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Stereoselective Approach to Optically Pure *syn* 2-Amino Alcohol Derivatives

Jesús de Blas, Juan C. Carretero*, and Esteban Domínguez

Departamento de Química, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

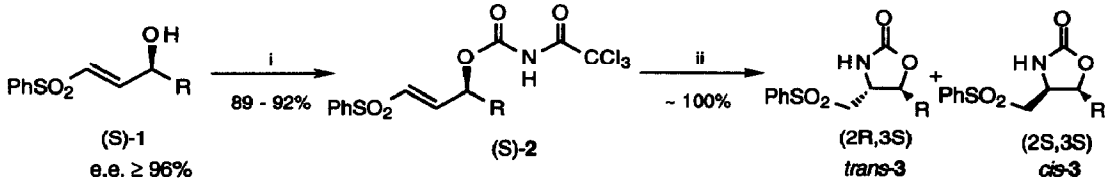
Abstract: *A highly stereoselective procedure for the preparation of a variety of syn 2-amino alcohol derivatives from enantiopure E-γ-hydroxy-α,β-unsaturated phenyl sulfones is described. The method is based on an intramolecular carbamate cyclization, followed by functionalization at α-position by reaction of the sulfonyl carbanion with electrophiles, and subsequent elimination of the sulfonyl group.*

The 2-amino alcohol unit[1] shows a widespread occurrence as a sub-structure in many biologically important natural products such as aminosugars, peptidic enzyme inhibitors, β-hydroxy-α-amino acids, glycosphingolipids and alkaloids. Furthermore, this kind of functionality has an increasing interest as peptidomimetics in pharmaceutical drug design. For instance, some C-2 symmetrical 2-amino alcohol derivatives are potent inhibitors of the protease of the human inmunodeficiency virus type 1 (HIV-1).[2] Thus, the development of general methods for the stereoselective and enantioselective synthesis of 2-amino alcohols is a matter of importance.[3] In this communication we report that a wide variety of optically pure *syn* 2-amino alcohols derivatives can be efficiently prepared in few steps starting from the readily available enantiopure γ-hydroxyvinyl sulfones **1**.[4]

To introduce stereoselectively the nitrogen moiety at β-position in substrates **1**, we applied the intramolecular carbamate cyclization of unsaturated alcohols reported by Hirama *et al* .[5] Alcohols (S)-**1** (ee > 96%) were converted to the trichloroacetylcarbamates (S)-**2** by treatment with a slight excess of CCl_3CONCO and K_2CO_3 in THF at r.t. After isolation and chromatographic purification (89-92% yield)[6], compounds (S)-**2** underwent mild cyclization under weakly basic conditions (K_2CO_3 in $MeOH/CH_2Cl_2$ at rt) to give the mixture of oxazolidinones **3** almost quantitatively.[7] As in the case of related 5-exo-trig carbamate cyclizations[5] the process was highly stereoselective affording *trans*-**3** as the major steroisomer regardless of the nature of R substituent (de= 82-92%, table 1). A significant increase in the stereoselectivity was observed with the increasing size of the R chain (R= Et de=82%, R= *n*-Bu de= 84%, R= *i*-Pr de=92%). The mixture of isomers **3** was readily separated by chromatography affording pure *trans*-**3** in excellent yields (80-94%, ee > 96%).[8] The stereochemical assignment of *cis*-**3** and *trans*-**3** was confirmed by ^{1}H-NMR.[9]

This procedure has also been applied to more complex optically pure γ-hydroxyvinyl sulfones[4c,d] (scheme 1). The reaction of **1d** and **1e** with CCl_3CONCO afforded the crude trichloroacetylcarbamates, which were directly treated under basic conditions. In both cases the reaction was highly stereoselective affording the corresponding *trans* oxazolidinones **3d** and **3e** in 85% and 70% yield, respectively, after silica gel chromatography.

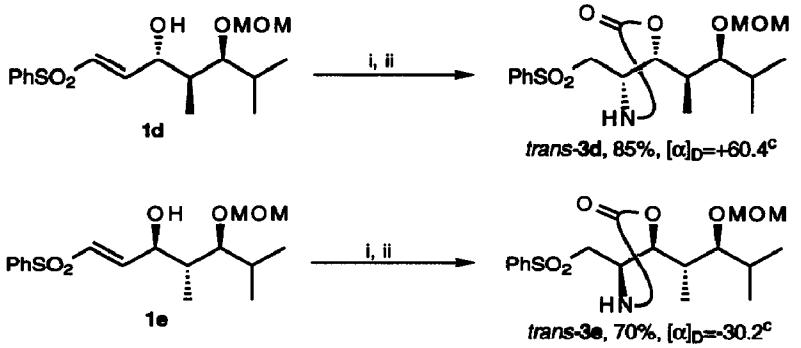
Table 1: Stereoselective preparation of α-sulfonyloxazolidinones **3** from vinyl sulfones (S)-**1**.



