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# Double diastereoselection in asymmetric [2+3] cycloaddition of chiral oxazoline *N*-oxides: application to the kinetic resolution of a racemic α,β-unsaturated δ-lactone

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**Abstract**

The asymmetric [2+3] cycloaddition reaction between chiral oxazoline *N*-oxide **1** and α,β-unsaturated lactone **2** was studied. A double diastereoselection was observed, (1*R*)-**1** and (*R*)-**2** gave a mismatched pair with almost no cycloadduct obtained. A transition state model is proposed, accounting for the destabilization of transition state in the cycloaddition reaction. This result has led to kinetic resolution studies, in which both enantiomers of **1** were reacted with racemic lactone **2**. The enantiomeric excess of the recovered lactone **2** was determined to be up to 70% ee, by $^{13}C$-{$^{1}H$} NMR analysis in a chiral liquid crystalline solvent. The experimental results are in agreement with predicted enantiomeric excesses and consistent with the transition state models. 

## 1. Introduction

In recent years, we have been exploring the scope and applications of asymmetric [2+3] cycloadditions between chiral, camphor-derived oxazoline *N*-oxide **1** and various electron-deficient alkenes.[1] This new type of dipole undergoes highly regio- and stereoselective cycloadditions with various α,β-unsaturated esters, nitriles and nitro compounds. The corresponding cycloadducts are transformed into highly functionalized, enantiomerically pure acyclic products, by oxidative hydrolysis of the chiral auxiliary; the overall process may be considered as an 'asymmetric alkene hydroxyacylation',[2,3] and has been applied to the total synthesis of spiroketals,[2] carbovir,[4] and β-lactonic natural products such as 1233A[5] (Eq. 1).

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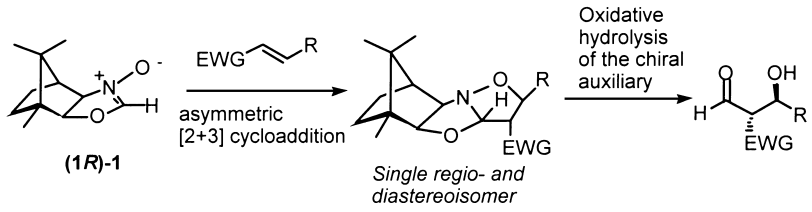
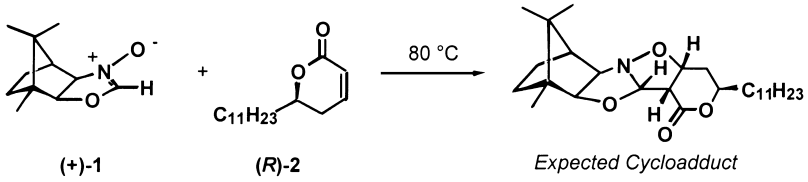



(1)

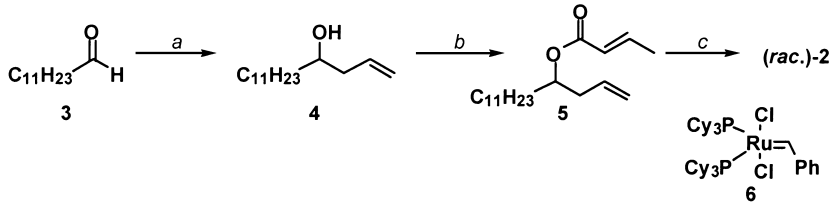
In a project connected to the total synthesis of the pancreatic lipase inhibitor tetrahydrolipstatin,[6] we were interested in the cycloaddition reaction between **1** and the enantiomerically pure α,β-unsaturated δ-lactone **2**. Since control experiments using racemic lactone as the dipolarophile showed good reactivity and complete regioselectivity in the cycloaddition reaction, we anticipated that the same reaction using optically active lactone **2** could be a valuable key step in the synthetic scheme (Scheme 1). In the present article, we wish to present our observations concerning double diastereoselection in the asymmetric [2+3] cycloaddition,[7] and kinetic resolution of the lactone **2**.




Scheme 1.

