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Journal
Chemistry - A European Journal, 22(26)

ISSN
0947-6539

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Publication Date
2016-06-20

DOI
10.1002/chem.201601957

Peer reviewed

ChemPubSoc Europe

DOI: 10.1002/chem.201601957

CHEMISTRY
A European Journal
Communication

Radical Reactions

Diastereoselective Coupling of Chiral Acetonide Trisubstituted Radicals with Alkenes

Daniel J. Tao, Mikko Muuronen, Yuriy Slutskyy, Alexander Le, Filipp Furche,* and Larry E. Overman*[a]

Abstract: The stereochemical outcome of reactions of chiral nucleophilic trisubstituted acetonide radicals with electron-deficient alkenes is dictated by a delicate balance between destabilizing non-bonding interactions and stabilizing hydrogen-bonding between substituents on the α and β carbons.

Recent publications have highlighted the exceptional utility of bimolecular reactions between nucleophilic carbon-centered radicals and electron-deficient alkenes to couple complex fragments and construct sterically congested C–C bonds.[1] For such bond formations between two prochiral carbon centers to yield a single stereoisomer of the product, high facial stereoselectivity at both the prochiral carbon radical and the prochiral alkene radical acceptor are required. In the example illustrated in Figure 1 A, the tertiary carbon radical generated from precursor **1**[2] reacts preferentially from the convex face of the *cis*-perhydroazulene ring system with the double bond from the sterically less-hindered face *anti* to the cyclopentenone side chain to lead exclusively to the formation of coupled product **2**.[1a] When the prochiral radical is harbored in a polycyclic ring system (as that formed from **1**), prediction of its preferred facial reactivity is relatively straightforward from consideration of steric and stereoelectronic effects.[3] However, when the carbon radical is acyclic or monocyclic, the prediction of stereoselection in its reactions is often less clear.

We recently encountered this issue in our studies directed at the total synthesis of (−)-chromodorolide B,[4] wherein we considered the coupling of a chiral acetonide (2,2-dimethyl-1,3-dioxolane) trisubstituted radical (**A** or **B** of Figure 1 B) with (*R*)-methoxybutenolide **4** to unite three of the five rings in the diterpenoid natural product and form the vicinal C-12 and C-13 stereocenters. It seemed assured that butenolide **4** would react from the face *anti* to the methoxy substituent;[5] however, from which face radical intermediates **A** or **B** would couple to set the C-12 stereocenter was not apparent. Barton had shown that disubstituted acetonide radicals such as **C** (Figure 1 C) react with high selectivity *anti* to the substituent adjacent to the radical center.[6] However, we are aware of only two related studies in which the acetonide radical carbon is trisubstituted.[7] Renauld showed that stereoselection in radical couplings

