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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo502404y • Publication Date (Web): 08 Dec 2014

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Unsaturated *syn*- and *anti*-1,2-Amino Alcohols by Cyclization of Allylic bis-Trichloroacetimidates. Stereoselectivity Dependence on Substrate Configuration.

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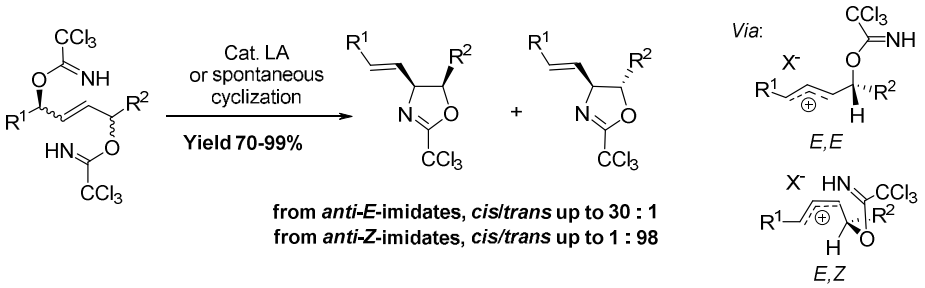
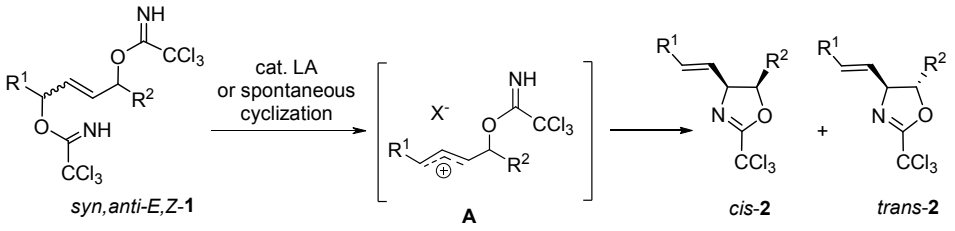


ABSTRACT: Disubstituted allylic bis-imidates undergo Lewis acid catalyzed or spontaneous cyclization to oxazolines which are precursors of unsaturated amino alcohols. Stereoselectivity of the cyclization is mainly determined by the substrate configuration. Highly selective *cis*-oxazoline formation is achieved starting from *anti*-*E*-bis-imidates while *trans*-oxazoline predominantly forms from *anti*-*Z*-bis-imidates. Based on DFT calculations, the stereoselectivity trends can be explained by the formation of the energetically most stable carbenium ion conformation followed by the cyclization *via* most favorable bond rotations.

Introduction

The abundance of 1,2-amino alcohol motif in pharmacologically active compounds and natural products stimulates the development of more efficient methods for the construction of this substructure.[1] Efficient synthetic approach to unsaturated 1,2-amino alcohols are particularly important because the double bond provides high derivatization potential.[2] Stereoselective synthesis of such compounds can be efficiently achieved *via* allylic substitution catalyzed by Pd(0)[3] or Pd(II)[4] complexes. Allylic substitution *via* activation of a leaving group by Lewis and Brønsted acid catalysts, have been intensively studied in recent years,[5] however, there are limited examples for the synthesis of 1,2-amino alcohols using this approach.[6] Recently we reported a method for the cyclization of mono-substituted allylic bis-trichloroacetimidates **1** to oxazolines **2** (R^1 = Alk, Ar; R^2 = H; Scheme 1). [6a-f] In this reaction, one of the imidates serves as a leaving group while the other as *N*-nucleophile. The allylic substitution is catalyzed by Lewis acids or occurs spontaneously if substrate contains carbenium ion stabilizing group.



Scheme 1. Cyclization of bis-trichloroacetimidates **1** to oxazolines **2**

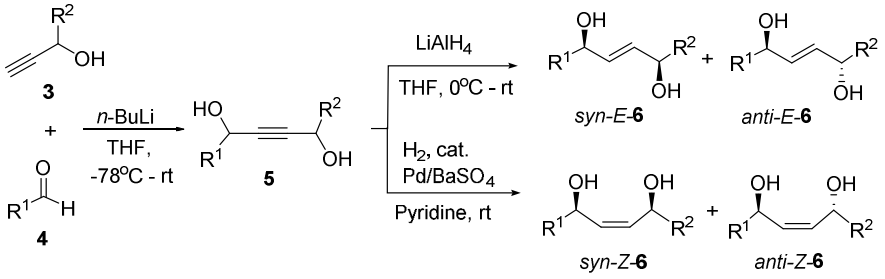
The cyclization of disubstituted allylic bis-imidates **1** would be a useful route towards unsaturated *syn* or *anti* amino alcohols if the reaction stereoselectivity and regioselectivity could be controlled. In this report we present studies of the reaction selectivity depending on the following parameters: a) bis-imidate **1** *E*-/*Z*-

configuration; b) *syn*/*anti* configuration of bis-imidate groups; c) substituents R^1 and R^2; d) reaction conditions (solvent, Lewis acid).

Results and discussion

Isomeric diols **6** for bis-imidate synthesis **1** were prepared in a non-stereoselective manner starting from propargylic alcohol **3** and aldehyde **4** (Table 1).[6a-d,7] The double bond in addition products **5** was reduced to give diol isomers *E*-**6** and *Z*-**6** depending on the reduction method. *Syn*-and *anti*- isomers for each double bond isomer *E*-**6** and ***Z*-6** were separated using column chromatography.

Table 1. Synthesis of diols **6**

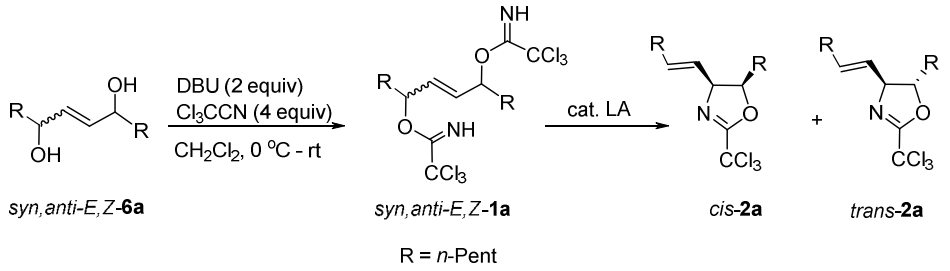


entry	R^1	R^2	**5**, yield%	*E*-**6**, yield (%)[a]	*Z*-**6**, yield (%)[a]
1	*n*-Pent	*n*-Pent	**5a**, 89	*E*-**6a**, 92	*Z*-**6a**, 63
2	Ph	*n*-Pent	**5b**, 88	*E*-**6b**, 74	*Z*-**6b**, 86
3	Ph	*i*-Pr	**5c**, 74	*E*-**6c**, 91	*Z*-**6c**, 85
4	Ph	Bn	**5d**, 70	*E*-**6d**, 93	*Z*-**6d**, 75
5	Ph	Ph	**5e**, 92	*E*-**6e**, 84	*Z*-**6e**, 75
6	Ph	4-$MeOC_6H_4$	**5f**, 70	*E*-**6f**, 97	*Z*-**6f**, 66

[a]Total yield for the mixture of *syn* and *anti* isomers

All four isomers of diol **6a** (R_1 = R_2 = *n*-Pent) were transformed to bis-imidates *syn*-*E*-**1a,** *anti*-*E*-**1a,** *syn*-*Z*-**1a**, *anti*-*Z*-**1a** (Figure 1). These imidate isomers were investigated as model compounds for oxazoline **2** formation with Lewis acid catalyst $AlCl_3$ or TMSOTf in the range of solvents (see Supporting information for results with $FeCl_3$ and $BF_3{\cdot}Et_2O$). In most cases, bis-imidates *syn*-*E*-**1**, *anti*-*E*-**1** gave oxazoline *cis*-**2a** in the preference to *trans*-**2a** (Figure 1). The degree of selectivity

was dependent on a substrate *syn*/*anti* configuration, Lewis acid catalyst and solvent. The best *cis*-selectivity (>10:1) for oxazoline *cis*-**2a** formation was achieved starting from *anti*-*E*-**1a** using multi-coordinating Lewis acid catalyst ($AlCl_3$) in CH_2Cl_2 or toluene. The use of mono-coordinating Lewis acid such as TMSOTf significantly decreased cyclization selectivity for both, *syn*- *E*-**1a** and *anti*-*E*-**1a**. In turn, *Z*-configured bis-imidates *syn*-*Z*-**1**, *anti*-Z-**1a** predominantly gave oxazoline *trans*-**2a** under all the conditions used. However, the highest *trans*-selectivity was achieved using mono-coordinating Lewis acid TMSOTf in either THF, toluene or Et_2O.