(S)-1	R	3	*trans:cis* [a]	de (%)	Yield *trans*-3 (%)[b]	$[\alpha]_D$[c]
1a	Et	**3a**	10 : 1	82	80	-67.2
1b	n-Bu	**3b**	11 : 1	84	81	-70.3
1c	i-Pr	**3c**	26 : 1	92	94	-77.3

[a] Determined by ^{1}H-RMN on the crude mixtures. [b] In pure product after silica gel chromatography. [c] (c=1 $CHCl_3$)

Scheme 1

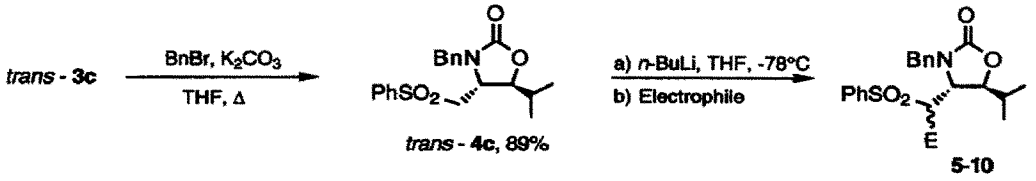


i: K_2CO_3 (1.2 eq), CCl_3CONCO (1.2 eq), THF, r.t.; ii: K_2CO_3 (1.1 eq), CH_2Cl_2:MeOH (1:1), r.t.

To prepare a variety of 2-amino alcohol derivatives by employing the nucleophilic character of the α-sulfonyl carbanion derived from sulfones *trans*-**3**, it was necessary to protect the acidic NH group.[10] Initially **3c** was protected as its BOC-derivative ($(BOC)_2O$, K_2CO_3, THF, rt; 93% yield). However, its α-sulfonyl carbanion, obtained by deprotonation with *n*-BuLi at -78°C, was rather unstable rapidly evolving by elimination of the β-nitrogen functionality with subsequent double bond formation[11]. In order to decrease the ability as a leaving group of the nitrogen functionality, *trans*-**3c** was protected as its benzyl derivative **4c** (benzyl bromide, K_2CO_3, THF, reflux; 85% yield). Really, after deprotonation of *trans*-**4c** with *n*-BuLi (1.1 equiv) in THF at -78°C and further reaction with several electrophiles (MeI, $BrCH_2CO_2Et$, PhCHO, *i*-PrCHO, $ClCO_2Et$ and $MeSO_2SMe$)[12] the substituted products **5-10** were achieved in high yields, usually as mixtures of epimers at α position (59 - 98% after chromatography, table 2).

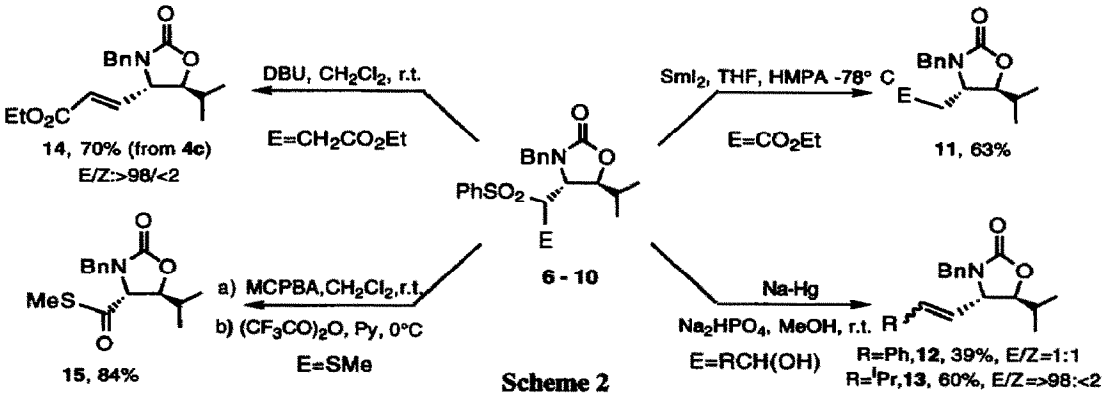
To show the synthetic interest of sulfones **5-10** in the preparation of differently functionalyzed oxazolidinones of *syn* 2-amino alcohols, four different methods for the elimination of the sulfonyl group were used (scheme 2). The reductive elimination fo the sulfonyl group in sulfone **9** (E= CO_2Et) by treatment with SmI_2 in THF-HMPA at -78°C afforded the ester **11** in 63% yield.[13] Additionally, the β-hydroxy sulfones **7** and **8** (E= PhCHOH and *i*-PrCHOH) rapidly reacted with Na(Hg) in methanol at rt to give the corresponding olefins **12** (E/Z=1:1) and **13** (E/Z=>98:<2) in 39% and 60% yield respectively. In the case of sulfone **9**, which bears an acid hydrogen at β-position, the elimination of the sulfonyl group was carried out under basic conditions (DBU, CH_2Cl_2, rt) to give the E-α,β-unsaturated ester **14** in 70% overall yield (from **4c**). Finally, substrate **10** was converted into the thioester **15** (synthetic equivalent of a β-hydroxy-α-amino acid) in 84% yield by applying the oxidative elimination strategy based on a Pummerer reaction reported for related compounds.[5a]

Table 2: Reaction of *trans*-**4c** with electrophiles.