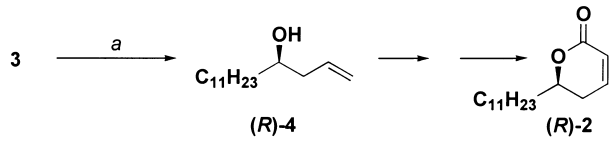
## 2. Results and discussion

6-Undecyl-5,6-dihydro-2-pyranone **2** was prepared in both its racemic and optically active form via an original route, starting from dodecanal **3** (Scheme 2).[8] Reaction with excess allylmagnesium bromide solution gave the sensitive, elimination-prone homoallylic alcohol **4** which was acylated with crotonic acid in the presence of DCC. The resulting ester **5** was subjected to ring-closing alkene metathesis using Grubbs' catalyst **6**[9] with added titanium tetraisopropoxide, as described by Fürstner and co-workers.[10] Under these conditions, a satisfying 70% yield of the lactone **2** was obtained (Scheme 2).



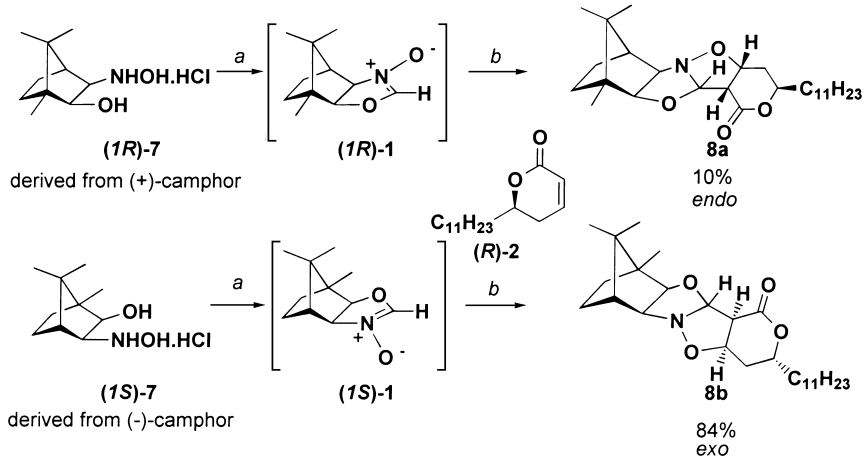

Scheme 2. a: AllylMgBr, $Et_2O$, 0°C, 70%; b: $CH_3CH{=}CHCO_2H$, DCC, DMAP, $CH_2Cl_2$, 96%; c: 15% **6**, 0.3 equiv. $Ti(OPr^i)_4$, $CH_2Cl_2$, reflux, 70%

The optically active lactone (*R*)-**2** was prepared via a similar route, in which dodecanal was treated with (−)-allyldiisopinocamphenylborane, obtained in situ by the reaction between allylmagnesium chloride and (−)-DIP chloride,[11] to give the optically active alcohol **4** with 60% yield and 90% ee, as determined by $^1H$ NMR analysis of the corresponding *O*-acetylmandelate ester (Scheme 3).[12] The alcohol **4** was then transformed in two steps into (*R*)-**2**.




Scheme 3. a: AllylMgBr, (−)-DIP-Cl, $Et_2O$, 78°C, 60%, 90% ee

With both racemic and optically active lactones in hand, their cycloaddition was investigated. Oxazoline *N*-oxide (1*R*)-**1** (derived from (+)-camphor) was prepared in situ by treatment of hydroxylamino alcohol **7** with excess trimethylorthoformate in the presence of calcium carbonate, at 45°C for 4 h.[2] The dipolarophile (1.15 equiv.) was then added, the temperature raised to 80°C and the reaction stirred for 12 h. When lactone (*R*)-**2** was used, a very slow reaction occurred, giving only 10% yield of the cycloadduct **8a**, with 85% recovered lactone. Careful analysis of the NMR spectrum (with NOE) revealed that the cycloadduct was issued from an *endo* transition state. Considering the very low kinetics of reaction, we thought that a disfavorable interaction between the long aliphatic chain and the chiral auxiliary could destabilize the transition state, thus inhibiting the reaction. At this stage, it was important to determine if the absolute configurations of the cycloaddition partners had an influence on the course of the reaction. Accordingly, a cycloaddition between (*R*)-**2** and the enantiomeric oxazoline *N*-oxide (1*S*)-**1** (derived from (−)-camphor) was undertaken. Under the same conditions, the cycloaddition reaction gave 84% yield of the cycloadduct **8b**, with 12% recovered starting lactone. NMR analysis of the cycloadduct **8b** showed this was issued from an *exo* transition state (Scheme 4).

