, L. *Helv. Chim. Acta* **2001**, *84*, 146−156.
(18) Grošelj, U.; Svete, J. *Arkivoc* **2015**, 175−205 and references cited therein.
(19) Pezdirc, L.; Jovanovski, V.; Bevk, D.; Jakše, R.; Pirc, S.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron* **2005**, *61*, 3977−3990.
(20) For details see the Supporting Information.
(21) Bruhn, T.; Schaumlöffel, A.; Hemberger, Y.; Bringmann, G. *Chirality* **2013**, *25*, 243−249.
(22) For compound sets **3e−h**, **3m−o**, and **3p−r**, the absolute configuration has been established by X-ray diffraction analysis of the representative compounds.
(23) Andernach, L.; Sandjo, L. P.; Liermann, J. C.; Buckel, I.; Thines, E.; Opatz, T. *Eur. J. Org. Chem.* **2013**, *2013*, 5946−5951.
(24) As demonstrated by the polarimetry, even a single-point measurement would suffice (cf. Table 4).
(25) *Spartan'10*; Wavefunction, Inc.: Irvine, CA, 2009.
(26) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.
(27) Neese, F. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2012**, *2*, 73−78.
(28) Stewart, J. J. P. *J. Mol. Model.* **2007**, *13*, 1173−1213.
(29) (a) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627. (e) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650−654. (f) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265−3269.
(30) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct.: THEOCHEM* **1999**, *464*, 211−226.
(31) (a) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571−2577. (b) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.
(32) Neese, F.; Wennmohs, F.; Hansen, A.; Becker, U. *Chem. Phys.* **2009**, *356*, 98−109.
(33) Klamt, A.; Schuurmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799−805.

DOI: 10.1021/acs.joc.6b02270
J. Org. Chem. 2016, 81, 11802−11812