ORGANIC LETTERS

2012
Vol. 14, No. 23
5844–5847

Enantioselective Synthesis of Spiroacetals via Silver(I)-Promoted Alkylation of Hemiacetals: Total Synthesis of Cephalosporolides E and F

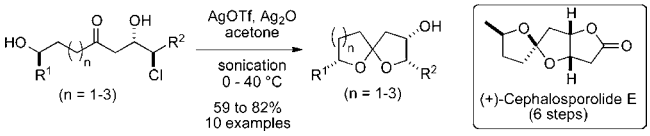
Stanley Chang and Robert Britton*

Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada

rbritton@sfu.ca

Received September 28, 2012

ABSTRACT



A silver(I)-promoted intramolecular hemiacetal alkylation has been developed that converts readily available keto-chlorodiols into functionalized spiroacetals containing 5,5-, 5,6-, and 5,7-membered ring systems. The efficiency of this process is demonstrated in a concise total synthesis of the fungal metabolites cephalosporolides E and F.

Spiroacetals are important structural components in many biologically active natural products, including several insect sex pheromones, polyketide antibiotics, and microtubule stabilizing agents.[1,2] Additionally, a growing family of 5,5-spiroacetal-containing fungal metabolites have been described, and several members of this family possess potentially useful biological activities.[3] For example, the cephalosporolides, penisporolides, and ascospiroketals (Figure 1) all possess a 5,5-spiroacetal motif and several of these compounds demonstrate anti-inflammatory activities.[3] Accordingly, the stereocontrolled syntheses of spiroacetals has been the subject of a large body of research.[1,2,4] Classical synthetic approaches to spiroacetals involve the dehydration of ketodiols,[4] oxa-Michael additions,[5] cycloadditions,[6] intramolecular hydrogen abstractions,[7] and furan oxidations.[8] Palladium(II)- or gold(I)-catalyzed cycloisomerization

(1) For reviews, see: (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699. (b) Fletcher, M. T.; Kitching, W. *Chem. Rev.* **1995**, *95*, 789. (c) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395. (d) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (e) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (f) Booth, Y.; Kitching, W.; De Voss, J. J. *Nat. Prod. Rep.* **2009**, *26*, 490.

(2) Zinzalla, G.; Milroy, L.-G.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1977.

(3) Li, X.; Yao, Y.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharm. Res.* **2007**, *30*, 812.

(4) For a review, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. For selected examples, see: (a) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Moessner, C. *Chem. Commun.* **2006**, 4186. (b) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 1083. (c) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennet, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783.

(5) For selected examples, see: (a) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. (b) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. (c) Iwata, C.; Hattori, K.; Uchida, S.; Imanishi, T. *Tetrahedron Lett.* **1984**, *25*, 2995. (d) Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; Imanishi, T. *Tetrahedron Lett.* **1985**, *26*, 2221. (e) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063. (f) Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1.

(6) (a) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1954**, 672. (b) Ireland, R. E.; Häbich, D. *Tetrahedron Lett.* **1980**, *21*, 1389. (c) Ireland, R. E.; Häbich, D. *Chem. Ber.* **1981**, *114*, 1418. (d) Sauvé, G.; Schwartz, D. A.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 2929. (e) Tietze, L. F.; Schneider, C. *J. Org. Chem.* **1991**, *54*, 2476. (f) Pale, P.; Bouquant, J.; Chuche, J.; Carrupt, P. A.; Vogel, P. *Tetrahedron* **1994**, *50*, 8035. (g) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365. (h) Wu, K.-L.; Wilkinson, S.; Reich, N. O.; Pettus, T. R. R. *Org. Lett.* **2007**, *9*, 5537. (i) Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.-L.; Pettus, T. R. R. *Org. Lett.* **2008**, *10*, 1477.

(7) For a recent review, see: Sperry, J.; Liu, Y.-C.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 29.

(8) (a) Bohlmann, F.; Jastrow, H.; Ertingshausen, G.; Kramer, D. *Chem. Ber.* **1964**, *97*, 801. (b) Dedek, V.; Trska, P.; Hofeditz, R. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3565. (c) Feringa, B. L.; Butselaar, R. J. *Tetrahedron Lett.* **1982**, *23*, 1941. (d) Feringa, B. L.; Butselaar, R. J. *Tetrahedron Lett.* **1983**, *24*, 1193. (e) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901. (f) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 2044. (g) Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Gleason, J. L. *J. Org. Chem.* **1992**, *57*, 5071. (h) Robertson, J.; Meo, P.; Dallimore, J. W. P.; Doyle, B. M.; Hoarau, C. *Org. Lett.* **2004**, *6*, 3861. (i) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001.