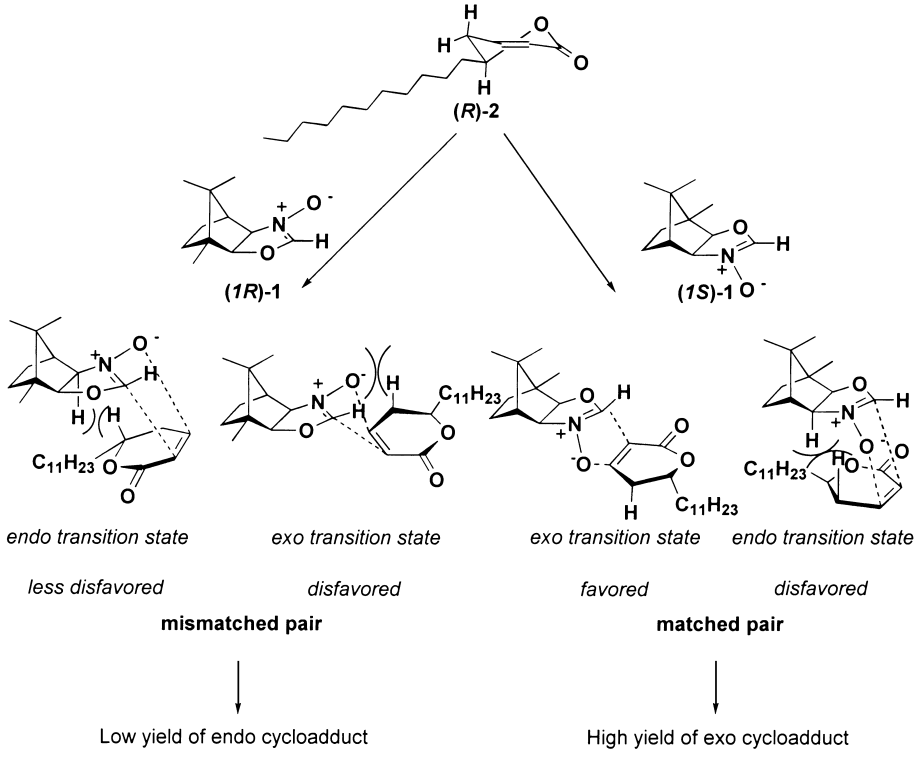



Scheme 4. a: $HC(OMe)_3$, $CaCO_3$, PhMe, 45°C, 4 h; b: 80°C, 12 h

These two experiments gave two crucial pieces of information on the course of the cycloaddition reaction.

(i) The asymmetric [2+3] cycloaddition between oxazoline *N*-oxide **1** and α,β-unsaturated lactone **2** is *exo* selective. This is probably due to destabilization of the *endo* transition state by allylic interactions between the cyclic hydrogens on the lactone and the *endo* hydrogen atoms on the bornane ring system, although this effect seems to be less important in the transition state of the cycloaddition between (*1R*)-**1** and (*R*)-**2** (Scheme 5).

(ii) There is a double diastereoselection effect in the cycloaddition, the oxazoline *N*-oxide (1*R*)-**1** and the lactone (*R*)-**2** forming a mismatched pair, whereas the enantiomeric oxazoline *N*-oxide (1*S*)-**1** forms a matched pair with (*R*)-**2**. In the case of the mismatched pair the reaction through the




Scheme 5.

normally favoured *exo* transition state is completely inhibited and a small amount of the *endo* product is formed.