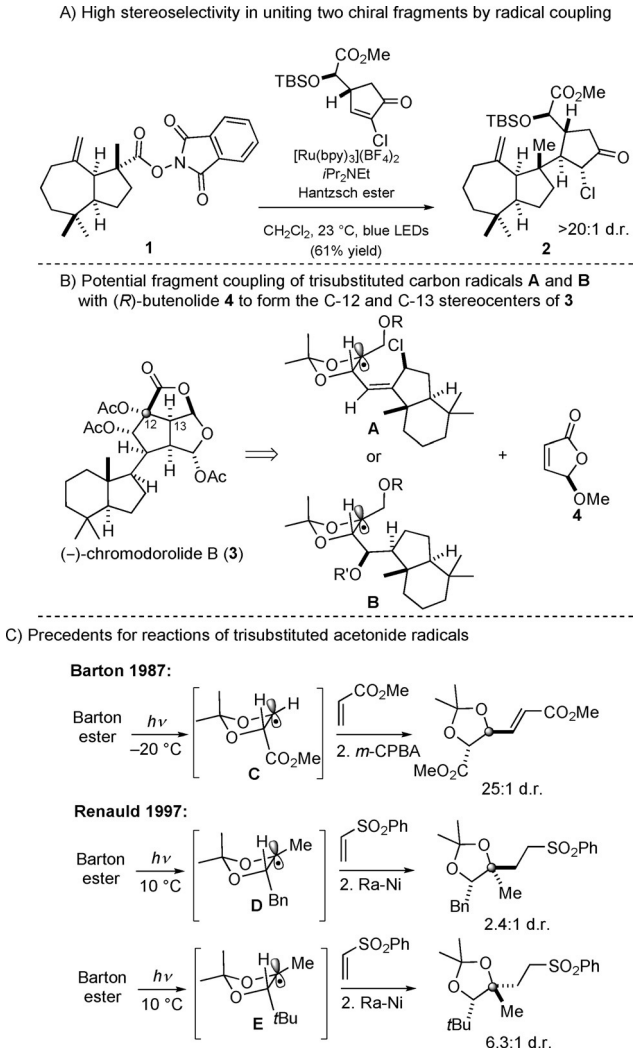

Figure 1. A) An example of the utility of bimolecular radical couplings to stereoselectively unite complex chiral fragments; B) a proposed diastereoselective coupling of this type in route to the diterpenoid (−)-chromodorolide B; and C) existing precedents for diastereoselectivity in reactions of chiral acetonide radicals with alkenes; Barton ester = 1-(acyloxy)-2(1*H*)-pyridinethione.

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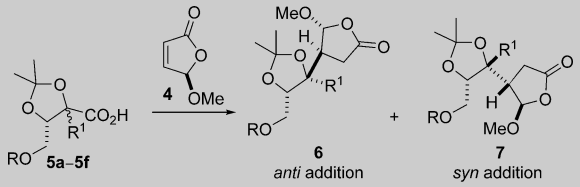
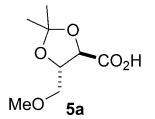
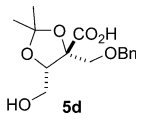
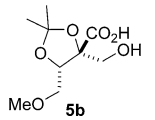
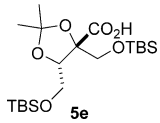
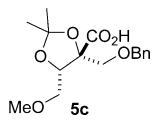
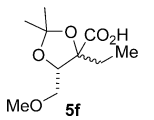
of this type was dependent on the nature of the β-substituent (compare reactions of radical intermediates **D** and **E**, Figure 1 C).[7a] In our exploratory investigations of the reaction of radicals of structure **B** (Figure 1 B) with butenolide **4**, we observed that stereoselection was quite sensitive to the nature of the alcohol-protecting groups R and R′. A systematic study of diastereoselection in radical coupling reactions of this type, involving both an experimental and computational analysis, is the subject of this report.

Our initial studies examined radical additions of structurally simple acetonide radicals, generated by visible-light photoredox catalyzed fragmentation of carboxylic acids[8] to chiral butenolide **4**. Employing a slight modification of MacMillan's conditions for generating the carbon radical,[8] we first examined the coupling of the disubstituted radical generated from acid **5a**. As expected, addition occurred preferentially *anti* to the adjacent methoxymethyl substituent (Table 1, entry 1).[6,9] We then turned our attention to precursors that would yield trisubstituted radical intermediates. In entries 2–5, the radical center bore a hydroxymethyl or protected-hydroxymethyl substituent, and addition occurred with low stereoselectivity *syn* to the β substituent. Only when the substituent at the radical center was an ethyl group was *syn* stereoselectivity high (9.3:1, entry 6). The relative configurations of products **6** and **7** were assigned by ^{1}H NOE experiments and confirmed in the case of the major product **7f** by single-crystal X-ray analysis.[10]

Table 1. Coupling of acetonide radicals generated by decarboxylation of acetonide acids **5a**-**5f** with (*R*)-methoxybutenolide **4**.[a]



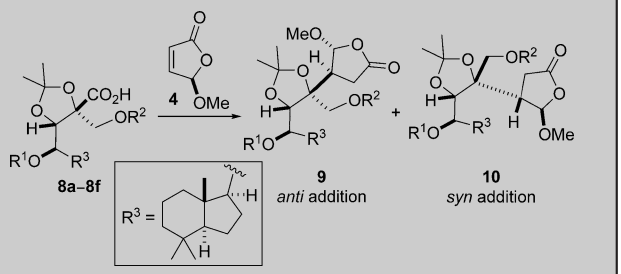
Entry	Acid	*anti*/*syn*[b] [% yield][c]	Entry	Acid	*anti*/*syn*[b] [% yield][c]
1	 **5a**	3.5:1 (37%)	4	 **5d**	1:2.6 (66%)
2	 **5b**	1:3.3 (54%)	5	 **5e**	1:2.2 (67%)
3	 **5c**	1:2.8 (64%,84%[d])	6	 **5f**	1:9.3 (68%)