(9) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279.

10.1021/ol302694s
Published on Web 11/12/2012

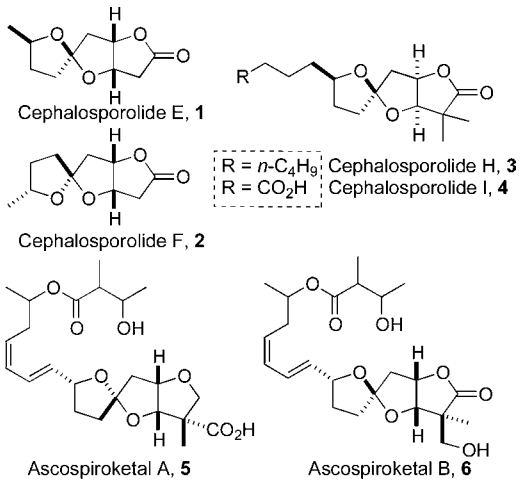
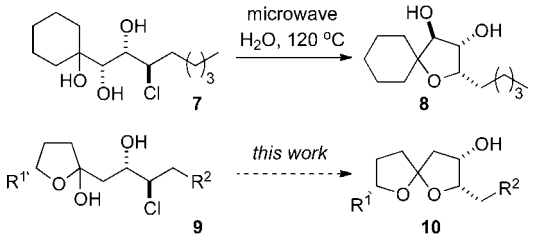


Figure 1. 5,5-Spiroacetal-containing natural products.

processes[9,10] involving alkynes as ketone surrogates have also been reported.[11] Within the context of our ongoing efforts to expand the utility of chlorohydrins in stereocontrolled heterocycle/natural product synthesis, we previously reported a general process for the preparation of tetrahydrofuranols (e.g., **8**; Scheme 1) that involved simple heating of chloropolyols in water.[12] Our success in the formation of the spirocyclic tetrahydrofuran **8** prompted us to examine a novel synthetic approach to spiroacetals that would involve intramolecular alkylation of a hemiacetal with an unactivated alkyl chloride (e.g., **9**; Scheme 1).[13] The development of this concise, stereocontrolled spiroacetal synthesis as well as its application in the syntheses of spiroacetal-containing fungal metabolites (e.g., cephalosporolides E (**1**) and F (**2**))[14] are detailed below.

Scheme 1. Synthesis of Tetrahydrofuran **8** and a Hemiacetal Alkylation Strategy for Spiroacetal Synthesis



As indicated in Table 1, we initially attempted to effect the spiroacetalization of ketochlorohydrin **11** utilizing conditions reported by us for the annulation of chlorotriol **7** (Scheme 1).[12] Unfortunately, heating of **11** in a variety of solvents at various temperatures led only to the production of 1-hydroxy-4,6-decandione or 2-(3-hydroxypropyl)-5-propylfuran (not shown). We next evaluated Ag-promoted cyclizations of **11**, following our earlier reported preparation of tetrahydrofuranols from chloropolyols.[15] As indicated in entry 1, treatment of ketochlorohydrin **11** with a combination of AgOTf/Ag_2O[15] in THF afforded a 1:1 mixture of the desired epimeric spiroacetals **12**, albeit in modest and variable yield (20−53%). Unfortunately, an exhaustive screen of both Ag(I) reagents and bases failed to identify improved conditions for this reaction (e.g., Table 1, entries 2−6). The effect of solvent was also examined, and it was found that the spiroacetalization occurred cleanly in both DMF and acetone and required significantly less time in the latter solvent (entry 7) in which spiroacetals **12** were produced in 69% yield. It is notable that Ag_2O plays a crucial role in this process by converting formed trifluoromethanesulfonic acid (TfOH) into AgOTf,[16] effectively buffering the reaction media. While it is conceivable then that substoichiometric amounts of AgOTf and/or Ag_2O would also promote the desired transformation, use of less than 1 equiv of either reagent required extended reaction times that coincided with increased formation of byproducts (e.g., furans), and lower isolated yields of the desired spiroacetals **12**. As part of an exhaustive evaluation of reaction conditions, repetition of the reaction described in entry 7 without stirring led to rapid decomposition of the starting material. As the conversion of TfOH into AgOTf occurs on the surface of the largely insoluble Ag(I) particles, this result inspired us to repeat this reaction with sonication, in an effort to increase the surface area and buffering capacity of the Ag_2O. Gratifyingly, as indicated in entry 12 (Table 1), repetition of the reaction described in entry 7 with sonication not only lowered the reaction time but also improved the reproducibility and overall yield of the reaction to 79%.