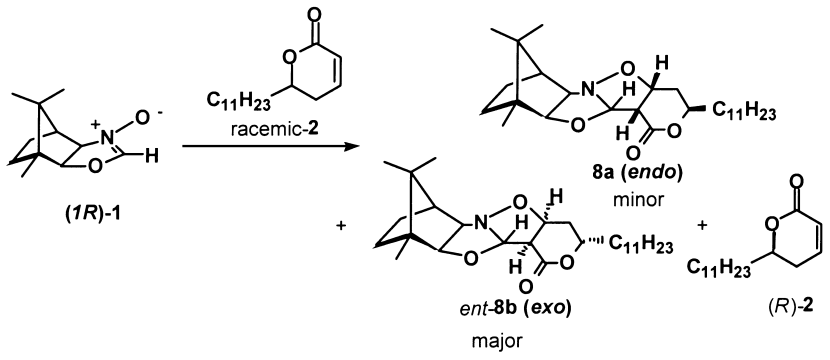
Molecular modelling shows that the probable preferred conformation in (*R*)-**2** is the one showed in Scheme 5, with the aliphatic chain in the pseudo-equatorial position. In its cycloaddition reaction with (1*R*)-**1**, an interaction between the pseudo-axial hydrogen on the carbon $C_5$ in the lactone ring and the negatively charged oxygen atom of the oxazoline *N*-oxide destabilizes the *exo* transition state, whilst this disfavorable interaction is not seen in the *exo* transition state of the reaction between (1*S*)-**1** and (*R*)-**2**. This could account for the very low reactivity of (1*R*)-**1** when reacted with (*R*)-**2**.

Despite the fact that a small amount of *endo* cycloadduct **8a** is formed in the cycloaddition with the mismatched pair, the great difference of reactivity for both enantiomers could allow the kinetic resolution of the racemic lactone **2**. Although kinetic resolution of racemates using various enantioselective reactions is well documented,[13] only a few examples of kinetic resolutions with asymmetric [2+3] cycloadditions are known, and they generally use a chiral nitrone.[14] On the basis of literature precedent, we thought it would possible to achieve high levels of resolution of lactone **2**. Consequently, a series of asymmetric [2+3] cycloadditions between each enantiomer of **1** and racemic **2** with various stoichiometry was undertaken. The analysis of product distribution is based on the following hypothesis:

(1*R*)-**1** and (*R*)-**2**: mismatched pair; *endo* cycloadduct **8a** only
(1*R*)-**1** and (*S*)-**2**: matched pair; *exo* cycloadduct *ent*-**8b** only
(1*S*)-**1** and (*R*)-**2**: matched pair; *exo* cycloadduct **8b** only
(1*S*)-**1** and (*S*)-**2**: mismatched pair; *endo* cycloadduct *ent*-**8a** only

Therefore, the reaction between (1*R*)-**1** and racemic **2** should result in the enantiomeric enhancement

of (*S*)-**2**, while the reaction between (1*S*)-**1** and racemic **2** should give predominantly recovered (*R*)-**2**. The expected products are shown in Scheme 6.




Scheme 6.

In order to check this hypothesis, the expected enantiomeric excess of optically active **2** was calculated, and then compared to the ee determined using the $^{13}C$-{$^{1}H$} NMR in a chiral liquid crystalline solvent. The yield of each cycloadduct and recovered lactone was calculated by integration of characteristic proton NMR signals and based on each enantiomer of the lactone. The expected ratio of enantiomers in recovered **2** was based on the following calculation (Eq. 2), where $Y_{minor}$ is the yield of minor cycloadduct (based on the enantiomerically pure lactone partner), and $Y_{major}$ is the yield of major cycloadduct (based on the enantiomerically pure lactone partner).

$$ee = \frac{(1-Y_{minor}) - (1-Y_{major})}{(1-Y_{major}) + (1-Y_{major})} \quad (2)$$