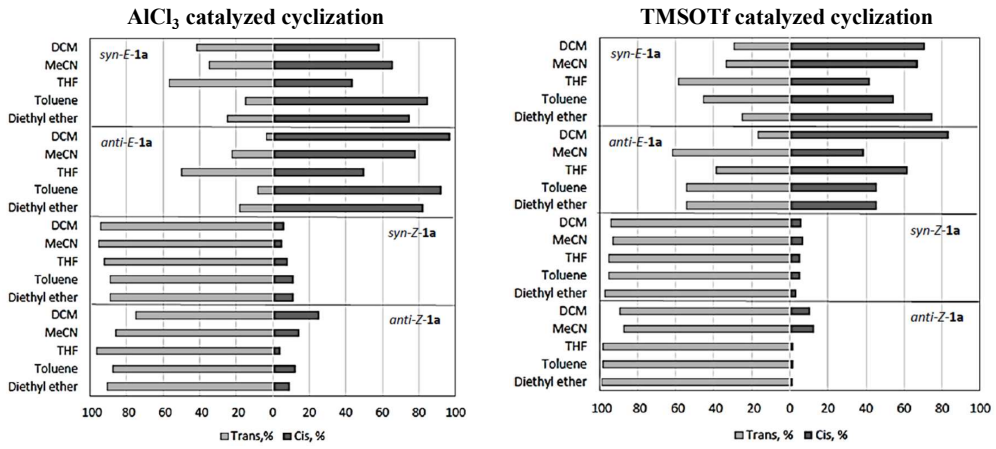


Figure 1 *Trans*- and *cis*-selectivity for oxazoline **2a** formation in LA catalyzed cyclization of bis-imidates *syn*-*E*-**1a**, *anti*-*E*-**1a**, *syn*-*Z*-**1a**, *anti*-*Z*-**1a**

To explain the stereoselectivity trends for oxazoline *cis*-**2** and *trans*-**2** formation, potential reaction mechanism was hypothesized. Concerted stereospecific *anti*-S_N2' or *syn*-S_N2' mechanism can be excluded. If this was the case, either bis-imidate *syn*-*E*-**1** or *anti*-*E*-**1** should provide oxazoline *cis*-**2** with *Z*-configuration of the double bond,[8]

however, only formation of oxazoline *E*-*cis*-**2** was observed. Next, S_N1-type mechanism was considered. According to this, coordination of **1** with Lewis acid followed by dissociation of complexed imidate would provide carbenium ion **A** which would then cyclize to oxazoline **2** (Scheme 1, Figure 2). However, it is difficult to explain preferential formation of *cis*-**2** oxazoline which should be apparently disfavored if diastereomeric transition states for the carbenium ion **A** cyclization are considered. To get an insight of the reaction energy profile, DFT calculations were performed. The calculations indicated that transition state energy $\Delta G^{\ddagger}$ value for carbenium ion **A** ($R^1 = R^2 = Me$) cyclization approaches 0 and is lower compared to bond rotation barriers (see Supporting Information). Based on these results we could assume that, the stereoselectivity is determined by the conformation of the intermediate carbenium ion **A** which undergoes cyclization *via* energetically preferred bond rotations. According to the Hammond's postulate,[9] it can be assumed that carbenium ion **A** with energetically most favored conformation is formed first. Using the DFT method, the lowest energy conformation of carbenium ion **A** resulting from each isomer of **1** was calculated (see Supporting Information). These calculations suggested that from bis-imidates *syn*-*E*-**1** and *anti*-*E*-**1** carbenium ion *E*-,*E*-**A** is generated in a conformation, which undergoes favorable C-O bond rotation (over H *vs* R) to form oxazoline *cis*-**2**. In turn, imidates *syn Z*-**1** and *anti*-*Z*-**1** led to carbenium ion *E*-,*Z*-**A** which has prerequisite conformation for the cyclization to oxazoline *trans*-*E*-**2**. Based on this stereoselectivity model, it can be considered that solvent and Lewis acid catalyst and *syn*/*anti* configuration of a substrate **1** have an impact on distribution between carbenium ion *E*-,*E*-**A** and *E*-,*Z*-**A** conformations.

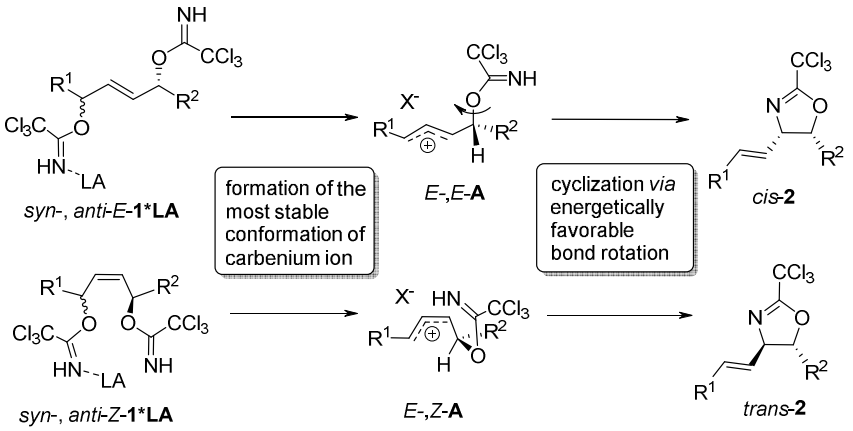


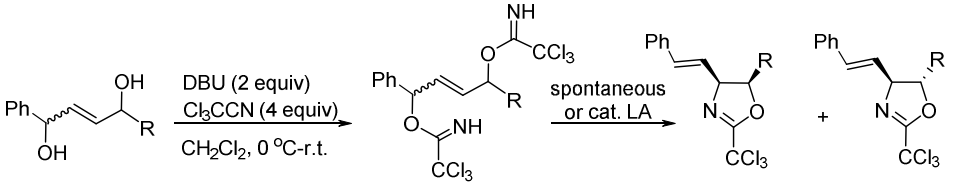
Figure 2. Stereoinduction model for *cis*-**2** and *trans*-**2** oxazoline formation

Subsequently, we further investigated the scope of cyclization by employing different substituted allylic bis-imidates **1b-e** containing carbenium ion stabilizing phenyl group (Table 2). These bis-imidates apeared to be quite labile and only isomers of intermediate *E*-**1c** could be isolated and subjected to cyclization. In all other cases, diols **6** were converted to imidates **1** which were transformed *in situ* to oxazolines **2.** As expected from ionization induced reaction mechanism, regioselective cyclization of unsymetrically substituted substrates **1b-d** was observed, providing compounds **2b-d** as the only regioisomers (Table 1, entries 1-10). *Cis*-/*trans*-selectivity again showed remarkable dependency on a substrate configuration. Imidates *E*-**1b-e** preferentially gave oxazolines *cis*-**2b-e**. *Cis*-selectivity was better for *anti*-*E*-**1b-e** compared to *syn*-*E*-**1b-e**. Imidates *anti*-*Z*-**1b-e** gave exclusively oxazolines *trans*-**2b-e.**

Since 4-methoxyphenyl group has better ability to stabilize carbenium ion compared to phenyl group, spontaneous cyclization of all bis-imidate **1f** isomers prepared *in situ* from diols **6f** led to regioselective formation of oxazoline **2f** (Table 3). Low *cis*-/*trans*-selectivity for oxazoline **2f** formation was observed starting from bis-imidates *syn*-*E*-**1f** and *anti*-*E*-**1f**. This could be explained by increased activation energy for the cyclization of more stabilized carbenium ion intermediate **A** (Figure 2).

