Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Diastereoselective Synthesis and Conformational Analysis of (2*R*)- and (2*S*)-Fluorostatines: An Approach Based on Organocatalytic Fluorination of a Chiral Aldehyde

Xiang-Guo Hu,[†,‡] Aggie Lawer,[‡] Matthew B. Peterson,[‡,§] Hasti Iranmanesh,[‡] Graham E. Ball,[‡] and Luke Hunter*[,‡]

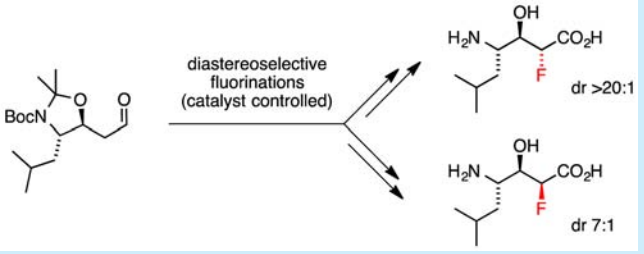
[†]National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, China

[‡]School of Chemistry, UNSW Australia, Sydney, NSW 2052, Australia

[§]Department of Chemistry and Biomolecular Sciences, Macquarie University, Sydney, NSW 2109, Australia

Supporting Information

**ABSTRACT:** Stereoselectively fluorinated analogues of the amino acid statine have been efficiently synthesized. The key step is an organocatalytic electrophilic fluorination of a chiral $\beta$-oxygenated aldehyde, which provided a test of both diastereoselectivity and chemoselectivity. The target statine analogues were found to adopt unique conformations influenced by the fluorine *gauche* effect, rendering them potentially valuable building blocks for incorporation into bioactive peptides.




Statines, or $\beta$-hydroxy-$\gamma$-amino acids, are key components of many therapeutically important peptides (Figure 1).[1] Such peptides usually act as protease inhibitors and hence hold great potential for the treatment of various diseases including cancer (cathepsin D), Alzheimer's disease (cathepsin D, BACE, $\alpha$-secretase), hypertension (renin), AIDS (HIV protease), and malaria (plasmepsins).[2] As a result, the synthesis of both natural statines and their analogues has been a subject of intense interest.[3]

The introduction of fluorine atoms into organic molecules can enhance the lipophilicity and biological stability, thus conferring the substances with favorable pharmacological properties.[4] The presence of fluorine also alters the electronic character of organic molecules in ways that can mimic the electron distributions of transition-state structures. Attempts have been made to harness such effects to improve the potency of aspartic protease inhibitors; for example, many fluorinated amino acids,[5,6] including trifluoromethylated[7] and *gem*-difluorinated[8] statines (e.g., **3**–**5** in Figure 1), have been prepared.

Another important effect of fluorine is that it can alter the molecular conformation though interaction of the polar C–F bond with neighboring functional groups.[9] Such effects can be exploited to optimize the potency of bioactive molecules such as amino acids by preorganizing them into the correct geometry.[5,6] For example, we recently synthesized $\alpha,\beta$-difluoro-$\gamma$-amino acids[10] and their homologated analogues $\alpha,\beta,\gamma$-trifluoro-$\delta$-amino acids;[11] different stereoisomers of the former possess different preferred conformations and thus lead to very different responses at GABA receptors.[12] Further application showed that they can successfully affect the overall shape of both linear[13] and cyclic[14] peptides. Building on these studies, we recently became interested in the hypothetical statine derivative **6** (Figure 1). Unlike the previous fluorinated statine derivatives (e.g., **3**–**5**), the new target **6** contains a stereogenic C–F bond and may therefore offer new opportunities for optimizing the potency of aspartic protease inhibitors through conformational control.

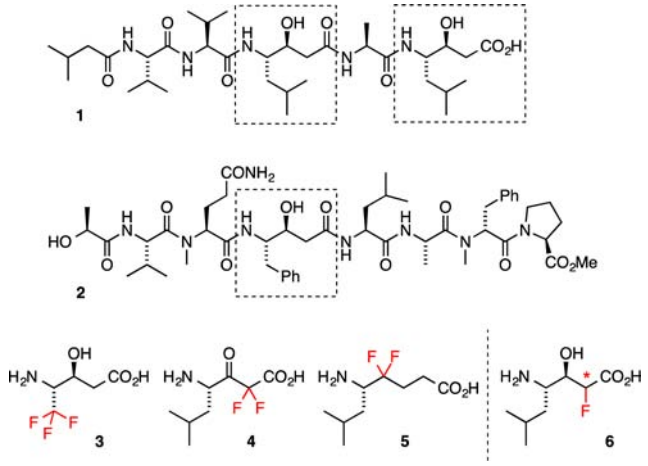



**Figure 1.** Statine residues are key components of aspartic protease inhibitors such as pepstatin A (**1**) and tasiamide B (**2**). Previous examples of fluorinated statine derivatives include **3**–**5**; compound **6** is the new target of this work.