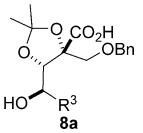
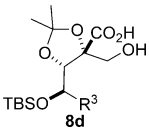
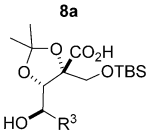
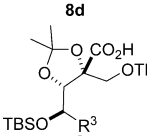
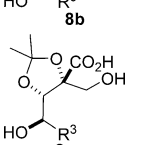
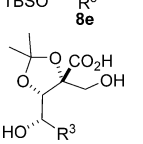
[a] Reaction conditions: 1.0 equiv of **5a**–**5f**, 1.1 equiv of **4**, 2 mol% of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, 1.1 equiv of K_2HPO_4, 10 equiv of H_2O in DME (0.1 M) at rt for 18 h with 34 W blue LEDs. [b] Diastereoselectivity determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard. [c] Isolated yield after silica gel chromatography. [d] Concentration = 0.4 M.

Having confirmed that trisubstituted acetonide radicals in this series react with butenolide **4** preferentially in a *syn* fashion, which is required for the synthesis of (−)-chromodorolide B (**3**),[4] we turned to examine structurally more elaborate substrates that harbored the trimethylhydrindane fragment found in **3** (Table 2). Because of the scarcity of the more elaborate radical precursors in this series and limited solubility of diol carboxylic acid precursor **8c**, the coupling reactions reported in Tables 1 and 2 were performed under identical conditions at a concentration of 0.1 M in DME. It should be recognized that a higher reaction concentration typically improves the yield of bimolecular radical coupling reactions of this type.[4,5] For example, carrying out the coupling reactions of precursors **5c** and **8e** at 0.4 M instead of 0.1 M increased the yield of the coupled products by more than 30%.

We anticipated that the greater bulk of the trimethylhydrindane fragment would result in enhanced *syn* stereoselection in the reactions reported in Table 2.[7] However, we found that depending upon the nature of the oxygen substituents R^1 and R^2

Table 2. Coupling of acetonide radicals generated by decarboxylation of trimethylhydindane-bearing acetonide acids **8a**–**8f** with (*R*)-methoxybutenolide **4**.[a]

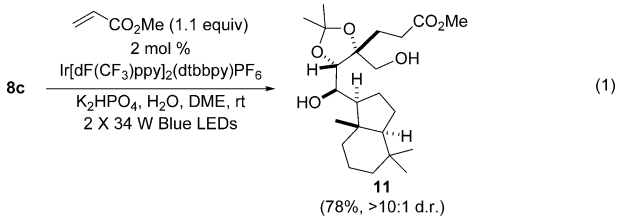


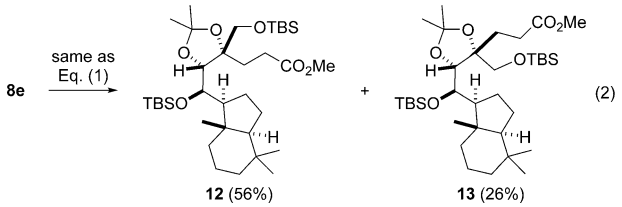
Entry	Acid	*anti*/*syn*[b] [% yield][c]	Entry	Acid	*anti*/*syn*[b] [% yield][c]
1	 **8a**	1.2:1 (49%)[d]	4	 **8d**	1:7.0 (22%)[d]
2	 **8b**	1.3:1 (71%)	5	 **8e**	1:8.2[e] (37%, 50%[g])
3	 **8c**	9.8:1[e] (45%)[f]	6	 **8f**	1:2.6 (43%)

[a] Reaction conditions: 1.0 equiv of **8a**–**8f**, 1.1 equiv of **4**, 2 mol% of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, 1.1 equiv of K_2HPO_4, 10 equiv of H_2O in DME (0.1 M) at rt for 18 h with 34 W blue LEDs. [b] Diastereoselectivity determined by ^{1}H NMR spectroscopy using an internal standard. [c] Isolated yield after silica gel chromatography. [d] Yield of the major product only. [e] Within experimental uncertainty, the isomer ratio was constant over time: **8c** 9.4:1 at 3 h, 9.3:1 at 6 h; **8e** 1:8.5 at 3 h, 1:8.6 at 6 h. [f] 45% combined yield by ^{1}H NMR analysis with an internal standard. The major diastereoisomer was isolated in 27% yield. [g] Concentration = 0.4 M.

of the acetonide carboxylic acid precursors **8**, either high *anti* or *syn* stereoselectivity was observed. When both oxygen substituents are alcohols (entry 3), *anti* stereoselection was 9.8:1; whereas when these substituents are *tert*-butyldimethylsiloxy groups, formation of the *syn* stereoisomer was favored by 8.2:1 (entry 5).