In this case, slower cyclization leads to equilibration of unequivalent diastereomeric transition states thus influencing *cis*-/*trans*-stereoselectivity for the product **2f** formation. Notably, bis-imidate *anti-Z*-**1f** gave oxazoline *trans*-**2f** as the only detectable isomer.

Table 2. Cyclization of bis-imidates **1** containing phenyl group

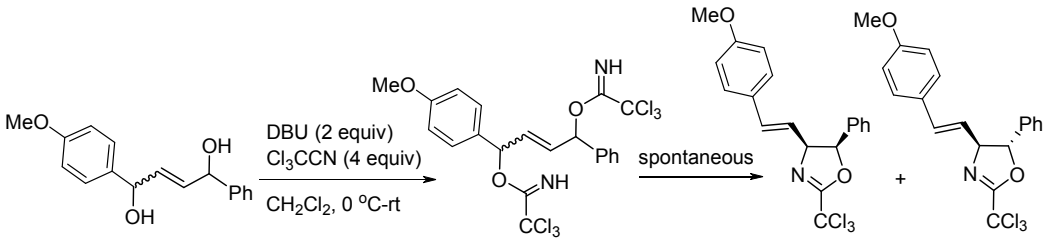


syn,anti-E,Z-**6b-e** *syn,anti-E,Z*-**1b-e** *cis*-**2b-e** *trans*-**2b-e**

entry	substrate	R	catalyst	time	solvent	product, yield (%)	*cis*-**2**/ *trans*-**2**[a]
1	*syn-E*-**6b**	*n*-Pent	-	6h	CH_2Cl_2	**2b**, 73	30:1
2	*anti-E*-**6b**		-	6 h	CH_2Cl_2	**2b**, 76	1:0
3	*anti-Z*-**6b**		-	12 h	CH_2Cl_2	**2b**, 70	0:1
4	*syn-E*-**1c**	*i*-Pr	$AlCl_3$	5 min	toluene	**2c**, 96	5:2
5	*anti-E*-**1c**		$AlCl_3$	5 min	CH_2Cl_2	**2c**, 93	6:1
6	*anti-Z*-**6c**		-	24 h	CH_2Cl_2	**2c**, 80	1:33
7	*anti-Z*-**6c**		TMSOTf	1 min	CH_2Cl_2	**2c**, 90	0:1
8	*syn-E*-**6d**	Bn	$AlCl_3$	2 min	CH_2Cl_2	**2d**, 92	1:1
9	*anti-E*-**6d**		$AlCl_3$	2 min	CH_2Cl_2	**2d**, 94	6:1
10	*anti-Z*-**1d**		TMSOTf	1 min	Et_2O	**2d**, 93	0:1
11	*syn-E*-**6e**	Ph	$AlCl_3$	2 min	CH_2Cl_2	**2e**, 88	3:2
12	*anti-E*-**6e**		$AlCl_3$	2 min	CH_2Cl_2	**2e**, 90	3:1
13	*anti-Z*-**6e**		TMSOTf	1 min	CH_2Cl_2	**2e**, 92	0:1

[a] *Cis*-/*trans*- ratio was determined using ^{1}H-NMR.

Table 3. Cyclization of bis-imidate **1f** containing 4-methoxyphenyl group



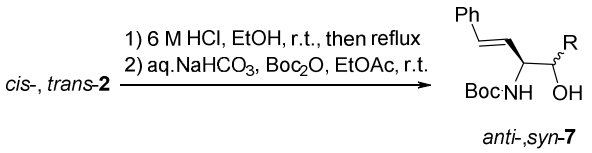
syn,anti-E,Z-**6f** *syn,anti-E,Z*-**1f** *cis*-**2f** *trans*-**2f**

entry	substrate	yield of **2f** (%)	cis-**2f**/trans-**2f**[a]
1	*syn-E*-**6f**	93	1:1.5
2	*anti-E*-**6f**	90	1:3.3
3	*anti-Z*-**6f**	89	0:1

[a] *Cis*-/*trans*- ratio was determined using ^{1}H-NMR.

Several oxazolines were isolated as pure isomers *cis*-**2** and *trans*-**2** and converted to Boc-protected amino alcohols *anti*-**7** and *syn*-**7** in high overall yields (Table 4).

Table 4. *N*-Boc amino alcohols **7** from oxazolines **2**



entry	oxazoline, R	product, yield (%)
1	*cis*-**2b**, *n*-Pent	*anti*-**7b**, 80
2	*trans*-**2b**, *n*-Pent	*syn*-**7b**, 87
3	*cis*-**2d**, Bn	*anti*-**7d**, 89
4	*cis*-**2c**, *i*-Pr	*anti*-**7c**, 88
5	*trans*-**2c**, *i*-Pr	*syn*-**7c**, 83
6	*cis*-**2e**, Ph	*anti*-**7e**, 87
7	*trans*-**2e**, Ph	*syn*-**7e**, 90

In summary, we have demonstrated efficient method for the stereoselective synthesis of amino alcohols *via* cyclization of disubstituted allylic bis-imidates. Stereoselectivity of bis-imidate cyclization is determined by the substrate configuration and can be enhanced by appropriate selection of Lewis acid and solvent. *Cis*-oxazoline predominantly forms from allylic *anti*-*E*-bis-imidates using multi-coordinating Lewis acid catalyst ($AlCl_3$) in non-coordinating solvents. Furthermore the *cis*-selectivity for *anti*-*E*-bis-imidate cyclization is highly dependent on the substitution pattern. *Trans*-oxazoline predominantly forms from allylic *anti*-*Z*-bis-imidates using mono-coordinating Lewis acid (TMSOTf) with a slight dependence on the reaction solvent. In this case cyclization is highly *trans*-selective independently of the bis-imidate substituents.

EXPERIMENTAL SECTION

General information.

Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. All reactions were performed under an inert atmosphere. Flash chromatography was carried out using Merck Kieselgel (230 – 400 mesh) silica gel. Thin layer chromatography was performed on silica gel and was visualized by staining with $KMnO_4$. NMR spectra were recorded on 400 MHz and 600 MHz spectrometers with chemical shift values (δ) in ppm using the residual chloroform signal as internal standard. Gas chromatographic analysis was performed on gas chromatographic system with mass selective detector. Exact molecular masses (HRMS) were determined on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source.

Diols **5** and **6** were prepared as described previously.[6a] Compounds **5a**[10], **5b,e**[11], *anti-E*-**6a**,[10] *syn-E*-**6a**,[10] *anti-Z*-**6a**,[3c] *anti-E*-**6c**[12], *syn-E*-**6c**[12] *anti-E*-**6e**,[13] *syn-E*-**6e**[13] have been previously described in literature. The stereochemistry of other diols **6** was assigned by comparing the chemical shift differences in NMR spectra.

5-Methyl-1-phenylhex-2-yne-1,4-diol (5c). 1.21 g, 74%. Purified by flash chromatography on silica gel using a mixture of light petroleum ether and EtOAc (2:1, 1:1, 0:1) as an eluent. Colorless solid. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.54 – 7.52 (m, 2H), 7.41 – 7.31 (m, 3H), 5.51 (s, 1H), 4.26 (d, J = 5.5 Hz, 1H), 2.35 (bs, 1H), 1.97 (bs, 1H), 1.91 (octet, J = 6.7 Hz, 1H), 1.02 (dd, J = 6.7 and 2.7 Hz, 3H), 1.00 (dd, J = 6.7 and 2.7 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 140.6, 128.6,

128.4, 126.6, 86.5, 85.3, 67.9, 64.6, 34.5, 18.1, 17.5. GC-MS: m/z (EI): 204 $(M)^+$. Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; Found: C, 76.22; H, 7.97.

