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# Enantiopure 1,4-Diols and 1,4-Aminoalcohols via Stereoselective Acyclic Sulfoxide−Sulfenate Rearrangement

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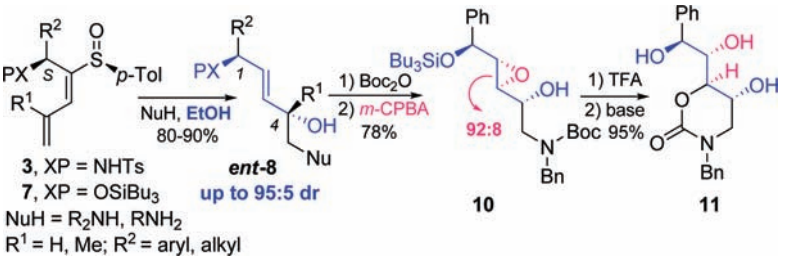
## ABSTRACT




**Treatment of acyclic α-hydroxy and α-tosylamino sulfinyl dienes with amines affords enantiopure 1,4-diol or 1,4-hydroxysulfonamide derivatives in good yields and diastereoselectivities. This one-pot procedure entails a conjugate addition that triggers a diastereoselective sulfoxide−sulfenate [2,3]-sigmatropic rearrangement.**

The diastereoselective preparation of acyclic 1,4-diols and 1,4-aminoalcohols constitutes an important field in synthetic organic methodology[1] and natural product synthesis.[2] In contrast to 1,2-, 1,3-, or 1,5-derivatives, there are few general methods to prepare these targets. On the other hand, unsaturated systems have attracted considerable attention due to their presence in natural products or their precursors[3] and the potential in being converted into interesting saturated derivatives. The main strategies developed to achieve stereocontrol in the synthesis of acyclic unsaturated 1,4-diols entail the addition of organometallic reagents,[4] or terminal alkynes,[5] to carbonyl derivatives. Alternatively, the stereoselective reduction of functionalized ketones has also been described, however with some substrate limitations.[6] Other recent methods have relied on 1,4-hydroxycarbonyl compounds,[7] epoxides,[8] or 1,3-dienes.[9]

Comparatively, the diastereoselective preparation of substituted 2-ene-1,4-aminoalcohol derivatives has been scarcely documented. Some of the approaches reported

(1) For leading examples on 1,4-diols: (a) Knapp, K. M.; Goldfuss, B.; Knochel, P. *Chem.—Eur. J.* **2003**, *9*, 5259–5265. (b) Martín-Matute, B.; Edin, M.; Bäckvall, J.-E. *Chem.—Eur. J.* **2006**, *12*, 6053–6061. (c) Bach, J.; Berenguer, R.; García, J.; López, M.; Manzanal, J.; Vilarrasa, J. *Tetrahedron* **1998**, *54*, 14947–14962. (d) Solladié, G.; Huser, N.; García-Ruano, J. L.; Adrio, J.; Carreño, M. C.; Tito, A. *Tetrahedron Lett.* **1994**, *35*, 5297–5300. (e) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569–592. (f) Tortosa, M. *Angew. Chem., Int. Ed.* **2011** (DOI: 10.1002/anie.201100613). For 1,4-aminoalcohols: Bäckvall, J. E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826–831.

(2) (a) König, C. M.; Gebhardt, B.; Schleth, C.; Dauber, M.; Koert, U. *Org. Lett.* **2009**, *11*, 2728–2731. (b) Kim, H. C.; Kang, S. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1827–1829.

(3) (a) Kobayashi, Y.; Asano, M.; Yoshida, S.; Takeuchi, A. *Org. Lett.* **2005**, *7*, 1533–1536. (b) Motoyoshi, H.; Ishigami, K.; Kitahara, T. *Tetrahedron* **2001**, *57*, 3899–3908.

(4) (a) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981–1998. (b) Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 5849–5852. (c) Bloch, R.; Brillet, C. *Tetrahedron: Asymmetry* **1992**, *3*, 333–336.

(5) (a) Amador, M.; Ariza, X.; García, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, *43*, 2691–2694. (b) Diez, R. S.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341–8344.

(6) (a) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1994**, *59*, 2676–2678. (b) Bach, J.; Berenguer, R.; García, J.; Loscertales, T.; Manzanal, J.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1091–1094. (c) See ref 1c.