To validate that the dramatic reversal in stereoselectivity between the trisubstituted acetonide radicals generated from **8c** and **8e** was not unique to butenolide radical acceptor **4**, these acids were also coupled with methyl acrylate. In this case, product **11** was formed in high yield and >10:1 *anti* stereoselectivity from diol acid **8c** [Eq. (1)], whereas the bis-TBS precursor **8e** provided preferentially product **12** resulting from *syn* addition with 2.1:1 stereoselectivity [Eq. (2)].





Since the stereoselectivities reported in Table 2 cannot be explained by simple steric arguments, extensive electronic structure calculations were performed to develop a rationale for the observed results. Our best theoretical estimates achieve excellent agreement with the experimental results observed in the reaction of trisubstituted acetonide radicals derived from carboxylic acid precursors **5** and **8** with butenolide **4** (Figure 2). The computational methodology includes extensive sampling of conformational freedom, thermal corrections within the quasi rigid-rotor harmonic-oscillator approximation,[11] geometry optimization using the TPSS-D3[12,13] functional, and single-point calculations at the random-phase approximation (RPA) level. RPA is parameter free and more accurate than state-of-the-art semi-local density functional theory for barrier heights;[14] moreover, RPA is comparable in computational cost to conventional second-order Møller-Plesset (MP2) theory but more reliable for weak interactions,[15] especially for the radical species considered here. Further details of the computational methodology and its validation are provided in the Supporting Information.

The observed selectivity arises from the free energy difference between two transition states (TS), TS-*anti* and TS-*syn* (Figure 3), which lead to the products of *anti* and *syn* addition respectively. In TS-*anti*, the R^1 and R^2 substituents are *cis* to each other, and the butenolide **4** is on the sterically less hindered side of the acetonide radical; in TS-*syn*, the R substituents are in a *trans* orientation and the butenolide **4** is on the sterically less favorable side of the radical.

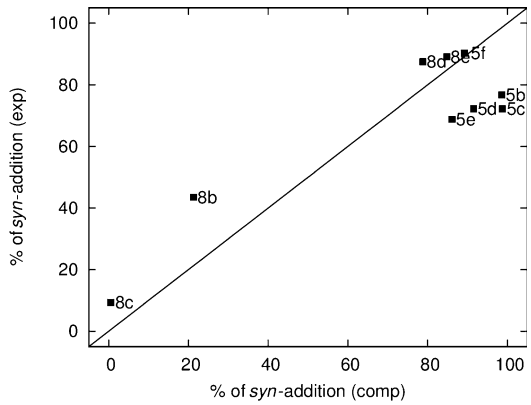


Figure 2. Correlation plot of experimental and computed (using RPA/def2-TZVP//TPSS-D3/def2-TZVP) diastereoselectivities of the reaction of trisubstituted acetonide radicals formed from carboxylic acids **5** and **8** with methoxybutenolide **4**.

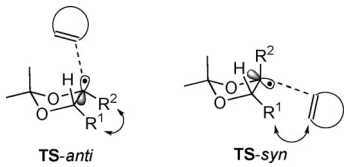


Figure 3. Transition state (TS) models for *anti* (TS-*anti*) and *syn* (TS-*syn*) additions. The distance between the acetonide radical and butenolide **4** is from 2.3 Å to 2.7 Å, depending on the complex. The arrow indicates non-covalent interactions, which can be attractive or repulsive.

Our results suggest that the selectivity is mainly determined by two effects: 1) Non-covalent interactions between R^1 and R^2; and 2) non-covalent interactions between the acetonide radical and the butenolide **4**. The magnitude and sign of these interactions depends strongly on the size and functionalization of R^1 and R^2 on the acetonide radical.