1,5-Diphenylpent-2-yne-1,4-diol (5d). 1.42 g, 70%. Purified by flash chromatography on silica gel using a mixture of light petroleum ether and EtOAc (2:1, 1:1, 0:1) as an eluent. Colorless oil. (^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.46 – 7.22 (m, 10H), 5.46 (s, 1H), 4.70 – 4.65 (m, 1H), 3.02 (dd, J = 6.7 and 2.4 Hz, 2H), 2.38 (bs, 1H) and 2.13 (bs, 1H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 140.2, 136.3, 129.8, 129.0, 128.6, 128.4, 126.9, 126.6, 87.0, 85.5, 64.5, 63.2, 43.8. GC-MS: m/z (EI): 252 $(M)^+$.

1-(4-Methoxyphenyl)-4-phenylbut-2-yne-1,4-diol (5f). 1.50 g, 70%. Crystallized from Et_2O. Colorless solid. M.p. 119-120^{o}C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.56 – 7.54 (m, 2H), 7.48 – 7.45 (m, 2H), 7.41 – 7.32 (m, 3H), 6.90 (d, J = 8.6 Hz, 2H), 5.56 (s, 1H), 5.51 (s, 1H), 3.81 (s, 3H), 2.29 (bs, 1H), 2.22 (bs, 1H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 159.8, 140.6, 132.5, 128.7, 128.5, 128.1, 126.6, 114.0, 86.6, 86.3, 64.7, 64.3, 55.5. GC-MS: m/z (EI): 268 $(M)^+$. Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; Found: C, 75.61; H, 5.92.

(1S*,4R*,E)-1-Phenylnon-2-ene-1,4-diol (syn-E-6b). 1.51 g, 74% as a mixture with diol *anti-E*-**6b**. Separated by flash chromatography on silica gel using a mixture of light petroleum ether and EtOAc (4:1, 1:1) as an eluent. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.38 – 7.26 (m, 5H), 5.88 (dd, J = 15.7 and 5.9 Hz, 1H), 5.79 (dd, J = 15.7 and 6.3 Hz, 1H), 5.22 (d, J = 5.9 Hz, 1H), 4.13 (q, J = 6.3 Hz, 1H), 2.09 (bs, 1H), 1.62 (bs, 1H), 1.57 – 1.22 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 142.8, 134.3, 132.7, 128.5, 127.7, 126.2, 74.5, 72.3, 37.2, 31.7, 25.1, 22.6, 14.0. GC-MS: m/z (EI): 233 $(M-H)^+$.

(1R*,4R*,E)-1-Phenylnon-2-ene-1,4-diol (anti-E-6b). 1.51 g, 74% as a mixture with diol *syn-E*-**6b**. Separated by flash chromatography on silica gel using a mixture of light petroleum ether and EtOAc (4:1, 1:1) as an eluent. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.35 – 7.24 (m, 5H), 5.86 (dd, *J* = 15.5 and 5.7 Hz), 5.78 (dd, *J* = 15.5 and 6.1 Hz, 1H), 5.19 (d, *J* = 5.7 Hz, 1H), 4.11 (q, *J* = 6.1 Hz, 1H), 2.34 (bs, 1H), 1.82 (bs, 1H), 1.57 – 1.23 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 142.8, 134.0, 132.6, 128.5, 127.7, 126.3, 74.4, 72.2, 37.1, 31.7, 25.0, 22.6, 14.0. GC-MS: m/z (EI): 233 $(M-H)^+$.

(1S*,4R*,Z)-1-Phenylnon-2-ene-1,4-diol (anti-Z-6b). 1.74 g, 86% as a mixture with diol *syn-Z*-**6b**. Separated by flash chromatography on silica gel using a mixture of light petroleum ether and EtOAc (4:1, 1:1) as an eluent. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.41 – 7.25 (m, 5H), 5.72 (dd, *J* = 11.3 and 8.2 Hz, 1H), 5.57 – 5.51 (m, 2H), 4.54 (q, *J* = 7.0 Hz, 1H,), 2.26 (bs, 1H), 1.73 (bs, 1H), 1.67 – 1.24 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 142.9, 134.4, 133.9, 128.6, 127.6, 126.0, 69.6, 67.6, 37.1, 31.7, 25.0, 22.5, 13.9. GC-MS: m/z (EI): 233 $(M-H)^+$.

(1S*,4R*,Z)-5-Methyl-1-phenylhex-2-ene-1,4-diol (anti-Z-6c). 405 mg, 85% as a mixture with diol *syn-E*-***6c.*** Separated by flash chromatography using a mixture of light petroleum ether and EtOAc (6:1, 1:1) as an eluent. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.43 – 7.26 (m, 5H), 5.79 (dd, *J* = 11.3 and 8.2 Hz, 1H), 5.59 – 5.55 (m, 2H), 4.29 (dd, *J* = 8.6 and 7.0 Hz, 1H), 2.33 (bs, 1H), 1.77 (octet, *J* = 6.7 Hz, 1H), 1.67 (bs, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 143.3, 134.5, 132.3, 128.7, 127.7, 126.0, 73.2, 70.4, 34.1, 18.2, 18.0. GC-MS: m/z (EI): 188 $(M-H_2O)^+$.

(1S*,4R*,E)-1,5-Diphenylpent-2-ene-1,4-diol (syn-E-6d). 421 mg, 93% as a mixture with diol *anti-E-**6d***. Separated by flash chromatography using a mixture of light petroleum ether and EtOAc (4:1, 1:1) as an eluent. Colorless crystals. M.p. 85 - 86°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.35 – 7.15 (m, 10H), 5.80 – 5.75 (m, 2H), 5.14 – 5.11 (m, 1H), 4.35 – 4.29 (m, 1H), 2.89 (bs, 1H), 2.80 (d, *J* = 6.7 Hz, 2H), 2.43 (bs, 1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 142.6, 137.5, 133.2, 133.1, 129.5, 128.39, 128.36, 127.5, 126.4, 126.1, 74.2, 72.8, 43.7. GC-MS: m/z (EI): 253 $(M-H)^+$. Anal. calcd. for $C_{17}H_{18}O_2 \cdot 1/3\ H_2O$: C, 78.43; H, 7.23; Found: C, 78.15; H, 7.02.

(1S*,4S*,E)-1,5-Diphenylpent-2-ene-1,4-diol (anti-E-6d). 421 mg, 93% as a mixture with diol ***anti-E-6d***. Separated by flash chromatography using a mixture of light petroleum ether and EtOAc (4:1, 1:1) as an eluent. Colorless crystals. M.p. 109 - 110°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.36 – 7.18 (m, 10H), 5.89 – 5.82 (m, 2H), 5.18 (d, *J* = 3.1 Hz, 1H), 4.40 – 4.35 (m, 1H), 2.87 (dd, *J* = 13.7 and 5.9 Hz, 1H), 2.83 (dd, *J* = 13.7 and 7.8 Hz, 1H), 2.27 (bs, 1H), 1.93 (bs,1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 142.5, 137.6, 133.0, 132.8, 129.5, 128.48, 128.46, 127.7, 126.5, 126.3, 74.2, 72.8, 43.8. GC-MS: m/z (EI): 236 $(M-H_2O)^+$. Anal. calcd. for $C_{17}H_{18}O_2 \cdot 1/6\ H_2O$: C, 79.35; H, 7.18; Found: C, 79.67; H, 7.11.