The α,β-unsaturated lactones are chiral compounds that are rather difficult to discriminate using one of the usual methods in the field of enantiomeric analysis, i.e. chiral HPLC and GC, chiral shift reagents etc. Consequently, it was of real interest to investigate and use new analytical tools such as NMR spectroscopy in chiral oriented media. It has been recently reported that the proton-decoupled deuterium, fluorine-19 or carbon-13 (at natural abundance level) NMR in chiral liquid crystals could provide an appropriate and competitive alternative to the current techniques.[15–17] This approach consists of using a polypeptide lyotropic chiral liquid crystal, made of a solution of poly-ɣ-benzyl-L-glutamate (PBLG) into various organic solvents (such as chloroform, DMF or THF), as NMR solvent.[15] The spectral discrimination between *R*- and *S*-isomers in a chiral anisotropic solvent originates from a difference in their ordering $((S_{\alpha\beta})^{R}$ $(S_{\alpha\beta})^{S})$[18], thus affecting all the order dependent NMR interactions, namely the quadrupolar splittings for spin $I > 1/2$ nuclei ($\Delta\nu_Q$), the dipolar couplings ($D_{ij}$) and the chemical shift anisotropies ($\Delta\sigma_i$). This method was successfully applied on a wide range of chiral site-specific deuterated materials using $^{2}H$-{$^{1}H$} NMR, including compounds with low polarity such as hydrocarbons or molecules which are only chiral by virtue of H/D isotopic substitution.[15] However, when deuteration of the chiral compound is not possible or simple to achieve, we have shown that proton-decoupled natural abundance carbon-13 NMR ($^{13}C$-{$^{1}H$}) may be used efficiently, and allows the measurement of enantiomeric excess with an accuracy of about 5%.[16] In this method, the enantiomeric discrimination is observed through a difference in the carbon-13 chemical shift anisotropies (C-13 CSA), leading to two separated peaks for each discriminated carbon-13 atoms of the chiral molecule. As the parameters governing the magnitude of the carbon-13 CSA increases with the hybridization state of the carbon atoms

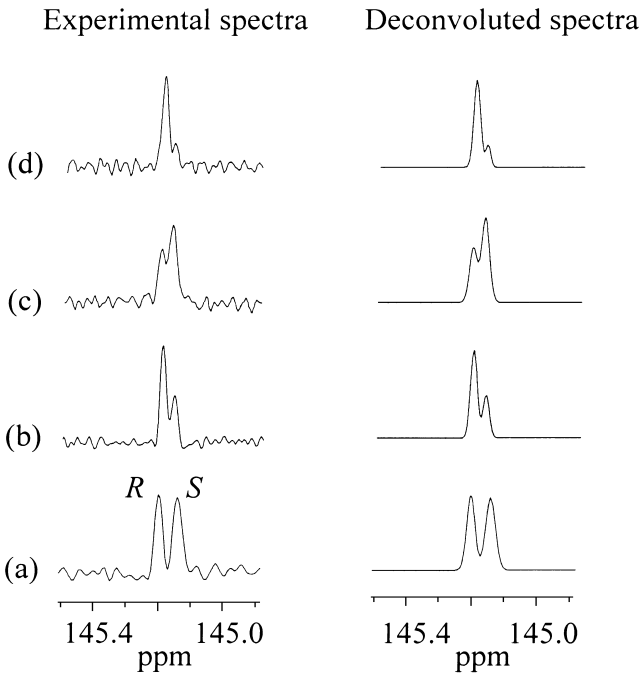



Figure 1. 100.62 MHz $^{13}C$-{$^{1}H$} NMR spectra associated to the C-4 ethylenic carbon of **2**. The NMR spectra were recorded at 298 K on a DRX 400 spectrometer using an inverse 5 mm multinuclear probe. WALTZ-16 pulse sequence (1 W of $R_f$ power) was used as broad-band proton decoupling. The carbon-13 interferograms were acquired using a pulse angle of ~60°, a recycle delay of ~2 s and 16 000 of data points. About 8000 scans were added for each spectrum. Zero filling to 32 K was applied to increase the digital resolution. A gaussian filtering was applied to enhance the spectral appearance. For the C-4 carbon: $\delta_R - \delta_S = 0.036$ ppm (3.5 Hz). The enantiomeric excess measured by numerical deconvolution on the (b), (c) and (d) spectra is of 36±5% (*R*-enriched), 21±5% (*S*-enriched) and 69±5% (*R*-enriched), respectively

($\Delta\sigma$ (*sp*) > $\Delta\sigma$ ($sp^2$) > $\Delta\sigma$ ($sp^3$))[16], we could then favorably anticipate to observe a measurable chiral discrimination on the ethylenic carbons of the lactone **2**.

For the present study, the NMR samples were made from 100 mg of PBLG (DP=562, MW 120 000 g $mol^{-1}$) purchased at Sigma Corp., about 40 mg of chiral solute and 350 mg of $CHCl_3$. The materials were weighed directly into a 5 mm o.d. NMR tube. Under these conditions, the total volume of the sample is optimal compared to the length of the coil of a 5 mm diameter probe. All tubes were sealed to avoid the evaporation of chloroform and centrifuged back and forth until an optically homogeneous birefringent phase was obtained.