For the reactions of trisubstituted acetonide radicals reported in Table 1, the repulsion between R^1 and R^2 dominates (effect 1) and *syn* stereoselectivity is observed. This conclusion is also supported by Renauld's experiments (Figure 1C) showing mostly *syn* addition when R^1 is a bulky *tert*-butyl group.[16] Effect (2) is less important in these cases, because the butenolide **4** is at a distance of ~2.4 Å from the acetonide radical in the TS according to our computations. This result is also experimentally supported by the stereoselectivities observed in the reaction of acetonide radicals formed from **8c** and **8e**, which does not change qualitatively when butenolide **4** is replaced by methyl acrylate.

For the reactions of certain radicals reported in Table 2, hydrogen bonding can significantly stabilize TS-*anti*.[17] This effect is illustrated by the lowest-energy TS-*anti* conformers for the coupling of radicals formed from **8b**, **8c** and **8d** (Figure 4), where the R-groups interact by a hydrogen-bond to form a seven-membered ring. The length of the H-bond correlates with the selectivity: it is shortest for **8c**, which also has the

highest *anti*-selectivity; and longest for **8d**, which favors *syn*-selectivity. In transition structure **8d**-*anti*, the structure is also in general sterically more crowded, which explains the large *syn*-selectivity. However, apart from hydrogen bonding, other noncovalent interactions such as electrostatic, induction and dispersion interactions also affect the reaction stereoselectivity. Thus, quantitative predictions of reaction stereoselectivities require accurate computations of the energy and entropy of both proposed transition states. The computational analysis reported here rationalizes all observed results for trisubstituted acetonide radicals, including why hydrogen bonding contributes significantly for **8c** but not for **5b** and **5d**.

Although our computational analysis predicts the stereoselectivities of reactions of trisubstituted acetonide radicals accurately, it does not predict the *anti*-selectivity of reaction of disubstituted radical formed from acid **5a** with methoxybutenolide **4** correctly. This is likely caused by small overestimation of the stability of TS-*syn* (~1 kcal mol^{-1}), which is also observed for other radicals produced from precursors **5**.[18] This is within the expected accuracy of our methods and illustrates their scope and limitations in predicting the selectivity of large synthetically relevant chemical systems.

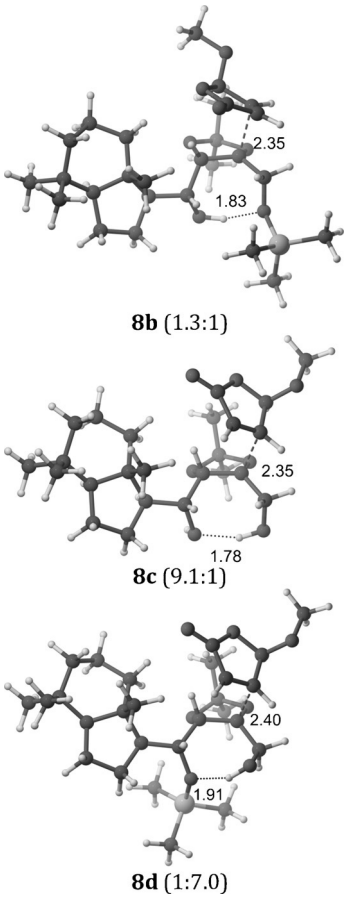


Figure 4. The *anti*-transition states for reactions of acetonide radicals formed from **8b**, **8c**, and **8d** with butenolide **4** and their *anti*/*syn* selectivities. The structures are optimized using TPSS-D3/def2-TZVP and the TBS-groups were replaced by TMS-groups for computational simplicity.

In summary, the coupling of chiral trisubstituted acetonide radicals with electron-deficient alkenes takes place predominantly from the face *syn* to a β substituent (TS-*syn*) to minimize non-covalent interactions between bulky substituents at the α and β carbons. However, stabilizing intramolecular hydrogen bonding between hydroxyl groups at C-1 of these substituents can lead to a preference for reaction from the face *anti* to the β substituent. The selectivities arise from a delicate balance of noncovalent interactions and their prediction requires high-level computational models of diastereomeric transition states.

Acknowledgements

Experimental studies were supported by the U. S. National Science Foundation (CHE1265964) and U. S. National Institute of General Medical Sciences by research grant R01M098601 and a graduate fellowship award to Y.S. (1F31M113494). NMR spectra, mass spectra, and the X-ray analyses were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation grants. Computational material is based upon work supported by the National Science Foundation under CHE-1464828. Prof. Dr. Stefan Grimme is acknowledged for providing the thermo-program for quasi-RRHO corrections and Dr. Vamsee Voora for his help with setting up RPA computations.