(1S*,4R*,Z)-1,5-Diphenylpent-2-ene-1,4-diol (anti-Z-6d). 365 mg, 75% as a mixture with diol ***syn-Z-6d***. Separated by flash chromatography using a mixture of light petroleum ether and EtOAc (6:1, 1:1) as an eluent. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.38 – 7.22 (m, 10H), 5.64 (dd, *J* = 11.3 and 8.2 Hz, 1H), 5.56 (dd, *J* = 11.3 and 8.0 Hz, 1H), 5.25 (d, *J* = 8.2 Hz, 1H), 4.81 (q, *J* = 7.2 Hz, 1H), 3.00 (dd, *J* = 13.1 and 6.7 Hz, 1H), 2.83 (dd, *J* = 13.1 and 7.0 Hz, 1H), 2.22 (bs, 1H), 1.70 (bs, 1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 142.5, 137.5, 133.9, 132.6, 129.7, 128.6, 128.4, 127.5, 126.8, 125.8, 69.5, 67.0, 44.0. GC-MS: m/z (EI): 236 $(M-H_2O)^+$.

(1S*,4S*,Z)-1,4-Diphenylbut-2-ene-1,4-diol (anti-Z-6e). 1.32 g, 87% as a mixture with diol ***syn-Z-6e*** (see Table 1). Separated by flash chromatography using a mixture of light petroleum ether and EtOAc (4:1, 0:1) as an eluent. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.46 – 7.28 (m, 10H), 5.80 – 5.78 (m, 2H), 5.71 – 5.69 (m, 2H), 2.31 (bs, 2H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 143.0, 133.5, 128.7, 127.8, 126.1, 70.4. GC-MS: m/z (EI): 222 $(M\text{-}H_2O)^+$.

(1S*,4S*,E)-1-(4-Methoxyphenyl)-4-phenylbut-2-ene-1,4-diol (syn-E-6f). 980 mg, 97% crude product as a mixture with diol ***anti-E*-6f**. Separated by flash chromatography on silica gel using a mixture of CH_2Cl_2 and MeOH (10:1) as an eluent. Recrystallized from Et_2O. Colorless solid. M.p. 106 - 107°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.36 – 7.26 (m, 7H), 6.91 – 6.86 (m, 2H), 6.02 – 5.94 (m, 2H), 5.24 – 5.16 (m, 2H), 3.82 (s, 3H), 2.60 (bs, 1H) and 2.52 (bs, 1H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 159.1, 142.6, 134.8, 133.3, 132.8, 128.5, 127.7, 127.6, 126.2, 113.9, 74.3, 73.8, 55.2. GC-MS: m/z (EI): 252 $(M\text{-}H_2O)^+$. Anal. calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71; Found: C, 75.31; H, 6.69.

(1R*,4S*,E)-1-(4-Methoxyphenyl)-4-phenylbut-2-ene-1,4-diol (anti-E-6f). 980 mg, 97%, crude product as a mixture with diol ***syn-E*-6f**. Separated by flash chromatography on silica gel using a mixture of CH_2Cl_2 and MeOH (10:1) as an eluent. Recrystallized from Et_2O. Colorless solid. M.p. 137 - 138°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.37 – 7.26 (m, 7H), 6.92 – 6.87 (m, 2H), 6.02 – 6.00 (m, 2H), 5.27 – 5.25 (m, 1H), 5.22 – 5.20 (m, 1H), 3.81 (s, 3H), 1.90 (d, J = 3.7 Hz, 1H), 1.84 (d, J = 3.7 Hz, 1H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 159.3, 142.6, 134.8, 133.3, 132.8, 128.6, 127.8, 127.7, 126.3, 114.0, 74.4, 73.9, 55.3. GC-MS: m/z (EI): 269 $(M\text{-}H)^+$. Anal. calcd for $C_{17}H_{18}O_3 \cdot 1/5\ H_2O$: C, 74.54; H, 6.77; Found: C, 74.89; H, 6.62.

(1S*,4S*,Z)-1-(4-Methoxyphenyl)-4-phenylbut-2-ene-1,4-diol (anti-Z-6f). 725 mg, 66% yield as a mixture with diol ***syn-Z-*6f** (see Table 1). Separated by flash chromatography using a mixture of light petroleum ether and EtOAc (4:1, 0:1) as an eluent. Oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.45 – 7.26 (m, 7H), 6.92 – 6.87 (m, 2H), 5.82 – 5.74 (m, 2H), 5.67 (d, *J* = 7.0 Hz, 1H), 5.64 (d, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 2.27 (bs, 1H), 1.63 (bs, 1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 159.2, 143.1, 135.3, 133.7, 133.1, 128.7, 127.8, 127.4, 126.0, 114.1, 70.3, 70.1, 55.3. GC-MS: m/z (EI): 252 $(M-H_2O)^+$.

General procedure for the synthesis of bis-imidates 1.

To a solution of diol **3** (1.0 mmol) in CH_2Cl_2 (10 mL) 4 Å molecular sieves were added. Reaction mixture was cooled to 0^{o}C, DBU (2 mmol, 2 equiv.) was added. Solution was stirred at 0 ^{o}C for 30 minutes. Trichloroacetonitrile (4 mmol, 4 equiv.) was added, and the reaction mixture was stirred at 0 ^{o}C temperature until TLC showed complete conversion. Solvent was removed and the residue was purified by flash column chromatography using mixture of light petroleum ether and EtOAc (8:1) as an eluent to give bis-trichloroacetimidate **1**.

Bis-trichloroacetimidate syn-E-1a. Prepared according to the general procedure (436 mg, 99%). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 8.26 (s, 2H), 5.87 – 5.79 (m, 2H), 5.44 – 5.37 (m, 2H), 1.83 – 1.65 (m, 4H), 1.47 – 1.24 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 6H). ^{13}C-NMR δ_C (100 MHz, $CDCl_3$): 161.8, 130.2, 91.9, 78.4, 34.0, 31.5, 24.5, 22.5, 14.0. HRMS (EI-TOF) m/z: Calcd for $C_{16}H_{27}Cl_3NO$ 354.1153; Found 354.1155 $[M-Cl_3CC(=O)NH_2)+H]^+$.

Bis-trichloroacetimidate anti-E-1a. Prepared according to the general procedure (413 mg, 95%). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 8.26 (s, 2H), 5.84 – 5.77

(m, 2H), 5.41 – 5.36 (m, 2H), 1.85 – 1.64 (m, 4H), 1.46 – 1.24 (m, 12H), 0.87 (t, J = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 161.7, 130.3, 91.9, 78.6, 34.1, 31.4, 24.5, 22.5, 13.9. HRMS (EI-TOF) m/z: Calcd for $C_{16}H_{27}Cl_3NO$ 354.1153; Found 354.1155 $[M\text{-}Cl_3CC(=O)NH_2)+H]^+$

Bis-trichloroacetimidate syn-Z-1a. Prepared according to the general procedure (2.20 g, yield 85%). Colorless oil. Two rotational isomers for *syn-Z*-**1a** was observed in ^{1}H- and ^{13}C-NMR spectra. Their inter-conversion with sufficiently high energy barrier was confirmed by exchange peaks in 2D NMR NOESY spectra (see Supporting Information). ^{1}H-NMR δ_H (600 MHz, $CDCl_3$, mixture of two rotamers ~ 1:1): 8.85 (s, 0.5H), 8.42 (s, 0.5H), 8.29 (s, 1H), 5.79 (q, J = 6.8 Hz, 1H), 5.63 (m, 1H), 5.53-5.61 (m, 1H), 5.33 (td, J = 9.0, 2.4 Hz, 0.5H), 5.27 (t, J = 6.9 Hz, 0.5H), 1.83-1.93 (m, 2H), 1.25 – 1.67 (m, 14H), 0.89-0.92 (m, 6H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$, mixture of two rotamers ~1:1): 162.8, 161.6, 159.7, 132.1, 131.0, 130.6, 93.0, 91.8, 91.4, 75.5, 75,1, 74.8, 36.0, 34.8, 34,2, 31.6, 31.3, 24.9, 24.6, 24.5, 22.51, 22.46, 13.9. Unstable under the conditions of HRMS analysis.

