

A stereodivergent synthesis of β -hydroxy- α -methylene lactone via vinyl epoxides

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General informations

NMR spectra were recorded on a Bruker DPX 250 (^1H : 250 MHz, ^{13}C : 63 MHz) or on a Bruker DRX 400 (^1H : 400 MHz, ^{13}C : 100 MHz) instruments in CDCl_3 unless indicated otherwise. Data appear in the following order: chemical shift δ in ppm, multiplicity (s singlet, d doublet, t triplet, m multiplet), number of protons, coupling constant J in Hz. TMS is the internal standard for the CDCl_3 solutions.

IR spectra were recorded on a Perkin-Elmer Spectrum-One ATR spectrophotometer. Vibrations ν were reported in cm^{-1} .

Mass spectra were recorded on a Varian GC/MS/MS instrument equipped with CP 3800 (GC) and Saturn 2000 (MS/MS) modules.

Exact mass spectra were recorded on a Waters Q-TOF Micro apparatus (LC/MS) with a Xterra MS column.

Purification by flash¹ chromatography of compounds was achieved with Merck 60 silica gel (40-63 μm).

Thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (1.1 mm, Merck) and the plates were visualised with UV light (254 nm), a potassium permanganate solution (1 g with 2 g of K_2CO_3 in 200 mL of water) or a phosphomolybdic acid solution (1 g in 100 mL of *i*-PrOH).

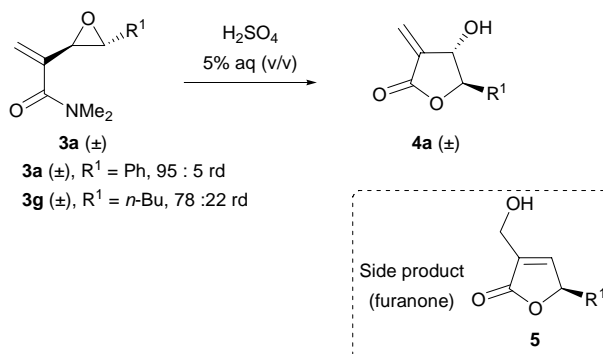
All reagents and solvents are commercially available and used without further purification unless otherwise noted.

Dry solvents were obtained from a PURESOLVTM apparatus developed by Innovative Technology Inc. (<http://www.solventpurification.com>). Toluene, CH_2Cl_2 , MeCN, THF and ether were passed through activated alumina columns under nitrogen pressure. Toluene was also treated by mean of a copper column to remove traces of oxygen. The content of water was measured with a Coulometer (Karl Fisher method). The system provided solvent with 5-15 ppm of water.

¹ Still W. C., Kahn M., Mitra A., *J. Org. Chem.*, **1978**, *43*, 2923.

Optimisation of the lactonisation of epoxide 3a

Scheme 1



R ¹	Acid	Solvent	Temp (°C)	Time	Conv ^a (%)	Yield 4 (%)	dr ^b (<i>trans/cis</i>)
Ph	H ₂ SO ₄ 6M (cat.)	THF	rt	21 h	100	15 ^c	92:8
Ph	H ₂ SO ₄ 5% aq	H ₂ O	60	0,5 h	100	13	64:36
Ph	HCl 2M	H ₂ O	60	1,5 h	100	14 ^c	52:48
Ph	BF ₃ .Et ₂ O	THF	0 to rt	3 h	100	0	-
Ph	Bi(OTf) ₂ (5 mol%)	MeCN/H ₂ O ^d	rt à 80	1 d	0	-	-
Ph	TFA, H ₂ O	THF	0 à rt	2 d	100	traces	100:0
Ph	APTS.H ₂ O	MeCN	Rt to 80	22 h	100	0	-
Ph	HClO ₄	H ₂ O/THF	rt	1 d	8	-	-
Ph	HClO ₄	H ₂ O/THF	40	3 d	0	-	-
Ph	Tartaric acid	H ₂ O/THF	rt	1 d	100	-	93:7
<i>n</i> -Bu	H ₂ SO ₄ 10% aq	H ₂ O	60	6,5 h	100	30	76:24
<i>n</i> -Bu	H ₂ SO ₄ 10% aq	H ₂ O	60	0,7 h	100	66	78:22 ^e
<i>n</i> -Bu	H ₂ SO ₄ 5% aq	H ₂ O	60	0,3 h	100	62	79:21 ^f