(10) Cycloisomerization of alkynes have also been reported through the use of platinum, mercury, rhodium, and iridium; see: (a) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (b) Yamamoto, M.; Yoshitake, M.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1983**, 991. (c) Ravinder, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420. (d) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (e) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, *78*, 385. (f) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031.

(11) For selected examples of alkyne cycloisomerization processes in total synthesis, see: (a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987. (b) Trost, B. M.; Weiss, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7664. (c) Trost, B. M.; O'Boyle, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 16190. (d) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698. (e) Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2011**, *7*, 570.

(12) Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716.

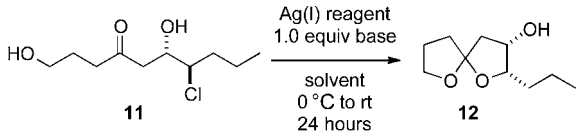
(13) A single example of an intramolecular alkylation of a hemiacetal with a benzylic chloride via solvolysis has been reported; see: Kishi, O. *J. Chem. Soc., Chem. Commun.* **1986**, 885.

(14) For the isolation and biological evaluation of cephalosporolides E (**1**) and F (**2**), see: (a) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843. (b) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953. (c) Oller-López, J. L.; Iranzo, M.; Mormeneo, S.; Oliver, E.; Cuerva, J. M.; Oltra, J. E. *Org. Biomol. Chem.* **2005**, *3*, 1172.

(15) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717.

(16) Brice, T. J.; Trott, P. W. (Minnesota Mining & Manufacturing Co.). Fluorocarbon sulfonic acids and derivatives. US Patent 2,732,398, January 24, 1956.

Table 1. Reaction Optimization for Formation of Spiroacetal **12**



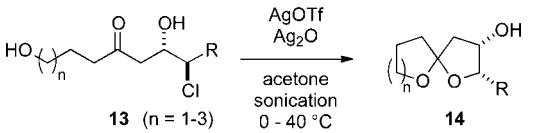
11 **12**

entry	reagent	base	solvent	yield **12**[a] (%)
1	AgOTf	Ag_2O	THF	20–53[b]
2	$AgPF_6$	Ag_2O	THF	19
3	$AgBF_4$	Ag_2O	THF	60
4	$AgSbF_6$	Ag_2O	THF	44
5	AgOTf	AgOAc	THF	49
6	AgOTf	Ag_2CO_3	THF	32
7	AgOTf	Ag_2O	acetone	69
8	AgOTf	MgO	acetone	43
9	AgOTf	NaOAc	acetone	30
10	AgOTf	K_2CO_3	acetone	3
11	AgOTf	Ag_2O	acetone	0[c]
12	AgOTf	Ag_2O	acetone	79[b,d]

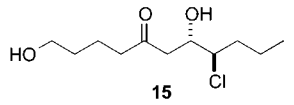
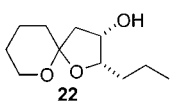
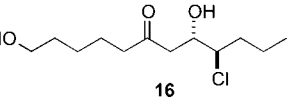
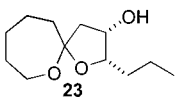
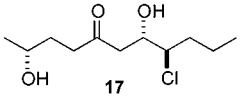
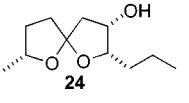
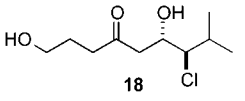
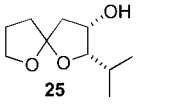
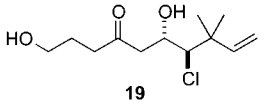
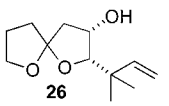
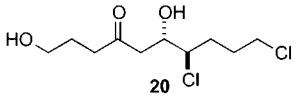
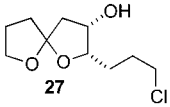
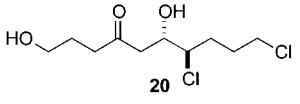
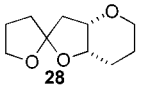
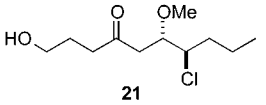
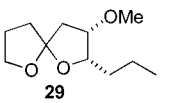
[a] Assay yield based on analysis of ^{1}H NMR spectra recorded on crude reaction mixtures with internal standard. [b] Isolated yield. [c] Reaction performed without stirring. [d] Reaction performed with stirring and sonication, 0–40 °C, 17 h.