(7) Hayashi, Y.; Yamaguchi, H.; Toyoshima, M.; Nasu, S.; Ochiai, K.; Shoji, M. *Organometallics* **2008**, *27*, 163–165.

(8) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *Org. Lett.* **2005**, *7*, 2305–2308.

(9) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134–9135.

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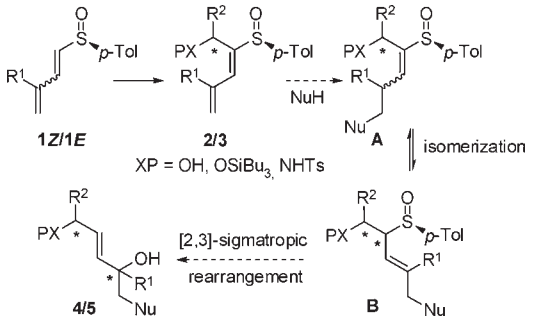
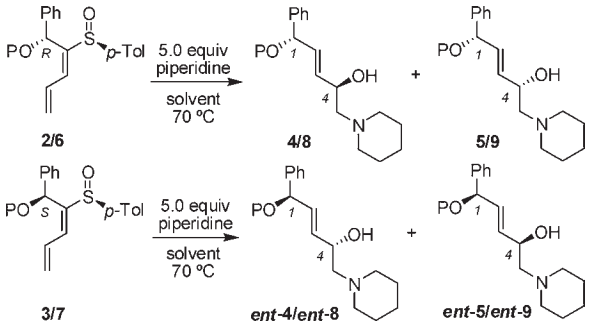
involve Pd-catalyzed allylic substitution,[10] enantioselective alkylation of 4-aminoaldehydes,[11] or reductive cleavage of functionalized cycloadducts.[12]

**Scheme 1.** Proposed Reaction Pathway




In recent years, readily available dienyl alcohols and amines **2** and **3** (Scheme 1) have been successfully applied to the stereoselective synthesis of a wide variety of heterocycles and densely functionalized products.[13] Within this context, and in connection with our interest in the [2,3]-sigmatropic rearrangement of allylic sulfoxides,[14] we envisioned that a conjugate addition of a suitable nucleophile[13d] would produce a vinyl sulfoxide **A**[15] that could undergo base-induced isomerization to allylic sulfoxide **B** with a thermodynamically favored *E*-alkene geometry. The diastereoselective formation of **B**, influenced by the contiguous chiral centers as well as the stereochemical outcome of the ensuing [2,3]-sigmatropic rearrangement would lead, after sulfenate cleavage, to valuable acyclic 1,4-diol or 1,4-aminoalcohol derivatives **4** and **5**. The [2,3]-sigmatropic rearrangement of allylic sulfoxides has been widely exploited for the preparation of optically pure allylic alcohols;[16] however, relatively few examples exist of the diastereocontrolled acyclic variant.[17]

**Table 1.** Solvent Screening for Synthesis of 1,4-Diols




| entry | SM | P | solvent | major product | *anti*/*syn* dr (yield %)[a,b,c] |
|---|---|---|---|---|---|
| 1 | **2a** | H | EtOH | **4a** | 60:40 (89) |
| 2 | **3a** | H | EtOH | *ent*-**4a** | 55:45 (90) |
| 3 | **2a** | H | toluene | **4a** | 90:10 (97) |
| 4 | **3a** | H | toluene | *ent*-**5a** | 35:65 (78) |
| 5 | **2a** | H | DMF | **4a** | 80:20 (72) |
| 6 | **3a** | H | DMF | *ent*-**5a** | 40:60 (90) |
| 7 | **6a** | $SiBu_3$ | EtOH | **8a** | 60:40 (88) |
| 8 | **7a** | $SiBu_3$ | EtOH | *ent*-**8a** | 90:10 (92) |
| 9 | **6a** | $SiBu_3$ | toluene | **8a** | 60:40 (93) |
| 10 | **7a** | $SiBu_3$ | toluene | *ent*-**8a** | 85:15 (92) |
| 11 | **6a** | $SiBu_3$ | DMF | **8a** | 82:18 (91) |
| 12 | **7a** | $SiBu_3$ | DMF | *ent*-**8a** | 78:22 (92) |

[a] Ratio determined by $^1$H NMR analysis. [b] Combined yield. [c] Absolute configuration at C-4 was determined by derivatization with (*S*)-MPA.