Entry	Electrophile (equiv, temp, time)	Product	E	Isomer ratio[a]	Yield(%)[b]
1	MeI (5, -78° to r.t, 15 min)	**5**	Me	>98:<2	79
2	$BrCH_2CO_2Et$ (2,-78° to r.t, 30 min)	**6**	CH_2CO_2Et	4:1	59
3	PhCHO (2, -78°C, 1 h)	**7**	CH(OH)Ph	1:1[c]	98
4	*i*-PrCHO (2, -78°C, 1 h)	**8**	CH(OH)*i*-Pr	3:1[c]	82
5	$ClCO_2Et$ (5, -78° to r.t, 30 min)	**9**	CO_2Et	2:1	75[d]
6	$MeSO_2SMe$ (2, -78°C, 15 min)	**10**	SMe	1:1	71

[a] Determined by ^{1}H-NMR on the crude mixtures. [b] In pure product after chromatography. [c] Only two isomers were detected by ^{1}H-NMR. [d] 23% of *trans*-**4c** was also recovered (97% yield in converted product).



Scheme 2

In summary a wide variety of oxazolidinones of *syn* 2-amino alcohols have been readily prepared in a highly stereoselective manner from enantiomerically pure E-γ-hydroxy-α,β-unsaturated phenyl sulfones. The application of this methodology to the synthesis of natural aminosugars is underway.

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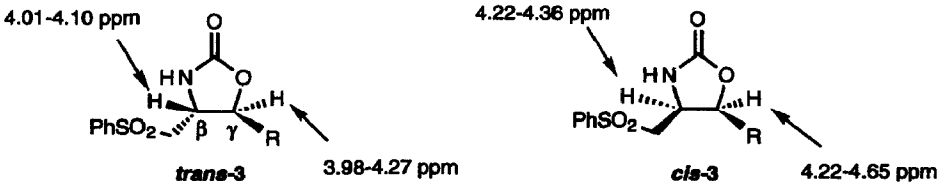
6.- Carbamates **2** can be directly used in the cyclization step without previous chromatographic purification. In this case higher overall yields in the preparation of *trans*-**3** (from **1**) were obtained. For instance, 94% overall yield of *trans*-**3c** was obtained without purification of (S)-**2c** instead of 85% overall yield from purified (S)-**2c**.

7.- General procedure for the preparation of *trans*-**3**: To a solution of 4.6 g of substrate (S)-**1c** in dry THF (65 ml) were added at rt 3.3 g (1.2 equiv) of K_2CO_3. The mixture was stirred during 30 min and then 2.84 ml (1.2 equiv) of $Cl_3CCONCO$ were slowly added. After 3 h at rt (control by tlc) the solvent was evaporated and the residue (crude (S)-**2c**) was dissolved in a 1:1 mixture of MeOH:THF. To this solution 3.0 g (1.1 equiv) of K_2CO_3 were added and the reaction was stirred during 4h at rt. Then, 65 ml of saturated solution NH_4Cl were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to afford 5.6 g (100 %) of a 26:1 mixture of *trans:cis* oxazolidinones **3c**. After flash chromatography (hexane/ethyl acetate 2:5) 5.3 g (94 %) of pure *trans*-**3c** were obtained.

8.- As it was expected the carbamate cyclization took place without epimerization at the γ-quiral center. The optical purity of *trans*-**3**, determined by ^{1}H-NMR in the presence of Pr(hfc)$_3$ (0.3 equiv), was higher than 96%.

9.- As in other substituted oxazolidinones (see for instance ref. 3e and 5a) the chemical shifts of H_β and H_γ in the *cis*-isomers are always higher than in the *trans* isomers (values in $CDCl_3$).



10.- For instance, the reaction of the dianion derived from **3c** (prepared by reaction with 2 equiv of n-BuLi) with 1 equiv of $ClCO_2Et$ gave a mixture of C-substituted, N-substituted and disubstituted products.

11.- For the use of β-*t*-butoxycarbonylamino sulfones in the synthesis of α-amino acids, see: Pauly, R.; Sasaki, N.A.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 237 and references cited therein.

12.- However the reaction with ketones did not occur. Only enolate formation was observed in the reaction with cyclohexanone and acetone.

13.- In the reaction of 5 and 9 with excess of Na (Hg) at r.t., the sulfonyl group was eliminated with simultaneous cleavage of the C-N bond and subsequent double bond formation.

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