Bis-trichloroacetimidate anti-Z-1a. Prepared according to the general procedure (624 mg, 71%). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 8.23 (s, 2H), 5.89 – 5.79 (m, 2H), 5.57 – 5.51 (m, 2H), 1.84 – 1.75 (m, 2H), 1.69 – 1.61 (m, 2H), 1.51 – 1.22 (m, 12H), 0.87 (t, J = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 161.8, 131.3, 91.9, 75.7, 34.3, 31.5, 24.6, 22.5, 14.0. Unstable under the conditions of HRMS analysis.

Bis-trichloroacetimidate syn-E-1c. Prepared according to the general procedure (173 mg, 78%). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 8.38 (s, 1H), 8.26 (s, 1H), 7.42 – 7.28 (m, 5H), 6.42 (d, J = 5.7 Hz, 1H), 6.05 (ddd, J = 15.7, 5.9, 1.2 Hz, 1H),

5.88 (ddd, *J* = 5.7, 6.3, 1.2 Hz, 1H), 5.25 (t, *J* = 6.1 Hz, 1H), 2.05 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 161.8, 161.2, 138.3, 130.8, 129.2, 128.5, 128.2, 127.0, 91.9, 91.6, 82.6, 79.5, 32.2, 18.1, 17.8. Unstable under the conditions of HRMS analysis.

Bis-trichloroacetimidate anti-E-1c. Prepared according to the general procedure (172 mg, 86%). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 8.37 (s, 1H), 8.24 (s, 1H), 7.24-7.41 (m, 5H), 6.42 (d, *J* = 5.7 Hz, 1H), 6.01 (ddd, *J* = 15.6, 5.9, 1.2 Hz, 1H), 5.87 (ddd, *J* = 15.6, 6.3, 1.2 Hz, 1H), 5.22 (t, *J* = 6.2 Hz, 1H), 1.99 - 2.08 (m, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 161.8, 161.2, 138.4, 130.8, 129.2, 128.5, 128.2, 126.8, 91.9, 91.6, 82.8, 79.5, 32.3, 17.9. Unstable under the conditions of HRMS analysis.

Bis-trichloroacetimidate anti-Z-1d. Prepared according to the general procedure (116 mg, yield 93%). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 8.40 (s, 1H), 8.27 (s, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.37 – 7.19 (m, 8H), 6.96 (d, *J* = 9.4 Hz, 1H), 6.27 (ddd, *J* = 9.0,7.2, 5.5 Hz, 1H), 5.79 (dd, *J* = 11.0, 9.0 Hz, 1H), 5.72 (dd, *J* = 11.0, 9.4 Hz, 1H), 3.14 – 3.10 (m, 2H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 161.5, 161.2, 138.8, 136.7, 131.4, 130.8, 129.8, 128.4, 128.2, 128.0, 126.6, 126.4, 91.6, 91.5, 75.84, 75.80, 40.9. Unstable under the conditions of HRMS analysis.

Synthesis of oxazolines 2.

Method A (from bis-imidates **1**). Molecular sieves (4 Å) and Lewis acid catalyst (0.05 mmol, 10 mol-%) were added to a stirred solution of bis-imidate **1** (0.50 mmol) in solvent (5 mL) at rt. After reaction was complete (TLC checking at the first minute of the reaction), TEA (50 mol-%) was added, and reaction solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel

eluting with a mixture of light petroleum ether and ethyl acetate (8:1) to afford the oxazoline **2**.

Method B (from diol **3**). To a solution of diol **3** (0.31 mmol) in solvent (5 mL) 4 Å molecular sieves were added. Reaction mixture was cooled to 0 ^{o}C, DBU (9 μL, 0.06 mmol, 20 mol-%) was added, and solution was stirred at 0^{o}C for 30 minutes. Then trichloroacetonitrile (0.13 mL, 1.25 mmol, 4 equiv.) was added, the reaction mixture was stirred until TLC showed complete conversion of starting material to bis-imidate **1**(~20 min). Catalytic amount of Lewis acid (25 mol-%) was added and the mixture was stirred until complete conversion of bis-imidate **1** to oxazoline **2**. After reaction was complete (TLC checking at the first minute of the reaction), TEA (50 mol-%) was added, and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using mixture of light petroleum ether and EtOAc (8:1) as an eluent to afford the oxazoline **2**.

Method C (from diol **3**). To a solution of diol **3** (1.0 mmol) in CH_2Cl_2 (10 mL) 4 Å molecular sieves were added. Reaction mixture was cooled to 0^{o}C, DBU (2 mmol, 2 equiv.) was added. Solution was stirred at 0 ^{o}C for 30 minutes. Trichloroacetonitrile (4 mmol, 4 equiv.) was added, and the reaction mixture was stirred at 0 ^{o}C temperature until TLC showed complete conversion to oxazoline **2**. Solvent was removed and the residue was purified by flash column chromatography using mixture of light petroleum ether and EtOAc (8:1) as an eluent to afford oxazoline **2**.

Oxazoline cis-2a. Prepared according to the method A (31-34 mg, the yield depended on the Lewis acid catalyst and the reaction solvent, see SI). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 5.75 (dt, J = 15.3, 7.0 Hz, 1H), 5.37 (dd, J = 15.3, 8.6 Hz, 1H), 4.86 (unresolved td, 1H,), 4.74 (t, J = 8.6 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.75 – 1.46

(m, 2H), 1.45 – 1.21 (m, 12H), 0.94 – 0.85 (m, 6H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.5, 136.4, 122.7, 87.8, 87.0, 70.7, 32.4, 31.5, 31.4, 30.2, 28.6, 25.6, 22.5, 22.4, 14.0, 13.9. GC-MS: m/z (EI): 354 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{16}H_{27}Cl_3NO$ 354.1153; Found 354.1153 $[M+H].^+$. See SI for 2D-NOESY spectra.

Oxazoline trans-2a. Prepared according to the method A (30-67 mg, the yield depended on Lewis acid catalyst and the reaction solvent, see SI). Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 5.73 (dt, *J* = 15.3, 6.7 Hz, 1H), 5.42 (dd, *J* = 15.3, 7.8 Hz, 1H), 4.53 (dt, *J* = 7.4, 5.5 Hz, 1H), 4.33 (t, *J* = 7.4 Hz, 1H), 2.11 – 1.98 (m, 2H), 1.82 – 1.63 (m, 2H), 1.51 – 1.22 (m, 12H), 0.91 – 0.86 (m, 6H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.0, 135.0, 127.6, 89.7, 86.9, 73.9, 34.1, 32.3, 31.43, 31.37, 28.5, 24.2, 22.5, 22.4, 14.0, 13.9. GC-MS: m/z (EI): 354 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{16}H_{27}Cl_3NO$ 354.1153; Found 354.1161 $[M+H].^+$ See SI for 2D-NOESY spectra.