Keywords: ab initio calculations · alkenes · radical reactions · stereoselectivity

[1] a) M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576; *Angew. Chem.* **2012**, *124*, 9714; b) Y. Sun, R. Li, W. Zhang, A. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 9201; *Angew. Chem.* **2013**, *125*, 9371; c) D. S. Müller, N. L. Untiedt, A. P. Dieskau, G. L. Lackner, L. E. Overman, *J. Am. Chem. Soc.* **2015**, *137*, 660.

[2] K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401.

[3] For reviews of stereoselectivity in reactions of carbon radicals, see: a) B. Giese, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969–980; *Angew. Chem.* **1989**, *101*, 993–1004; <lit b>D. P. Curran, N. A. Porter, B. Giese in *Stereochemistry of Radical Reactions*, Wiley-VCH, Weinheim, **1996**; c) G. Bar, A. F. Parsons, *Chem. Soc. Rev.* **2003**, *32*, 251; d) Y.-H. Yang, M. P. Sibi in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Vol. 2 (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Hoboken, **2012**, pp. 655–692.

[4] D. J. Tao, Y. Slutskyy, L. E. Overman, *J. Am. Chem. Soc.* **2016**, *138*, 2186.

[5] G. L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 15342.

[6] a) D. H. R. Barton, A. Gateau-Olesker, S. D. Gero, B. Lacher, C. Tachdjian, S. Z. Zard, *J. Chem. Soc. Chem. Commun.* **1987**, 1790; b) D. H. R. Barton, A. Gateau-Olesker, S. D. Gero, B. Lacher, C. Tachdjan, S. Z. Zard, *Tetrahedron* **1993**, *49*, 4589.

[7] a) M. Gerster, P. Renauld, *Synthesis* **1997**, 1261; b) K. Yamada, Y. Yamamoto, M. Maekawa, K. Tomioka, *J. Org. Chem.* **2004**, *69*, 1531.

[8] L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 10886.

[9] This lower stereoselectivity observed in the reaction of entry 1 is not a reflection of a chirality mismatch between the (*R*)-methoxy butenolide **4** and the chiral radical, as the coupling of the *S* enantiomer of **4** with the radical generated from **5a** gave a 4.0:1 ratio of the products of *anti* and *syn* addition. The nature of the butenolide radical acceptor and the 40 °C difference in reaction temperature must be responsible for the lower stereoselectivity that we observe compared to that reported by Barton. Our experiments were conducted with the (*R*)-bute-

nolide **4** because this enantiomer was required for the synthesis of (−)-chromodorolide B.[4]

[10] a) Diagnostic NOE enhancements are shown in the Supporting Information; b) CCDC 146074 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[11] S. Grimme, *Chem. Eur. J.* **2012**, *18*, 9955.

[12] a) S. Grimme, J. Antony, S. Ehrlich, H. J. Krieg, *Chem. Phys.* **2010**, *132*, 154104; b) S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456.

[13] J. Tao, J. P. Perdew, V. N. Staroverov, G. E. Scuseria, *Phys. Rev. Lett.* **2003**, *91*, 146401.

[14] H. Eshuis, J. E. Bates, F. Furche, *Theor. Chem. Acc.* **2012**, *131*, 1084.

[15] H. Eshuis, F. Furche, *J. Chem. Phys.* **2012**, *136*, 084105.

[16] A rationale related to the one we advance here was suggested by Gerster and Renauld.[7a].

[17] For early examples of the effect of hydrogen-bonding on stereoselectivity in reactions of carbon free radicals, see: a) D. J. Hart, R. Krishnamurthy, *J. Org. Chem.* **1992**, *57*, 4457; b) S. Hanessian, H. Yang, R. Schaum, *J. Am. Chem. Soc.* **1996**, *118*, 2507; c) S. Hanessian, H. Yang, *Tetrahedron Lett.* **1997**, *38*, 3155; and references [2d], [4], [5] and [9] therein.

[18] The Boltzmann distribution is exponential, and small energetic errors accumulate: 1 kcal mol^{-1} error changes the selectivity from 2.3:1 to 1:2.3 ($\pm$0.5 kcal mol^{-1}).

Received: April 27, 2016
Published online on May 30, 2016