We began our investigation by submitting alcohols **2a** and **3a**,[18] epimers at C-1, to treatment with piperidine in ethanol. Unfortunately, equimolecular mixtures of the desired 1,4-diols were obtained for both diastereomers (Table 1, entries 1 and 2). In contrast, the use of toluene led to a clear improvement of diastereoselectivity for diastereoisomer **2a** that led to **4a** in excellent dr (Table 1, entries 3 and 4). The use of DMF did not improve the diastereoselectivities found with toluene (Table 1, entries 5 and 6).

Having established the viability of the process, we envisioned that protection of the hydroxyl group could improve

(10) (a) Farthing, C. N.; Kočovský, P. *J. Am. Chem. Soc.* **1998**, *120*, 6661–6672. (b) Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676–3686. (c) Pyne, S. G.; Dong, Z. *Tetrahedron Lett.* **1999**, *40*, 6131–6134.

(11) Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron* **1998**, *54*, 6385–6402.

(12) Martin, S. F.; Hartmann, M.; Josey, J. A. *Tetrahedron Lett.* **1992**, *33*, 3583–3586.

(13) (a) Fernández de la Pradilla, R.; Castellanos, A.; Osante, I.; Colomer, I.; Sánchez, M. I. *J. Org. Chem.* **2009**, *74*, 170–181. (b) Viso, A.; Fernández de la Pradilla, R.; Ureña, M.; Colomer, I. *Org. Lett.* **2008**, *10*, 4775–4778. (c) Fernández de la Pradilla, R.; Alhambra, C.; Castellanos, A.; Fernández, J.; Manzano, P.; Montero, C.; Ureña, M.; Viso, A. *J. Org. Chem.* **2005**, *70*, 10693–10700. (d) Fernández de la Pradilla, R.; Manzano, P.; Montero, C.; Priego, J.; Martínez-Ripoll, M.; Martínez-Cruz, L. A. *J. Org. Chem.* **2003**, *68*, 7755–7767.

(14) Fernández de la Pradilla, R.; Lwoff, N.; del Águila, M. A.; Tortosa, M.; Viso, A. *J. Org. Chem.* **2008**, *73*, 8929–8941.

(15) At short reaction times small amounts of vinyl sulfoxides **A** are frequently isolated, leading to **4/5** under reaction conditions.

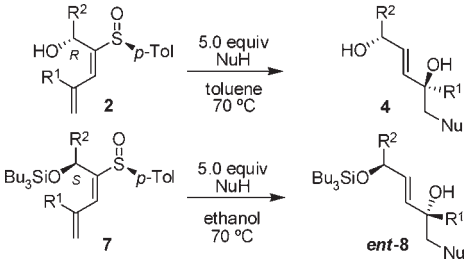
(16) (a) Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421–3426. (b) Grieco, P. A.; Finkelhor, R. S. *J. Org. Chem.* **1973**, *38*, 2245–2247. (c) Vedejs, E.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4357–4364. (d) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.

(17) (a) Motofumi, M.; Toriyama, M.; Kawakubo, T.; Yasukawa, K.; Takido, T.; Motohashi, S. *Org. Lett.* **2010**, *12*, 3882–3885. (b) Raghavan, S.; Vinoth Kumar, V.; Raju Chowhan, L. *Synlett* **2010**, 1807–1810. (c) The SPAC (Sulfoxide Piperidine And Carbonyl) reaction involves the isomerization from vinyl to allylic sulfoxides, followed by [2,3]-sigmatropic rearrangement in acyclic systems. For leading references, see: (d) Nokami, J.; Kataoka, K.; Shiraishi, K.; Osafune, M.; Hussain, I.; Sumida, S.-I. *J. Org. Chem.* **2001**, *66*, 1228–1232. (e) Guerrero de la Rosa, V.; Ordóñez, M.; Llera, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1089–1094. (f) Domínguez, E.; Carretero, J. C. *Tetrahedron Lett.* **1990**, *31*, 2487–2490. Some diastereoselective examples of this process, see: (g) Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1991**, *56*, 3189–3192. (h) Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050–2058. (i) Burgess, K.; Henderson, I. *Tetrahedron* **1991**, *47*, 6601–6616.