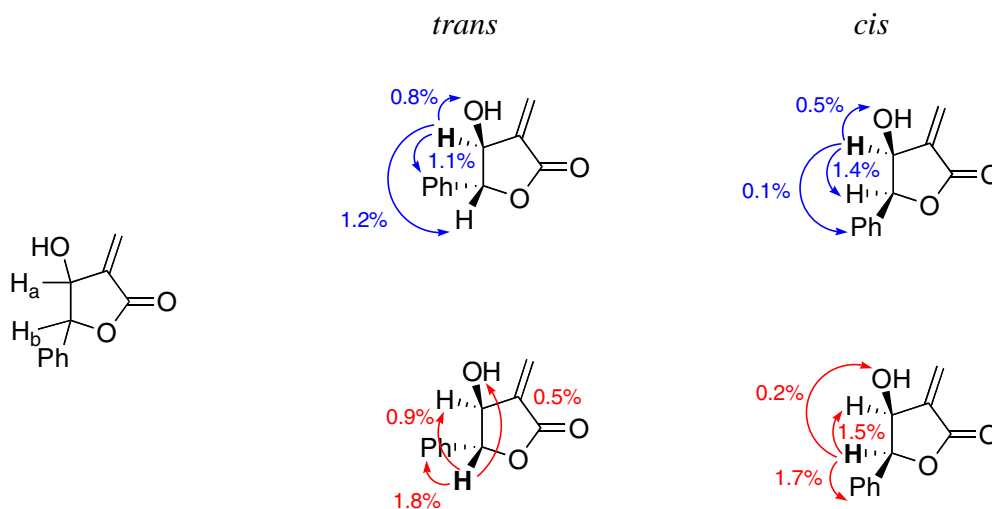
^a With respect to the epoxide. ^b Determined on the NMR of the crude product. ^c Traces of furanone **5**. ^d MeCN/H₂O (10:1). ^e 86:14 (**4:5**). ^f 90:10 (**4:5**).

NOE experiments carried out on lactone 4a

NOE 1D selective: determination of the relative configuration *trans/cis*.

lactone	irradiated H	H _a -H _b ^a	H-OH ^a	H-Ph ^a	H-CH ₂ ^a
<i>trans</i>	H _a	1.2	0.8	1.1	0.1 + 0.4
	H _b	0.9	0.5	1.8	-
<i>cis</i>	H _a	1.4	0.5	0.1	ε + 0.2
	H _b	1.5	0.2	1.7	-

^a Correlation values are obtained from NOE selective 1D spectra which have been normalized to the irradiated peak intensity, and are given in percentage (%).

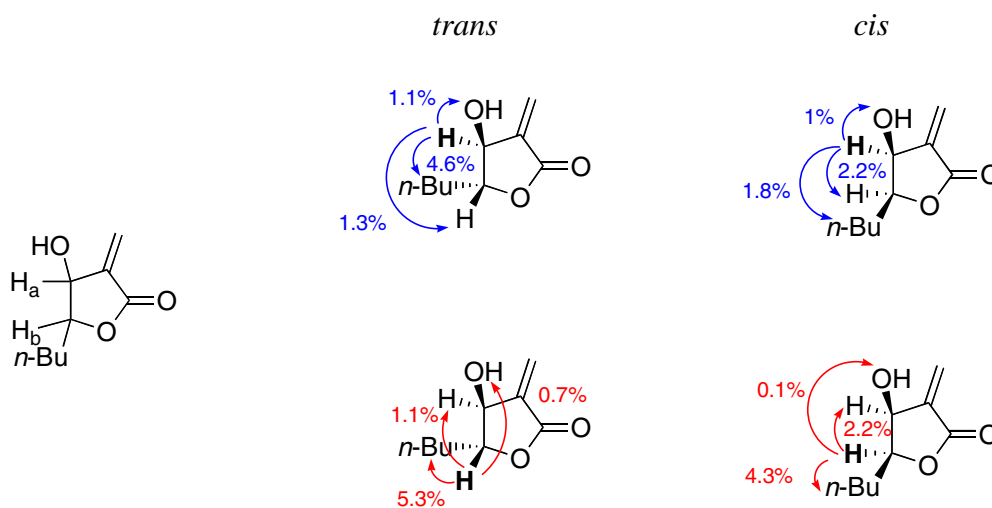


NOE experience carried out on lactone 4g

NOE 1D selective: determination of the relative configuration *trans/cis*.

lactone	Irradiated H	H _a -H _b ^a	H-OH ^a	H-(<i>n</i> -Bu) ^a	H-CH ₂ ^a
<i>trans</i>	H _a	1.3	1.1	4.6	0.1 + 0.7
	H _b	1.1	0.7	5.3	-
<i>cis</i>	H _a	2.2	1	1.8	0.1 + 0.8
	H _b	2.2	0.1	4.3	-

^a Correlation values are obtained from NOE selective 1D spectra which have been normalized to the irradiated peak intensity, and are given in percentage (%).