**Received:** December 17, 2015
**Published:** February 10, 2016

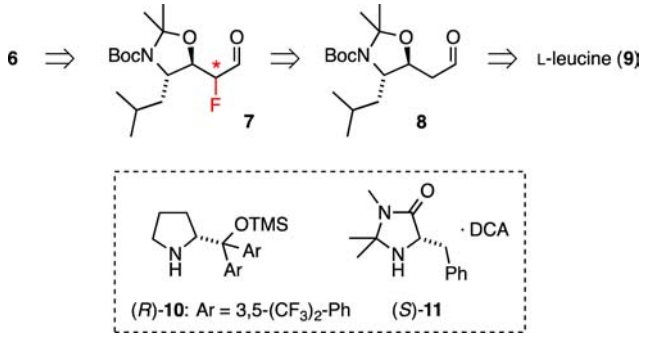




DOI: 10.1021/acs.orglett.5b03592
*Org. Lett.* 2016, 18, 662–665

Retrosynthetically, we anticipated that target **6** could be obtained from the protected precursor **7** (Scheme 1), which in turn could be secured via an organocatalytic electrophilic fluorination[15−17] of chiral aldehyde **8**.[18] It was desired to obtain the two stereoisomers of **7** separately, so the success of this strategy would hinge on the ability of an appropriate organocatalyst (e.g., **10**[15] or **11**[16]) to override any inherent substrate control in the fluorination reaction. The match/mismatch phenomenon has very rarely been investigated in the context of organocatalytic electrophilic fluorination,[19] despite the recent explosion of interest in this general class of reaction.[20] We also recognized that the presence of a potential leaving group at the $\beta$-position of substrate **8** would test the chemoselectivity of the process. Hence, we expected that our synthetic investigations would be noteworthy from a methodological perspective as well as for the target molecules' potential biological importance.

**Scheme 1. Target 6 Could Be Obtained via Diastereoselective Electrophilic Fluorination of Aldehyde 8 Mediated by an Organocatalyst Such as 10 or 11**

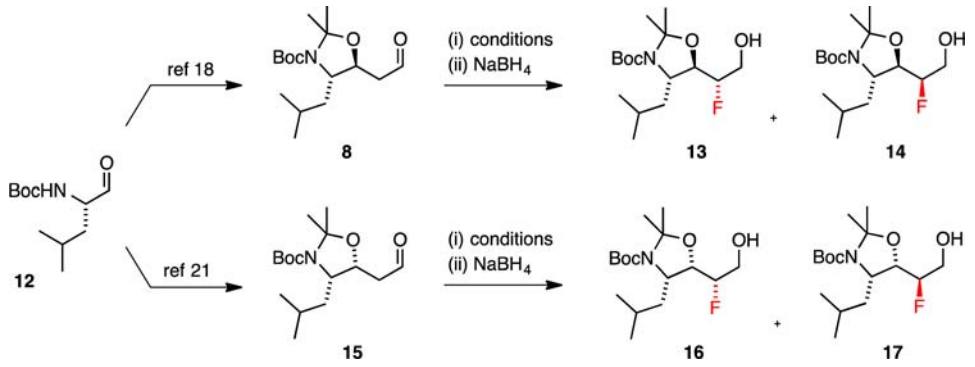



The required aldehyde **8** was readily synthesized following a procedure reported by Ghosh and co-workers (Table 1).[18] With substrate **8** in hand, a series of diastereoselective fluorination reactions were then attempted, followed by in situ reduction.[15] To our delight, the fluorination of **8** proceeded in good yield with excellent diastereoselectivity when catalyzed by (*R*)-**10** (Table 1, entry 1). The product **13** gave twin sets of NMR signals, presumably due to the presence of slowly interconverting rotameric species, and this initially complicated the analysis; however, global deprotection of **13** gave a single species by NMR analysis, confirming that **13** was stereochemically pure.[21] The relative stereochemistry of **13** was determined by X-ray crystallographic analysis of a derivative (vide infra), and this revealed that the fluorination had proceeded in accordance with the model of stereoinduction proposed by Jørgensen.[15] The optimized yield of product **13** (Table 1, entry 1) was achieved when 1 molar equiv of NFSI and 5 mol % catalyst were employed. No side products arising from either elimination or difluorination were observed. When the fluorination of **8** was repeated using the enantiomeric catalyst (*S*)-**10**, the epimeric product **14** was obtained as the major product in reasonable yield (Table 1, entry 2). This result confirmed that the direction of selectivity was indeed under catalyst control in each case. However, the diastereoselectivity of the latter reaction (Table 1, entry 2) was somewhat lower, indicative of a substrate−catalyst mismatch effect.