(18) Dienyl sulfoxides **1** are available in one step using the procedure by Craig: Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263–11304. Lithiation and trapping with aldehydes or sulfonimines lead to the substrates of this study **2**/**3**.

the diastereocontrol and lead to differentially protected 1,4-diols. Thus, silyl ethers **6a** and **7a** were submitted to the reaction conditions. In ethanol, while **6a** yielded a 60:40 mixture of 1,4-diols **8a** and **9a**, diastereoisomer **7a**, with an *S* configuration at C-1, afforded ***ent*-8a** with highly improved diastereoselectivity (90:10, Table 1, entries 7 and 8). The use of toluene did not significantly alter the results found in ethanol (Table 1, entries 9 and 10). Finally, **6a** (C-1 *R*) led to a significant improvement in selectivity in DMF and **7a** (C-1 *S*) gave a slightly less selective mixture (Table 1, entries 11 and 12). In conclusion, each epimer at C-1 (**2a** and **7a**) holds a favorable array of stereocenters under the appropriate reaction conditions to afford *anti* 1,4-diol derivatives with high yields and selectivities.

**Table 2.** Scope of the Method for Synthesis of 1,4-Diols



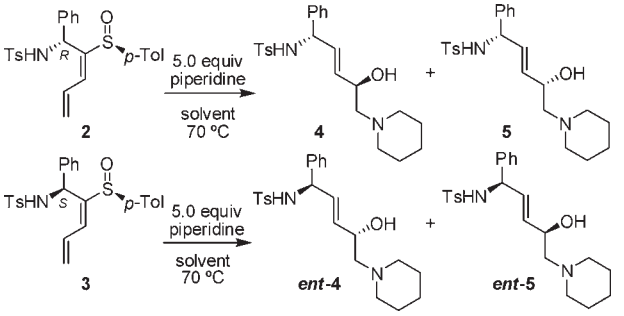

| entry | SM | $R^1$ | $R^2$ | NuH | *anti/syn* dr (yield %)[a,b,c] |
|---|---|---|---|---|---|
| 1 | **2a** | H | Ph | piperidine | 90:10 (97) |
| 2 | **2c** | H | Et | piperidine | 85:15 (95) |
| 3 | **2d** | Me | Ph | piperidine | 90:10 (72) |
| 4 | **2a** | H | Ph | $BnNH_2$ | 85:15 (90) |
| 5 | **7a** | H | Ph | piperidine | 90:10 (92) |
| 6 | **7b** | H | 1-Napht | piperidine | 95:5 (90) |
| 7 | **7c** | H | Et | piperidine | 75:25 (91) |
| 8 | **7d** | Me | Ph | piperidine | 90:10 (81) |
| 9 | **7a** | H | Ph | $BnNH_2$ | 90:10 (85) |

[a] Ratio determined by $^1$H NMR analysis. [b] Combined yield. [c] Absolute configuration at C-4 was determined by derivatization with (*S*)-MPA.

The scope of the process was then examined by varying the nature of $R^1$, $R^2$, and the nucleophile on the stereoreinforcing diastereoisomer of the alcohol (**2**) in toluene. Thus, ethyl derivative **2c** led mainly to diol **4c** with slight erosion of the dr (Table 2, entry 2). The viability of generating a tertiary alcohol was examined by employing 4-substituted alcohol **2d** which led to the desired product **4d** in good yield and excellent diastereoselectivity (Table 2, entry 3). Finally, using benzylamine as the nucleophile did not significantly affect the reaction, affording **4a′** in good yield and stereoselectivity (Table 2, entry 4).

Similarly, the behavior of stereoreinforcing silylated isomer **7** in EtOH was examined, with better results for **7b** and with slightly diminished selectivity for **7c** (Table 2, entries 6 and 7). Introduction of a new substituent at C-4 afforded tertiary alcohol ***ent*-8d** again in good yield and excellent diastereoselectivity (Table 2, entry 8). Finally, the use of benzylamine produced ***ent*-8a′** with 90:10 dr (Table 2, entry 9).