Having optimized production of the 5,5-spiroacetals **12** from ketochlorohydrin **11**,[17] the scope of this transformation was investigated through the conversion of a range of ketochlorodiols **15**–**21** into the corresponding spiroacetals. As indicated in Table 2, the formation of 5,5-, 5,6-, and 5,7-spiroacetals[18] proceeded in good yields (71 to 79%) using the optimized reaction conditions (Table 1, entry 12). While secondary alcohols were good substrates for this reaction (Table 2, entry 3), branching at the position adjacent to the chloromethine function slowed the reaction considerably, and led to lower isolated yields of the corresponding spiroacetals (e.g., Table 2, entry 4). In this latter case, the yield of **25** could be improved to 75% through the use of 2.0 equiv of both AgOTf and Ag_2O. Not surprisingly then, the presence of a quaternary center adjacent to the chloromethine function (Table 2, entry 5) reduced the reactivity entirely. While various other combinations of Ag(I) salts/bases failed to effect the formation of spiroacetals from **19**, the desired spiroacetal **26**, which bears structural resemblance to the cephalosporolides (e.g., **3** and **4**, Figure 1), was available in modest yield by heating the ketochlorodiol **19** for extended periods of time in pH 7 buffer.[12] Interestingly, subjection of the dichloride **20** to the optimized conditions (Table 2, entry 6) resulted in the formation of spiroacetal **27** in good yield (65%), whereby the primary alkyl chloride function did not react.

Table 2. Synthesis of 5,5-, 5,6-, and 5,7-Spiroacetals



13 (n = 1-3) **14**

entry	chlorohydrin	product	yield (%)
1	 **15**	 **22**	74
2	 **16**	 **23**	71
3	 **17**	 **24**	72
4	 **18**	 **25**	46 75[a]
5	 **19**	 **26**	0 22[b]
6	 **20**	 **27**	65 82[c]
7	 **20**	 **28**	31[a] 66[d]
8	 **21**	 **29**	59

[a] 2.0 equiv of AgOTf and Ag_2O. [b] 50 °C in pH 7 buffer for 5.5 days. [c] 1.0 equiv of $AgPF_6$ and AgOAc, 0 °C to rt, 8 h. [d] Following addition of NaH to **27** in THF (yield over two steps).

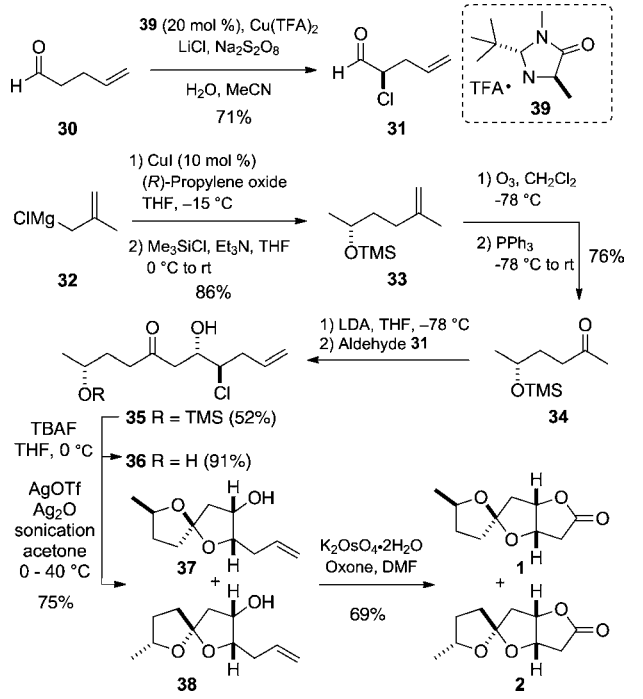
The yield for this material could be further improved by use of a combination of $AgPF_6$ and AgOAc (82%). Notably, while increasing the equivalents of silver reagents resulted in the formation of small amounts of the tricycles **28** (entry 7), formation of the tetrahydropyran ring in **28** could be effected in good yield by treatment of the crude 5,5-spiroacetals **27** with sodium hydride (66% yield over two steps). As indicated in entry 8, the methyl ether **21** also proved to be an effective substrate for this reaction,

(17) General procedure for formation of spiroacetals: To a cold (0 °C), stirred, and sonicated 0.1 M solution of β-ketochlorohydrin (1 equiv) in acetone was added silver(I) oxide (1 equiv), and the resulting mixture was stirred for 5 min. Silver(I) trifluoromethanesulfonate (1 equiv) was then added, and the reaction mixture was stirred and sonicated for 17 h, over which time the temperature increased to 40 °C. The resulting mixture was then filtered through Celite, diluted with Et_2O, and washed with saturated aqueous $NaHCO_3$. The aqueous layer was then extracted with Et_2O, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography.