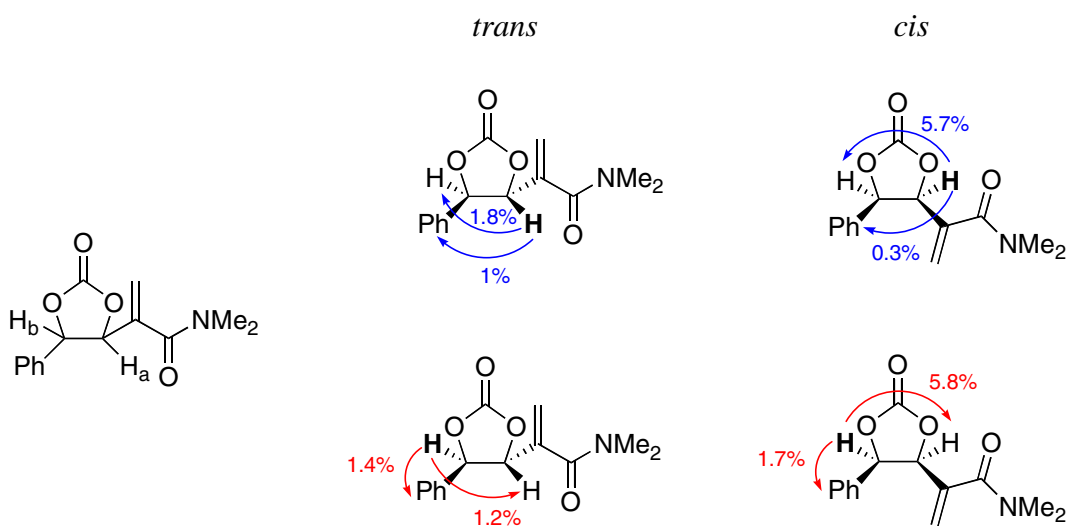


NOE experience carried out on carbonate 11a

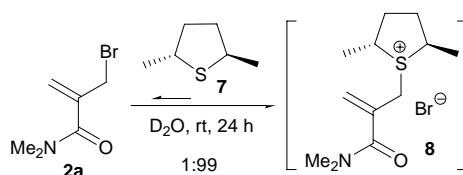
NOE 1D selective: determination of the relative configuration *trans/cis*.

carbonate	irradiated H	H _a -H _b ^a	H-Ph ^a
<i>trans</i>	H _a	1.8	1
	H _b	1.2	1.4
<i>cis</i>	H _a	5.7	0.3
	H _b	5.8	1.7

^a Correlation values are obtained from NOE selective 1D spectra which have been normalized to the irradiated peak intensity, and are given in percentage (%).



NMR of the sulfonium salt **8**²



In a NMR tube, a heterogeneous mixture of allylic bromide **2a** (62 mg, 0.32 mmol) and thiolane **7** (29 mg, 0.25 mmol) in D₂O (50 μ L) were stirred for 24 hours at room temperature. CD₃CN (450 μ L) was added to the resulting homogeneous solution (corresponding to the soluble sulfonium salt **8**) and the mixture was immediately analyzed by NMR. A virtually complete formation of the sulfonium salt with respect to the sulfide **7** was observed by ¹H NMR.

δ_{H} (400 MHz): 6.03 (s, 1H, =CH₂), 5.63 (s, 1H, =CH₂), 4.25-4.16 (m, 1H, CH), 4.08-3.97 (m, 3H, CH and SCH₂), 3.05 (s, 3H, NMe₂), 2.90 (s, 3H, NMe₂), 2.52-2.49 (m, 1H, CH₂), 2.48-2.41 (m, 1H, CH₂), 2.23-2.12 (m, 1H, CH₂), 1.90-1.78 (m, 1H, CH₂), 1.54 (d, $J = 7.0$ Hz, 3H, Me), 1.51 (d, $J = 7.0$ Hz, 3H, Me).

² For the use and comments in ylide promoted epoxidation by a pre-formed sulfonium salt in water, see: V. Schulz, M. Davoust, M. Lemarié, J.-F. Lohier, J. Sopkova de Oliveira Santos, P. Metzner and J.-F. Brière, *Org. Lett.*, 2007, **9**, 1745.