**Table 3.** Diastereoselective Preparation of 1,4-Aminoalcohols




| entry | SM | solvent | major product | *anti/syn* dr (yield %)[a,b,c] |
|---|---|---|---|---|
| 1 | **2e** | EtOH | **4e** | 64:36 (85) |
| 2 | **3e** | EtOH | ***ent*-4e** | 60:40 (88) |
| 3 | **2e** | toluene | **4e** | 83:17 (70) |
| 4 | **3e** | toluene | ***ent*-4e** | 70:30 (79) |

[a] Ratio determined by $^1$H NMR analysis. [b] Combined yield. [c] Absolute configuration at C-4 was determined by derivatization with (*S*)-MPA.

To extend the scope of the method to the synthesis of 1,4-hydroxysulfonamides we briefly examined the behavior of sulfonamides **2e** and **3e** in EtOH and toluene. While the use of EtOH led to low diastereocontrol for both isomers (Table 3, entries 1 and 2), a significant enhancement of selectivity was found in toluene (Table 3, entries 3 and 4).[19]

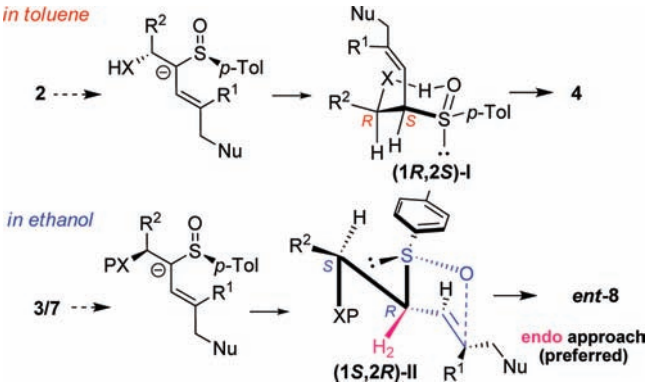
Our proposal to account for the stereochemical outcome of the process is shown in Scheme 2.[20] In toluene, an intramolecular hydrogen bond between the sulfoxide and the OH group would determine the major chairlike six-membered conformation for the allylic sulfoxides generated from **2**, resulting in epimer (1*R*,2*S*)-**I**, that has no serious 1,3-diaxial interactions, being more favored than (1*R*,2*R*)-**I** (not shown). Subsequent sigmatropic rearrangement would lead predominantly to *anti* 1,4-diols **4**. The decreased selectivity found for 1,4-aminoalcohols is consistent with the lower ability of the NH to form a hydrogen bond with the sulfinyl oxygen. Alternatively, in ethanol, gauche interactions would be responsible for the relative stability of allylic sulfoxides (1*S*,2*R*)-**II** vs (1*S*,2*S*)-**II** (not shown) generated from silyl ethers **7**. In reactive conformer (1*S*,2*R*)-**II**, allylic strain is also minimized by situating $H_2$ and $R^1$ (H or Me) in a 1,3-*syn* relative disposition and by positioning the substituents at $C_1$ to reduce the steric interaction with the sulfur *p*-tolyl group[21] to give *anti* ***ent*-8** with high diastereoselectivity.

(19) We are currently examining different nucleophiles to extend the scope of the process and improve the stereocontrol.

(20) For a full discussion see the Supporting Information.

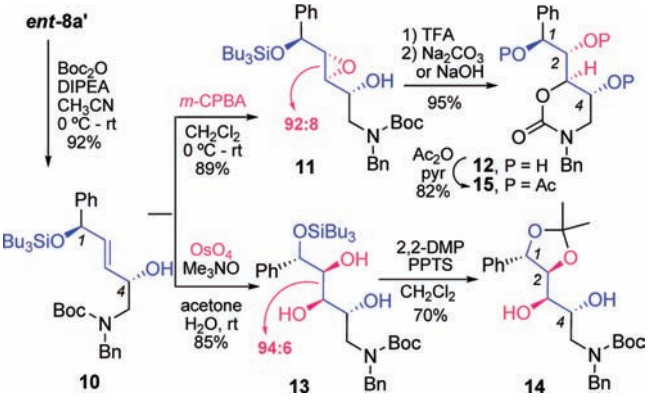
(21) (a) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1995**, *117*, 9077–9078. (b) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Org. Chem.* **1995**, *60*, 6682–6683.