(18) Spiroacetals depicted in Table 2 epimerize at the spiroacetal center upon standing in various organic solvents (e.g., $CHCl_3$, Et_2O) and rapidly convert to the corresponding furan in mildly acidic media.

however, when a mixture containing equal amounts of **21** and **11** were subjected to the standard reaction conditions, the ketochlorohydrin **11** was consumed at a much faster rate. This result indicates that the free hydroxyl group adjacent to the chloromethine function in chlorodiols **15**–**20** may play a key role by coordinating to the Ag(I) reagent and facilitating activation of the chloromethine function.

Scheme 2. Total Synthesis of Cephalosporolides E and F



Finally, this novel spiroacetal formation strategy was applied to the synthesis of both cephalosporolides E (**1**) and F (**2**).[19] As depicted in Scheme 2, the synthesis of **1** and **2** initiated with the enantioselective α-chlorination[20] of commercially available 4-pentenal (**30**) to afford the chloroaldehyde **31** in good yield. The required methyl ketone **34** was prepared following a standard sequence of reactions involving copper-mediated addition of 2-methylallylmagnesium chloride to (*R*)-propylene oxide[21] followed by direct treatment with chlorotrimethylsilane and subsequent oxidative cleavage. A lithium aldol reaction between the methyl ketone **34** and α-chloroaldehyde **31** afforded the ketochlorohydrin **35** in good yield and excellent diastereoselectivity (dr >13:1). Removal of the TMS protecting group then revealed the key spiroacetalization substrate **36**. Gratifyingly, subjection of this latter material to the optimized reaction conditions for spiroacetal formation led to the smooth production of spiroacetals **37** and **38**, which were isolated in excellent yield (75%). Finally, the pendant alkene was cleaved under oxidative conditions[22] to provide cephalosporolides E (**1**) and F (**2**). The spectral data derived from these compounds (^{1}H NMR, ^{13}C NMR, HRMS, IR) were in complete agreement with that reported in the literature.[23]

In summary, we have developed a novel spirocyclization method that involves the use of inexpensive silver(I) reagents and readily available ketochlorohydrins. Spiroacetals containing 5,5-, 5,6-, and 5,7- motifs as well as other more elaborate systems have been synthesized and studied. This process was also applied in a total synthesis of cephalosporolides E (**1**) and F (**2**). Notably, the synthesis of these natural products (six steps, 16% overall yield) compares well with those reported for this class of compounds and highlights this silver-promoted spiroacetalization strategy as an effective means to access both these and other biologically active spiroacetals, work that is currently ongoing in our laboratory.

Acknowledgment. This work was supported by an NSERC Discovery Grant to R.B., a Michael Smith Foundation for Health Research Career Investigator Award to R.B., and a NSERC Postgraduate Scholarship to S.C.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) For previous syntheses, see: (a) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842. (b) Fernandes, R. A.; Ingle, A. B. *Synlett* **2010**, *1*, 158. (c) Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P.; O'Connor, P. D. *Tetrahedron Lett.* **2011**, *67*, 995. (d) Tlais, S. F.; Dudley, G. B. *Beilstein. J. Org. Chem.* **2012**, *8*, 1287.

(20) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121.

(21) Castaldi, M. P.; Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 3362.

(22) (a) Schomaker, J. M.; Travis, B. R.; Borhan, B. *Org. Lett.* **2003**, *5*, 3089. (b) Harb, H. Y.; Collins, K. D.; Altur, J. V. G.; Bowker, S.; Campbell, L.; Procter, D. J. *Org. Lett.* **2010**, *12*, 5446.

(23) The specific rotation for synthetic (+)-**1**: $[\alpha]^{20}_D$ +35 (*c* 0.40, $CHCl_3$) [lit.[19c] $[\alpha]^{20}_D$ +27.3 (*c* 0.41, $CHCl_3$)]. The specific rotation for synthetic (−)-**2**: $[\alpha]^{20}_D$ −71 (*c* 0.56, $CHCl_3$) [lit.[19b] $[\alpha]^{25}_D$ −69.1 (*c* 0.15, $CHCl_3$)]. Despite these similarities, these values differ from other reported specific rotations for both natural and synthetic samples of these compounds, which also differ significantly. The variance in reported specifc rotations for **1** and **2** may relate to the propensity of both diastereomers to rapidly epimerize at the spiroacetal center.

The authors declare no competing financial interest.