To gain further insight into the power of organocatalyst **10**, the epimeric substrate **15** was also prepared (Table 1).[21] When substrate **15** was subjected to the fluorination reaction mediated by catalyst (*R*)-**10**, the product **16** was obtained in moderate yield with modest diastereoselectivity (Table 1, entry 3). In contrast, when the fluorination of **15** was repeated using the enantiomeric catalyst (*S*)-**10**, the epimeric product **17** was formed with markedly higher yield and diastereoselectivity (Table 1, entry 4). The latter reaction appears to represent a "matched" substrate−catalyst combination. It should be noted that the relative stereochemistry of **16** and **17** was not unambiguously determined but rather assigned by analogy with that of **13** and **14**.

Overall, catalyst **10**[15] was found to be a powerful mediator in these fluorination reactions (Table 1, entries 1−4), delivering the products **13**, **14**, **16**, and **17** in moderate to good yields with mostly good to excellent catalyst-controlled stereoselectivity. In all cases, the major product could be isolated by flash chromatography in a synthetically useful quantity. By way of comparison, the alternative catalyst (*S*)-**11**[16] was subsequently found to also deliver excellent diastereocontrol in one case

**Table 1. Diastereoselective Fluorination Reactions**

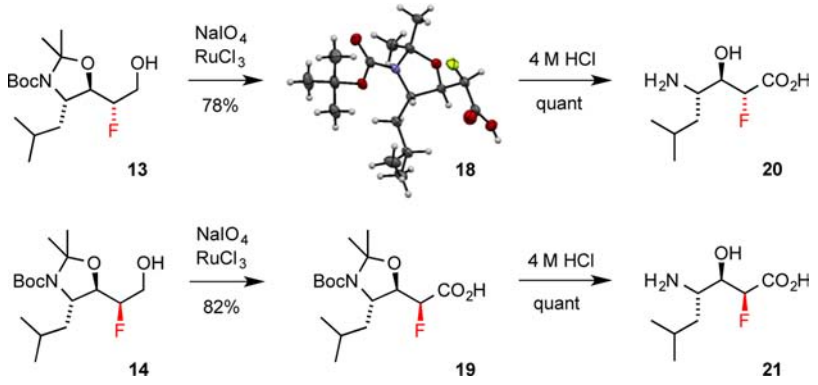



| entry | substrate | conditions | products | combined yield (%) | dr |
|---|---|---|---|---|---|
| 1 | **8** | (*R*)-**10** (5 mol %), NFSI, MTBE, rt, 10 h | **13**, **14** | 64 | >20:1 |
| 2 | **8** | (*S*)-**10** (5 mol %), NFSI, MTBE, rt, 10 h | **13**, **14** | 62 | 1:7 |
| 3 | **15** | (*R*)-**10** (5 mol %), NFSI, MTBE, rt, 10 h | **16**, **17** | 43 | 3:1 |
| 4 | **15** | (*S*)-**10** (5 mol %), NFSI, MTBE, rt, 10 h | **16**, **17** | 60 | <1:20 |
| 5 | **15** | (*S*)-**11** (20 mol %), NFSI, THF/iPrOH (9:1), −10 °C to rt, 48 h | **16**, **17** | 35 | <1:20 |



DOI: 10.1021/acs.orglett.5b03592
*Org. Lett.* 2016, 18, 662−665

**Scheme 2. Elaboration of 13 and 14 into Statine Derivatives 20 and 21**




(Table 1, entry 5), but a higher catalyst loading and a longer reaction time were required to achieve similar results.