**Scheme 2.** Stereochemical Outcome




To explore upcoming synthetic applications we have examined the reactivity toward epoxidation and dihydroxylation of diastereomerically pure carbamate **10** (Scheme 3), obtained from silyl ether ***ent*-8a′** (90:10) under standard conditions. Treatment of **10** with *m*-CPBA afforded epoxide **11** with high diastereoselectivity (92:8) and excellent yield.[22] Deprotection with TFA and subsequent treatment with base provided 1,3-oxazin-2-one **12**, regio- and stereoselectively through a nucleophilic carbamate oxygen attack on the epoxide.[23] Alternatively, dihydroxylation of **10** with a nonreinforcing array of stereocenters gave triol **13** with excellent yield and very high dr (94:6). The remarkable selectivity of this dihydroxylation of an acyclic substrate is noteworthy.[24] A reasonable explanation for this result, based on steric effects, could be found in a zigzag arrangement of the carbon chain, where the bulky silyl group would be in the plane of the chain. Then, $OsO_4$ would approach from the opposite face of the hydroxyl group at C-4, in an *anti* fashion. To secure the configuration of the new centers, we synthesized cyclic 1,3-dioxolane **14**, and after inspection of the NMR data, the coupling constant $J_{1,2}$ (8.9 Hz) revealed a trans configuration at C1−C2.[25]

**Scheme 3.** Stereoselective Epoxidation and Dihydroxylation




In summary, we have outlined a novel method for the diastereoselective synthesis of enantiopure unsymmetrical 1,4-diols and 1,4-hydroxysulfonamides from sulfinyl butadienes. This protocol involves a one-pot cascade of events consisting of an intermolecular conjugate addition, [2,3]-sigmatropic rearrangement of the *in situ* generated allylic sulfoxide, and sulfenate cleavage. We have illustrated the highly stereoselective dihydroxylation and epoxidation of our diol derivatives, as well as a regio- and stereoselective epoxide opening via intramolecular nucleophilic carbamate attack, leading to valuable enantiopure polyols. We are currently addressing the application of this process to the synthesis of natural products.

**Acknowledgment.** This research was supported by MICINN (CTQ2009-07752). We also thank CM for additional support to MU and MEC for a fellowship to I.C.

**Supporting Information Available.** Experimental procedures, compound characterization, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

(22) For similar results on *m*-CPBA epoxidation of 1,4-silyloxyalcohols: (a) Uchiyama, M.; Kimura, Y.; Ohta, A. *Tetrahedron Lett*. **2000**, *41*, 10013–10017. (b) Johnson, C. R.; Miller, M. W. *J. Org. Chem*. **1995**, *60*, 6674–6675. (c) Saito, S.; Itoh, H.; Ono, Y.; Nishioka, K.; Moriwake, T. *Tetrahedron: Asymmetry* **1993**, *4*, 5–8 and references therein.

(23) For related processes, see: (a) Yoshida, M.; Ohshima, M.; Toda, T. *Heterocycles* **1993**, *35*, 623–626. (b) Vanucci, C.; Brusson, X.; Verdel, V.; Zana, F.; Dhimane, H.; Lhommet, G. *Tetrahedron Lett*. **1995**, *36*, 2971–2974. (c) Urabe, H.; Aoyama, Y.; Sato, F. *Tetrahedron* **1992**, *48*, 5639–5646.

(24) For related dihydroxylations of nonreinforcing cyclic substrates, see: (a) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J. *Tetrahedron Lett*. **1991**, *32*, 7309–7312. (b) Arjona, O.; Candilejo, A.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J. *J. Org. Chem*. **1992**, *57*, 6097–6099. (c) Arjona, O.; de Dios, A.; Plumet, J.; Saez, B. *J. Org. Chem*. **1995**, *60*, 4932–4935. (d) Trost, B. M.; Crawley, M. L.; Lee, C. B. *Chem.—Eur. J*. **2006**, *12*, 2171–2187.

(25) It is known that vicinal coupling constants for *trans*-1,3-dioxolanes (8.0−9.0 Hz) are higher than those for cis isomers (6.0−7.0 Hz). See: (a) Anet, F. A. L. *J. Am. Chem. Soc*. **1962**, *84*, 747–752. (b) Adamczeski, M.; Quiñoá, E.; Crews, P. *J. Am. Chem. Soc*. **1988**, *110*, 1598–1602. (c) Adamczeski, M.; Quiñoá, E.; Crews, P. *J. Am. Chem. Soc*. **1989**, *111*, 647–654 and ref 24d.