Fig. 1a presents the 100.62 MHz $^{13}C$-{$^{1}H$} spectrum associated with the C-4 ethylenic carbon of (*rac*)-**2** (34 mg) in the PBLG/$CHCl_3$ phase at 298 K. As expected, the result obtained was successful since the analysis of the spectrum showed two peaks for this carbon with a chemical shift difference of 0.036 ppm (3.5 Hz) for the two enantiomers. However, no visible separation was obtained on the C-3 carbon of (*rac*)-**2**. Actually it appears that the DOE, $\delta_R - \delta_S$, for the C-3 carbon was negligible and led to a failure of the chiral discrimination.[16] In order to confirm this result and assign the C-13 signal for the *R*- and *S*-isomers, we then added 17 mg of pure (*R*)-**2** to the previous racemic mixture, thus leading to 33% ee for the mixture. Fig. 1b presents the $^{13}C$-{$^{1}H$} spectrum of **2** enriched in (*R*)-**2**. When comparing this spectrum with that of (*rac*)-**2**, we clearly observed a difference in peak intensity, and we showed, therefore, that (*R*)-**2** exhibits the most deshielded signal in the spectrum.

Although the peak separation is rather small, the measurement of the ee on spectrum 1b is possible

Table 1

| Entry | Dipole (eq.) | Dipolaro-phile (eq.) | Yield **8a** (*endo*)[a] | Yield **8b** (*exo*)[a] | $Y_{major}$[b] | $Y_{minor}$[b] | Yield of recovered **2**[a] | Calculated ee (absolute configura-tion) | Observed ee (absolute configura-tion)[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (1*R*)-**1** (2) | *rac*-**2** (1) | 2.3% | 41.7%[d] | 83.4% | 4.6% | 58.7% | 70% (*S*) | / |
| 2 | (1*R*)-**1** (1) | *rac*-**2** (1) | 1.4% | 31.5%[d] | 63% | 2.8% | 63% | 45% (*S*) | / |
| 3 | (1*R*)-**1** (1) | *rac*-**2** (2) | 1.2% | 38.3%[d] | 38.3% | 1.2% | 78% | 23% (*S*) | 21% (*S*) |
| 4 | (1*S*)-**1** (2) | *rac*-**2** (1) | 2.5%[e] | 42% | 84% | 5% | 58% | 71% (*R*) | 69% (*R*) |

All reactions were performed in toluene at 80 °C for 12h; [a]: determined by NMR analysis of the crude product; [b]: based on the enantiomeric lactone partner; [c]: based on the analysis of the $^{13}C$-{$^{1}H$} spectrum in the chiral anisotropic phase; [d]: *ent*-**8b**; [e]: *ent*-**8a**

using a numerical deconvolution. From the deconvoluted spectrum given in the right side of Fig. 1, we could determine an ee of 36%, i.e. an experimental error within 3% of the true value. Such a result indicates that the confidence interval on the ee measurements is satisfactory and allows quantitative studies within an accuracy of about 5%.

With this tool for the determination of enantiomeric excess of **2** in hand, several kinetic resolution studies (entries 1–4) were carried out. The results are reported in Table 1. Among these various studies, we have compared the ee calculated in the isotropic phase with that determined on the $^{13}C$-{$^{1}H$} spectrum in the chiral anisotropic phase for two optically active mixtures (entries 3 and 4). As an illustration, the experimental and deconvoluted spectra of **2** for the studies 3 and 4 are presented in Fig. 1c and d. The two spectra show clearly that an enantiomeric excess was obtained in both cases with the inversion of enantiomer in excess, and the comparison with the spectrum 1b allows their assignment unambiguously. The enantiomeric excess measured by deconvolution of (c) and (d) spectra is of 21±5% ((*S*)-enriched) and 69±5% ((*R*)-enriched), respectively. These results are, therefore, in full agreement with the predicted ones and show the efficiency of two approaches in the determination of the enantiomeric excess for **2**.

In conclusion, these results proved an effective kinetic resolution of lactone **2** occurring in the [2+3] cycloaddition between racemic **2** and each enantiomer of **1**, the best enantiomeric excess (ee 70%) being obtained when two equivalents of the dipole were used. In addition, the absolute configuration and enantiomeric excess of recovered **2** found using NMR in a chiral liquid crystal are in full agreement with the predicted ones in isotropic phase, thus confirming the initial hypothesis in kinetic resolution: one enantiomer of **2** is rapidly consumed in the cycloaddition whereas the other enantiomer is more slowly consumed. Work is now in progress to improve the enantiomeric excess of the kinetic resolution.