After this brief investigation of the scope of the diastereoselective organocatalytic fluorination reaction, attention was returned to completing synthesis of the fluorinated statine targets (Scheme 2). Initially, in order to maximize the redox efficiency,[22] attempts were made to directly oxidize[23] the $\alpha$-fluoroaldehydes that were the immediate products of the fluorination of **8** (Table 1); unfortunately, however, this led to complex product mixtures from which the desired carboxylic acids **18** and **19** could not be fully purified. It transpired that the primary alcohols **13** and **14** were more appropriate substrates for oxidation (Scheme 2); in both cases, treatment with $NaIO_4/RuCl_3$ smoothly delivered the protected statine derivatives **18** and **19** in good yields. The relative stereochemistry of **18** was confirmed by X-ray crystallographic analysis.[24] Finally, global deprotection under acidic conditions furnished the target statines **20** and **21** in quantitative yield.

With the fluorinated statines **20** and **21** in hand, it became possible to test the hypothesis that stereoselective fluorination would lead to conformational differences that might be valuable for future biological applications. The NMR spectra of **20** and **21** yielded sets of $^3J_{HH}$ and $^3J_{HF}$ values that provided information on the corresponding dihedral angles between the various pairs of vicinal C−H and C−F bonds.[25] The observed $J$ values for **20** were mostly rather intermediate in magnitude (Figure 2), suggesting that significant conformational averaging occurs across the C2−C3 and C3−C4 bonds, where both the fluorine/hydroxy and hydroxy/amino groups can align *gauche* in two alternative ways (i.e., geometries **20a−d**).[26] It is noteworthy that all four of the geometries **20a−d** contain a "bent" amino acid backbone shape. A quite different pattern of conformational behavior was observed for the diastereoisomeric statine **21**. The NMR spectra of **21** gave a clearer set of large and small $J$ values (Figure 2) that corresponded to *anti* and *gauche* dihedral angles, respectively, suggesting that a single geometry (**21a**) is dominant in solution. Geometry **21a** contains an "extended" amino acid backbone shape. Some conformational averaging across the C3−C4 bond of **21** was deduced (Figure 2), but the resulting geometry **21b** is only a minor contributor.[26] Overall, the contrasting conformations of **20** versus **21** can be rationalized in terms of the fluorine *gauche* effect,[9] an outcome reminiscent of our previous results with difluorinated amino acids[12] and Myers' results with related fluorohydroxy compounds.[6]

In conclusion, an efficient stereocontrolled synthesis of (2*R*)- and (2*S*)-fluorostatines has been developed, exploiting an organocalytic electrophilic fluorination as the key step. The aldehyde substrates in these fluorination reactions presented challenges due their chirality and their dense functionality, yet Jørgensen's catalyst[15] was found to deliver good diastereoselectivity in most cases and excellent chemoselectivity in all cases. Preliminary conformational investigations of the fluorinated statine products revealed that the different stereoisomers adopt quite distinct molecular shapes, consistent with the fluorine *gauche* effect. Biological applications of these novel shape-controlled building blocks are being actively pursued in our laboratories and will be communicated in due course.

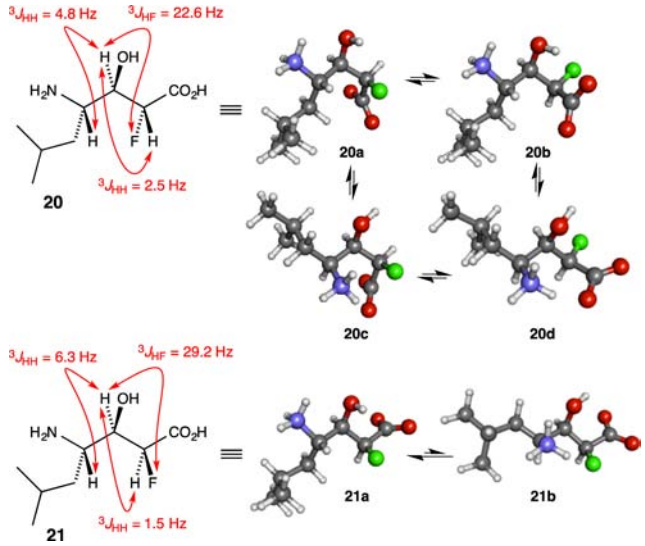



**Figure 2.** NMR $J$-based analysis reveals that statines **20** and **21** adopt distinct conformations. The illustrated structures were optimized at the M06-2X/6-31+G(d) level of theory in SMD water solvent.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03592.

Crystallographic data for **18** (CIF)

Experimental procedures, characterization data, reproductions of NMR spectra, and details of the computational $J$-based analysis (PDF)



DOI: 10.1021/acs.orglett.5b03592
*Org. Lett.* 2016, 18, 662−665

## AUTHOR INFORMATION

### Corresponding Author

*l.hunter@unsw.edu.au

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was funded by the Australian Research Council (DE120101653). Crystallographic data were collected at the MX2 beamline at the Australian Synchrotron under a Collaborative Access Program (AS143_MXCAP_8503). This research was undertaken with the assistance of resources provided at the NCI National Facility, Canberra, which is supported by the Australian Government, and by Intersect Australia Ltd.