Oxazoline cis-2b. Prepared according to the method C (Table 2), 380 mg, 76% from *anti-E*-**6b** and 113 mg, 73% from *syn-E*-**6b**. Purified by flash chromatography. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.40 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.28 – 7.24 (m, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.12 (dd, *J* = 15.7, 7.8 Hz, 1H), 5.01 – 4.95 (m, 2H), 1.80 – 1.26 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.9, 136.3, 134.1, 128.6, 128.0, 126.6, 123.4, 88.0, 87.3, 70.6, 31.5, 30.4, 25.7, 22.4, 13.9. GC-MS: m/z (EI): 360 $[M]^+$. Calcd for $C_{17}H_{21}Cl_3NO$ 360.0683; Found 360.0685 $[M+H]^+$ See SI for 2D-NOESY spectra**.**

Oxazoline trans-2b. Prepared according to the method C (Table 2), 161 mg, 70% from *anti-Z*-**6b**. Purified by flash chromatography. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.31 (d, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.3 Hz,

1H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.08 (dd, *J* = 15.7, 7.4 Hz, 1H), 4.59 (q, *J* = 7.4 Hz, 1H), 4.48 (m, 1H), 1.80 – 1.61 (m, 2H), 1.49 – 1.21 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.5, 136.1, 132.9, 128.6, 128.1, 127.0, 126.6, 89.7, 86.8, 73.8, 34.2, 31.4, 24.3, 22.4, 13.9. GC-MS: m/z (EI): 360 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{17}H_{21}Cl_3NO$ 360.0683; Found 360.0657 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline cis-2c. Prepared according to the method A, 86 mg, 96% from *syn-E*-**1c** and 96 mg, 93% from *syn-E*-**1c** in a mixture with isomer *trans*-***2c*** (Table 2). Purified by flash chromatography. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.39 – 7.24 (m, 5H), 6.66 (d, *J* = 15.7 Hz, 1H), 6.12 (dd, *J* = 15.7, 8.2 Hz, 1H), 4.93 (unresolved t, 1H), 4.57 (t, *J* = 8.6 Hz, 1H), 2.06 (m, 1H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 163.2, 136.3, 134.5, 128.6, 128.1, 126.7, 123.0, 93.0, 87.0, 70.2, 28.8, 19.2, 19.0. GC-MS: m/z (EI): 331 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{15}H_{17}Cl_3NO$ 332.0370; found 332.0343 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline trans-2c. Prepared according to method B, 208 mg, 90% from *anti-Z*-**6c**. Prepared according to method C, 251 mg, 80% from *anti-Z*-**6c**. Purified by flash chromatography. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.41 – 7.24 (m, 5H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.16 (dd, *J* = 15.7, 7.4 Hz, 1H), 4.67 (unresolved t, 1H), 4.47 (t, *J* = 6.7 Hz, 1H), 2.04 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.5, 136.1, 132.7, 128.6, 128.1, 127.7, 126.6, 93.9, 86.8, 71.2, 32.1, 17.2, 17.1. GC-MS: m/z (EI): 331 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{15}H_{17}Cl_3NO$ 332.0370; Found 332.0344 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline cis-2d. Prepared according to the method B, 111 mg, 94% from *anti-E*-**6d** and 136 mg, 92% from *syn-E*-**6d** in a mixture with isomer *trans*-***2d*** (Table 2). Purified by flash chromatography on silica gel. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.42 – 7.23 (m, 10H), 6.72 (d, *J* = 15.7 Hz, 1H), 6.18 (dd, *J* = 15.7, 7.8 Hz, 1H), 5.23 (unresolved td, 1H), 5.07 (unresolved t, 1H), 3.05 (dd, *J* = 14.9, 9.4 Hz, 1H), 2.90 (dd, *J* = 14.9, 4.3 Hz, 1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 162.7, 136.9, 136.1, 134.4, 129.2, 128.6, 128.5, 128.1, 126.8, 126.7, 123.2, 88.1, 86.8, 70.5, 36.9. GC-MS: m/z (EI): 380 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{19}H_{17}Cl_3NO$ 380.0370; Found 380.0361 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline trans-2d. Prepared according to the method A (Table 2). 42 mg, 93% from *anti-Z*-**1d** Purified by flash chromatography. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.38 – 7.20 (m, 10H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.05 (dd, *J* = 15.8, 7.4 Hz, 1H), 4.90 (unresolved ddd, 1H), 4.68 (t, *J* = 7.4 Hz, 1H), 3.22 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.04 (dd, *J* = 14.1, 6.1 Hz, 1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 162.3, 136.0, 135.1, 132.9, 129.6, 128.8, 128.5, 128.1, 127.2, 126.61, 126.58, 89.6, 86.7, 72.9, 40.1. GC-MS: m/z (EI): 380 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{19}H_{17}Cl_3NO$ 380.0370; Found 380.0370 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline cis-2e. Prepared according to the method B. 139 mg, 90% from *anti-E*-**6e** and 308 mg, 88% from *anti-E*-**6e** as a mixture with oxazoline *trans*-***2e*** (Table 2). Purified by flash chromatography on silica gel. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.38 – 7.14 (m, 8H), 7.05 – 7.03 (m, 2H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 5.50 (dd, *J* = 15.8, 7.9 Hz, 1H), 5.30 (dd, *J* = 10.2, 7.9 Hz, 1H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 162.6, 136.3, 135.2, 133.1, 128.6, 128.5, 128.3, 127.7, 126.5, 126.2, 124.9, 87.8, 86.7, 72.4. GC-MS: m/z (EI): 366 $[M]^+$. HRMS (EI-

TOF) m/z: Calcd for $C_{18}H_{15}Cl_3NO$ 366.0214; Found 366.0184 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline trans-2e. Prepared according to the method B, 142 mg, 92% from *anti-Z*-**6e** (Table 2). Purified by flash chromatography on silica gel. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.46 – 7.25 (m, 10H), 6.65 (d, J = 15.7 Hz, 1H), 6.31 (dd, J = 15.7, 7.8 Hz, 1H), 5.58 (d, J = 8.0 Hz, 1H), 4.88 (t, J = 7.8 Hz, 1H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.2, 138.4, 135.9, 133.6, 129.1, 129.0, 128.6, 128.2, 126.7, 126.3, 125.5, 90.3, 86.6, 77.5. GC-MS: m/z (EI): 366 $[M]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{18}H_{15}Cl_3NO$ $[M]^+$ 366.0214; Found 366.0218 $[M+H]^+$. See SI for 2D-NOESY spectra

Oxazoline cis-2f. Prepared according to the method C (Table 2), 272 mg, 93% from *syn-E*-**6f** and 79 mg, 90% from *anti-E*-**6f**. Purified by flash chromatography. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.41 – 7.25 (m, 5H), 6.99 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 15.5 Hz, 1H), 6.05 (d, J = 10.0 Hz, 1H), 5.36 (dd, J = 15.5, 8.0 Hz, 1H), 5.28 (unresolved t, 1H), 3.75 (s, 3H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.5, 159.3, 135.4, 132.7, 129.1, 128.48, 128.45, 127.7, 126.3, 122.6, 113.8, 87.8, 86.7, 72.7, 55.2. GC-MS: m/z (EI): 395 $[M-H]^+$. HRMS (EI-TOF) m/z: Calcd for $C_{19}H_{17}Cl_3NO_2$ 396.0319; Found 396.0317 $[M+H]^+$. See SI for 2D-NOESY spectra.

Oxazoline trans-2f. Prepared according to the method C (Table 2), 144 mg, 89% from *anti-Z*-**6f**. Purified by flash chromatography. Colorless solid. M.p. 126 - 127°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.46 – 7.33 (m, 7H), 6.87 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 15.7 Hz, 1H), 6.15 (dd, J = 15.7, 7.7 Hz, 1H), 5.57 (d, J = 8.0 Hz, 1H), 4.84 (unresolved t, 1H), 3.82 (s, 3H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 162.1, 159.7,

138.5, 133.2, 129.1, 128.9, 128.7, 128.0, 125.6, 124.1, 114.0, 90.4, 86.6, 77.7, 55.3. GC-MS: m/z (EI): 395 $[M-H]^+$. Anal. Calcd, for $C_{19}H_{16}Cl_3NO_2 \cdot 1/3\ H_2O$: C, 56.67; H, 4.17; N, 3.48; Found: C, 56.88; H, 4.11; N, 3.38. HRMS (EI-TOF) m/z: Calcd for $C_{19}H_{17}Cl_3NO_2$ 396.0319; Found 396.0307 $[M+H]^+$. See SI for 2D-NOESY spectra.

General procedure for the synthesis of amino alcohols 7.

To a solution of oxazoline **2** (1 mmol) in EtOH (2 mL) 6 M aq. HCl (2 mL) was added and the reaction mixture was stirred at r.t. for 1–2 h, then refluxed for 10 h. Resulting solution was cooled to r.t. and concentrated in vacuum. The residue was dissolved in a mixture of saturated aq. $NaHCO_3$ (10 mL) and EtOAc (10 mL). Boc_2O (1.2 mmol, 1.2 equiv.) was added to the resulting biphasic mixture and vigorous stirring was continued overnight. Organic phase was separated and washed with water and brine, dried with Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (gradient 4:1 to 1:1) to afford product **7**.