## 3. Experimental

### *3.1. General*

Melting points are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded at 200 or 250 MHz and 50 or 62.5 MHz, respectively. NMR studies in chiral liquid were performed on a Bruker DRX-400 spectrometer. Optical rotations were recorded at 25°C. Chromatographic purifications were performed on 230–400 mesh silica gel (Merck 9385) using the indicated solvent system. Dichloromethane and trimethylorthoformate were distilled from calcium hydride. Toluene, diethyl ether and THF were distilled

from sodium metal/benzophenone ketyl. Dodecanal, dicyclohexylcarbodiimide and titanium tetraisopropoxide were distilled under vacuum prior to use. Chloroform used for optical measurements was filtered through basic alumina before use. The Grubbs' catalysts were obtained from Fluka. Unless otherwise stated, all non-aqueous reactions were performed under an argon atmosphere using oven-dried glassware.

### 3.2. (4RS)-1-Pentadecen-4-ol **4**

A solution of dodecanal **3** (5 g, 27.17 mmol) in dry diethyl ether (100 mL) was cooled to −78°C with stirring and an allylmagnesium bromide solution (1 M in diethyl ether, 27 mL, 27 mmol) was added dropwise. The reaction mixture was stirred at −78°C for 3 h, then quenched by careful addition of water (5 mL) and warmed to room temperature. The mixture was then poured into water (50 mL) and extracted with diethyl ether (3×50 mL). The combined organic layer was washed with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification by chromatography (20% diethyl ether/heptane; $R_f$: 0.26) gave the homoallylic alcohol **4** as a colorless oil (4.3 g, 70% yield).

### 3.3. (4R)-1-Pentadecen-4-ol **4**

A solution of (−)-*B*-chlorodiisopinocampheynyl borane ((−)-DIP-Cl, derived from (+)-pinene, 9.6 g, 30 mmol) in dry diethyl ether (30 mL) was cooled to −40°C and an allylmagnesium bromide solution (1 M in diethyl ether, 25 mL, 25 mmol) was added dropwise. The solution was stirred for 1 h at room temperature, then cooled to −78°C. A solution of freshly distilled dodecanal **3** (4.41 mL, 20 mmol) in dry diethyl ether (10 mL) was added very slowly. The mixture was stirred for 6 h at −78°C then warmed to 0°C; acetaldehyde (10 mL, 180 mmol) was then added. After stirring for 18 h at room temperature, the reaction was quenched by successive addition of a 3 M aqueous sodium acetate solution (20 mL) and 35% hydrogen peroxide solution (10 mL). After 30 min, the solution was diluted with water (50 mL) and extracted with diethyl ether (3×100 mL). The combined organic layer was washed with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification by chromatography (20% diethyl ether/heptane; $R_f$: 0.26) gave the homoallylic alcohol **4** as a colorless oil (2.68 g, 60% yield.) The enantiomeric excess was determined to be 90% by NMR analysis of the (+)-*O*-acetylmandelate ester.

Data for **4**: IR (film): $\nu$ ($cm^{-1}$): 3360, 2920, 2840, 1700, 1455, 1115, 1075, 1018, 985, 900; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ (ppm): 5.82 (1H, m, $C_2$-H), 5.11 (2H, m, $C_1$-H×2), 3.62 (1H, m, $C_4$-H), 2.19 (2H, m, $C_3$-H×2), 1.47 (2H, m, $C_5$-H×2), 1.25 (18H, broad s, $C_6$-$C_{14}$-H), 0.87 (3H, t, J=7 Hz, $C_{15}$-H×3; $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm): 134.9 ($C_2$), 117.9 ($C_1$), 70.6 ($C_4$), 41.9 ($C_3$), 36.8 ($C_5$), 31.9, 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.6, 22.6 ($C_6$-$C_{14}$), 14.1 ($C_{15}$); $[\alpha]_D$=+5.4 (c=1.06, $CHCl_3$); lit.[11]: $[\alpha]_D$=+5.8 (c=2.89, $CHCl_3$).