## REFERENCES

(1) (a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259. (b) Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 1006. (c) Kwan, J. C.; Eksioglu, E. A.; Liu, C.; Paul, V. J.; Luesch, H. *J. Med. Chem.* **2009**, *52*, 5732. (d) Sun, Y.; Takada, K.; Nogi, Y.; Okada, S.; Matsunaga, S. *J. Nat. Prod.* **2014**, *77*, 1749.

(2) Cooper, J. B. *Curr. Drug Targets* **2002**, *3*, 155.

(3) Zhang, W. *Youji Huaxue* **2012**, *32*, 2203.

(4) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(5) (a) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (b) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, *2011*, 3261. (c) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. Biodiversity* **2012**, *9*, 2410. (d) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V.; Sorochinsky, A. *Synthesis* **2011**, *2011*, 3045. (e) Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. *Synthesis* **2012**, *44*, 1591.

(6) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207.

(7) Pesenti, C.; Arnone, A.; Bellosta, S.; Bravo, P.; Canavesi, M.; Corradi, E.; Frigerio, M.; Meille, S. V.; Monetti, M.; Panzeri, W.; Viani, F.; Venturini, R.; Zanda, M. *Tetrahedron* **2001**, *57*, 6511.

(8) (a) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M. *J. Med. Chem.* **1985**, *28*, 1553. (b) Deniau, G.; Seebach, D. *Helv. Chim. Acta* **2009**, *92*, 1720.

(9) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 38. (c) Hu, X.-G.; Hunter, L. *Beilstein J. Org. Chem.* **2013**, *9*, 2696.

(10) (a) Hunter, L.; Jolliffe, K. A.; Jordan, M. J. T.; Jensen, P.; Macquart, R. B. *Chem. - Eur. J.* **2011**, *17*, 2340. (b) Wang, Z.; Hunter, L. *J. Fluorine Chem.* **2012**, *143*, 143.

(11) Cheerlavancha, R.; Lawer, A.; Cagnes, M.; Bhadbhade, M.; Hunter, L. *Org. Lett.* **2013**, *15*, 5562.

(12) (a) Yamamoto, I.; Jordan, M. J. T.; Gavande, N.; Doddareddy, M. R.; Chebib, M.; Hunter, L. *Chem. Commun.* **2012**, *48*, 829. (b) Absalom, N.; Yamamoto, I.; O'Hagan, D.; Hunter, L.; Chebib, M. *Aust. J. Chem.* **2015**, *68*, 23.

(13) Hunter, L.; Butler, S.; Ludbrook, S. B. *Org. Biomol. Chem.* **2012**, *10*, 8911.

(14) Hu, X.-G.; Thomas, D. S.; Griffith, R.; Hunter, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6176.

(15) Marigo, M.; Fielenbach, D. I.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.

(16) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

(17) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.

(18) (a) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. (b) Ghosh, A. K.; Cappiello, J. *Tetrahedron Lett.* **1998**, *39*, 8803. (c) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003**, *2003*, 821.

(19) (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (b) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356. (c) Altiti, A. S.; Bachan, S.; Alrowhani, W.; Mootoo, D. R. *Org. Biomol. Chem.* **2015**, *13*, 10328. (d) Buckingham, F.; Kirjavainen, A. K.; Forsback, S.; Krzyczmonik, A.; Keller, T.; Newington, I. M.; Glaser, M.; Luthra, S. K.; Solin, O.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2015**, *54*, 13366.

(20) References 15−17 have already garnered >800 total citations. For relevant reviews, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Gouverneur, V.; Lozano, O. In *Science of Synthesis: Stereoselective Synthesis*; de Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2011; Vol. 3, p 851.

(21) See the Supporting Information.

(22) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(23) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

(24) CCDC-1442797 contains the crystallographic information for compound **18**.

(25) Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7887.

(26) All of the geometries **20a−d** were subsequently found among an ensemble of low-energy structures arising from an independent *in silico* conformational search. The calculated *J* values for the four individual geometries **20a−d** averaged to give a close match with the experimental *J* values for **20**, further supporting the analysis. Similar computational evidence was secured for **21a** and **21b**. See the Supporting Information.



DOI: 10.1021/acs.orglett.5b03592
*Org. Lett.* 2016, 18, 662−665