N-Boc protected amino alcohol syn-7b. Prepared according to the general procedure, 305 mg, 87%. Colorless solid. M.p. 56 - 57°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.39 – 7.21 (m, 5H), 6.58 (d, J = 15.7 Hz, 1H), 6.18 (dd, J = 15.7, 5.9 Hz, 1H), 5.00 (bs, 1H), 4.36 – 4.22 (m, 1H), 3.79 – 3.69 (m, 1H), 1.96 (bs, 1H), 1.59 – 1.41 (m, 2H), 1.46 (s, 9H), 1.41 – 1.24 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$NMR δ_C (100 MHz, $CDCl_3$): 155.9, 136.5, 131.3, 128.5, 128.3, 127.6, 126.4, 79.6, 73.7, 56.5, 33.7, 31.7, 28.4, 25.3, 22.5, 14.0. Anal. calcd for $C_{20}H_{31}NO_3 \cdot 0.2\ H_2O$: C, 71.27; H, 9.39; N, 4.16; Found: C, 71.04; H, 9.19; N, 4.04. HRMS (EI-TOF) m/z: Calcd for $C_{20}H_{31}NO_3Na$ 356.2196; Found 356.2171 $[M+Na]^+$.

N-Boc protected amino alcohol anti-7b. Prepared according to the general procedure, 44 mg, 80%. Colorless solid. M.p. 93 - 94°C. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.39 – 7.22 (m, 5H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 7.0 Hz, 1H), 5.10 (bs, 1H), 4.33 – 4.27 (m, 1H), 3.80 – 3.72 (m, 1H), 1.86 (bs, 1H), 1.57 – 1.22 (m, 8H), 1.45 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 155.5, 136.6, 133.0, 128.5, 127.7, 126.5, 124.9, 79.7, 74.3, 57.1, 34.1, 31.7, 28.4, 25.5, 22.5, 14.0. Anal. calcd for $C_{20}H_{31}NO_3 \cdot 0.25\ H_2O$: C, 71.08; H, 9.39; N, 4.14; Found: C, 71.34; H, 9.26; N, 4.06. HRMS (EI-TOF) m/z: Calcd for $C_{20}H_{31}NO_3Na$ 356.2196; Found 356.2170 $[M+Na]^+$.

N-Boc protected amino alcohol syn-7c. Prepared yield according to the general procedure, 118 mg, 83%. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.39 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 16.0, 7.4 Hz, 1H), 5.23 (bs, 1H), 4.49 – 4.40 (m, 1H), 3.37 – 3.31 (m, 1H), 1.87 (bs, 1H), 1.71 – 1.61 (m, 1H), 1.45 (s, 9H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 155.9, 136.6, 131.1, 128.8, 128.5, 127.6, 126.4, 79.6, 79.0, 54.4, 30.5, 28.3, 19.2, 18.2. Oil. HRMS (EI-TOF) m/z: Calcd for $C_{18}H_{27}NO_3Na$ 328.1883; Found 328.1856 $[M+Na]^+$.

N-Boc protected amino alcohol anti-7c. Prepared according to the general procedure, 42 mg, 88%. Colorless oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.38 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 15.8, 7.4 Hz, 1H), 5.24 (bs, 1H), 4.49 – 4.39 (m, 1H), 3.39 – 3.35 (m, 1H), 1.86 (bs, 1H), 1.72 – 1.60 (m, 1H), 1.45 (s, 9H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 155.2, 136.6, 132.9, 128.5, 127.7, 126.5, 124.7, 79.7, 79.5, 54.6, 31.4, 28.4, 19.0, 18.7. HRMS (EI-TOF) m/z: Calcd for $C_{18}H_{27}NO_3Na$ 328.1883; Found 328.1857 $[M+Na]^+$.

N-Boc protected amino alcohol anti-7d. Prepared according to the general procedure, 33 mg, 89%. Colorlessn oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.40 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.20 (m, 8H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.26 (dd, *J* = 16.0, 7.8 Hz, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.36 – 4.26 (m, 1H), 4.06 – 3.94 (m, 1H), 2.82 (dd, *J* = 13.7, 4.0 Hz, 1H), 2.69 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.23 (bs, 1H), 1.44 (s, 9H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 155.4, 137.8, 136.6, 133.4, 129.3, 128.64, 128.55, 127.8, 126.6, 126.5, 124.9, 79.7, 75.0, 57.1, 40.6, 28.4. HRMS (EI-TOF) m/z: Calcd for $C_{22}H_{27}NO_3Na$ 376.1183; Found 376.1860 $[M+Na]^+$.

N-Boc protected amino alcohol syn-7e. Prepared according to the general procedure (149 mg, 90%) as an oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$):7.39 – 7.22 (m, 10H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 5.9 Hz, 1H), 4.95 (d, *J* = 7.4 Hz, 1H), 4.86 – 4.82 (m, 1H), 4.61 – 4.55 (m, 1H), 2.87 (bs, 1H), 1.38 (s, 9H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 155.8, 140.7, 136.5, 131.7, 128.5, 128.3, 127.8, 127.7, 127.0, 126.5, 79.8, 76.1, 58.3, 28.3. HRMS (EI-TOF) m/z: Calcd for $C_{21}H_{25}NO_3Na$ 362.1727; Found 362.1702 $[M+Na]^+$.

N-Boc protected amino alcohol anti-7e. Prepared according to the general procedure (64 mg, 87% yield) as an oil. ^{1}H-NMR δ_H (400 MHz, $CDCl_3$): 7.39 – 7.15 (m, 10H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.97 (dd, *J* = 16.0, 5.7 Hz, 1H), 4.95 (d, *J* = 7.4 Hz, 1H), 4.91 – 4.82 (m, 1H), 4.59 – 4.46 (m, 1H), 2.97 (bs, 1H), 1.38 (s, 9H). ^{13}C{^{1}H}NMR δ_C (100 MHz, $CDCl_3$): 155.8, 146.7, 140.4, 136.5, 132.6, 128.5, 128.2, 127.7, 126.4, 126.3, 124.8, 80.0, 76.6, 58.5, 28.4. HRMS (EI-TOF) m/z: Calcd for $C_{21}H_{25}NO_3Na$ 362.1727; Found 362.1700 $[M+Na]^+$.

DFT calculations of the reaction energy profile. All calculations were performed using Gaussian 09.[14] Geometry optimizations were performed without any restrains

using density functional theory method B3LYP with 6-31++g(d,p) basis set (for all atoms). For compounds that had multiple conformations lowest-energy conformation was found by comparing the structures optimized from different starting points. Stationary points were verified to be real minima (zero imaginary frequency) or transition states (one imaginary frequency) by performing frequency calculations at the same level of theory. Thermochemical analysis was done at 298.15 K. Transition states were located using either Berny or QST2 algorithm. Intrinsic reaction coordinates (IRC) were calculated for the transition states to confirm that the saddle point connected the correct reactant and product on the potential energy surface. Single-point energy calculations were performed on the stationary points using a larger basis set 6-311++G(3df,2p). Thermal correction to Gibbs free energy from lower level frequency calculations combined with single-point energies was used to describe reaction energetics.

Supporting Information.

Full set of bis-imidate **1** cyclization results and DFT calculations. Copies of NMR spectra of compounds **1-7**. This material is available free of charge via the Internet at http://pubs.acs.org/."

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Acknowledgements

This work has been supported by the European Social Fund within the project «Support for the implementation of doctoral studies at Riga Technical University». Financial support from the European Regional Development Fond (grant number

ERAF 2010/2DP/2.1.1.1.0./10/APIA/ VIAA/074) is gratefully acknowledged. We thank A. Maleckis for assistance in manuscript preparation and Prof. E. Liepins for 2-NMR investigations.

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