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

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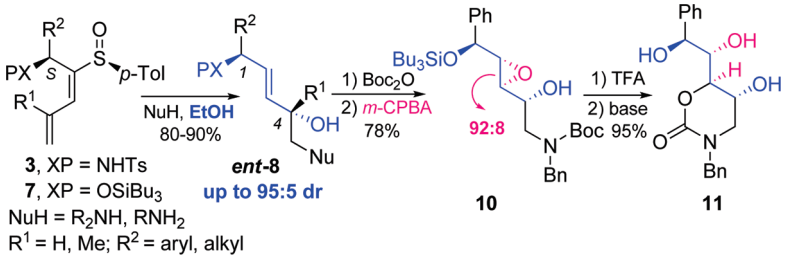
ABSTRACT



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

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

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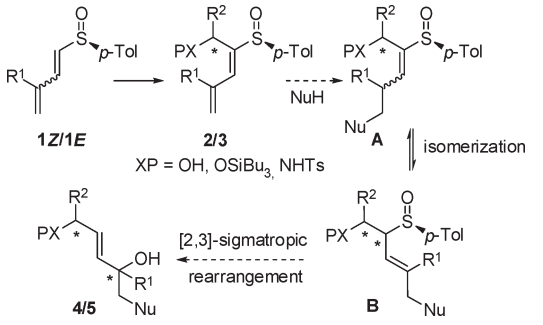
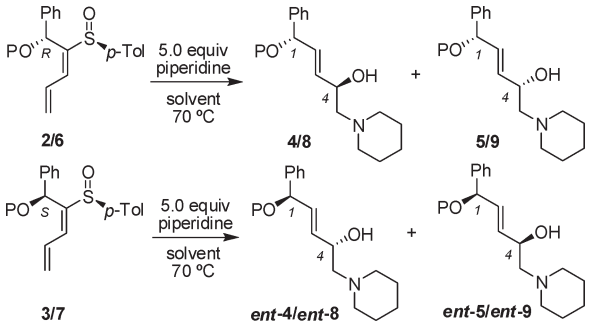
involve Pd-catalyzed allylic substitution,[10] enantioselective alkylation of 4-aminoaldehydes,[11] or reductive cleavage of functionalized cycloadducts.[12]

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

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(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.

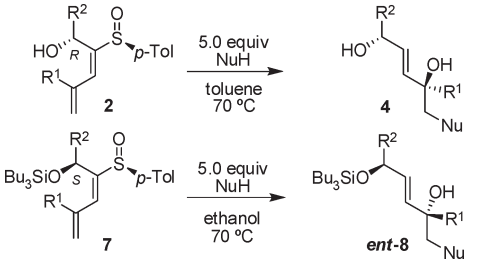
(16) (a) Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421–3426. (b) Grieco, P. A.; Finkelhor, R. S. *J. Org. Chem.* **1973**, *38*, 2245–2247. (c) Vedejs, E.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4357–4364. (d) Evans, D. A.; Andrews, G.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



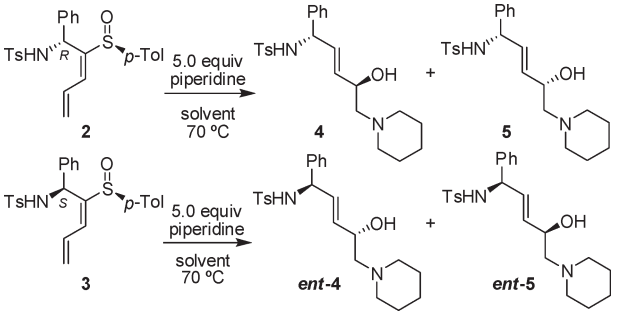
entry	SM	R^1	R^2	NuH	*anti/syn* dr (yield %)[a,b,c]
1	**2a**	H	Ph	piperidine	90:10 (97)
2	**2c**	H	Et	piperidine	85:15 (95)
3	**2d**	Me	Ph	piperidine	90:10 (72)
4	**2a**	H	Ph	$BnNH_2$	85:15 (90)
5	**7a**	H	Ph	piperidine	90:10 (92)
6	**7b**	H	1-Napht	piperidine	95:5 (90)
7	**7c**	H	Et	piperidine	75:25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

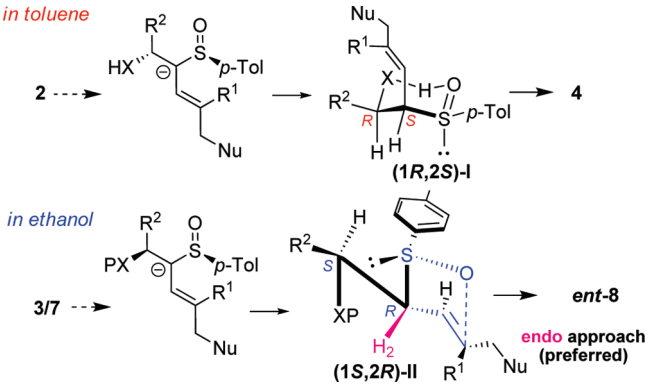
Our proposal to account for the stereochemical outcome of the process is shown in Scheme 2.[20] In toluene, an intramolecular hydrogen bond between the sulfoxide and the OH group would determine the major chairlike six-membered conformation for the allylic sulfoxides generated from **2**, resulting in 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.

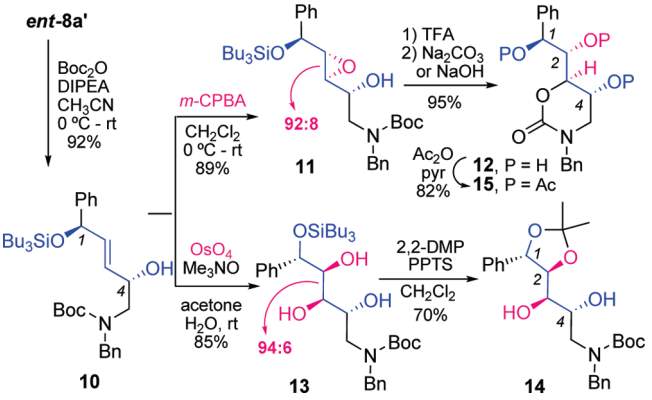
(21) (a) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1995**, *117*, 9077–9078. (b) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Org. Chem.* **1995**, *60*, 6682–6683.

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.