### 3.4. (4RS)- and (4R)-4-(2-Butenoyloxy)-1-pentadecene **5**

This procedure applies for both racemic and optically active material.

A solution of the homoallylic alcohol **4** (6.2 g, 27.5 mmol, previously dried by azeotropic evaporation with toluene), crotonic acid (9.45 g, 110 mmol, 4 equiv.) and 4-dimethylaminopyridine (3.35 g, 27.5 mmol) in dry dichloromethane (150 mL) was cooled to 0°C and dicyclohexylcarbodiimide (22.64 g, 110 mmol, 4 equiv.) was added portionwise. The mixture was successively stirred for 2 h at 0°C, 1 h at room temperature, then 1 h at reflux. After cooling to room temperature, the reaction mixture was filtered through a pad of silica gel, eluting with dichloromethane. The filtrate was concentrated in vacuo and the

crude product purified by chromatography (3% diethyl ether/heptane) to give the ester **5** as a colorless oil (7.4 g, 96% yield).

IR (film): ν ($cm^{-1}$): 3400, 2920, 2118, 1710, 1645, 1435, 1280, 1250, 1175, 1090; $^1$H NMR (250 MHz, $CDCl_3$): δ (ppm): 6.93 (1H, dq, J=15.5 and 6.9 Hz, C*H*=$CH_3$-$CH_3$), 5.80 (1H, dq, J=15.5 and 1.5 Hz, CH=C*H*-$CH_3$), 5.72 (1H, m, $C_2$-H), 4.99 (3H, m, $C_4$-H and $C_1$-H×2), 2.30 (2H, m, $C_3$-H×2), 1.85 (3H, dd, J=6.9 and 1.5 Hz, CH=CH-C*H*$_3$), 1.55 (2H, m, $C_5$-H×2), 1.22 (18H broad s, $C_6$-$C_{14}$-H), 0.84 (3H, t, J=6.5 Hz, $C_{15}$-H×3); $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 166.2 (CO), 144.2 (CH=*C*H-$CH_3$), 133.8 ($C_2$), 123.0 (*C*H=CH-$CH_3$), 117.4 ($C_1$), 73.0 ($C_4$), 38.6 ($C_3$), 34.9 ($C_5$), 33.6, 31.9, 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.2 ($C_6$-$C_{14}$), 17.9 (CH=CH-*C*$H_3$), 14.1 ($C_{15}$); mass (electrospray): m/z: 317.2 ($M^{+\cdot}$+23); $[\alpha]_D$=+14.2 (c=1.15, $CHCl_3$); high resolution mass spectrum, calcd for $C_{19}H_{34}NaO_2$: 317.2456; found: 317.2456.

### 3.5. *(6*RS*)- and (6*R*)-6-Undecyl-5,6-dihydro-2-pyranone **2***

The following procedure applies for both racemic and optically active material.

Freshly distilled titanium tetraisopropoxide (0.455 mL, 1.53 equiv.) was added to a solution of the above crotonate **5** (1.43 g, 5.1 mmol) in dry, degassed dichloromethane (500 mL), and the resulting solution was stirred at reflux for 1 h. After cooling to room temperature, the Grubbs' catalyst **6** [bis(tricyclohexylphosphine)benzylidene ruthenium dichloride] was rapidly added. Ethylene was then bubbled for 5 min into the solution. After the gas inlet was removed, the purple solution was stirred at reflux under an atmosphere of ethylene (ethylene balloon) for 24 h. The mixture was then cooled to room temperature, filtered through a pad of silica gel, eluting with diethyl ether. The filtrate was concentrated in vacuo. The residue was purified by chromatography (25% diethyl ether/heptane) to give the α,β-unsaturated δ-lactone **2** as a white solid (0.9 g, 70% yield).

Mp: 32°C; lit.[8]: mp: 32–34°C; IR (film): ν ($cm^{-1}$): 3400, 3020, 2903, 2830, 1705, 1450, 1375, 1255, 1030, 805, 735; $^1$H NMR (200 MHz, $CDCl_3$): δ (ppm): 6.86 (1H, ddd, J=9.8, 8.3, 2.0 Hz, $C_4$-H), 5.98 (1H, dt, J=9.8, 2.0, $C_3$-H), 4.38 (1H, m, $C_6$-H), 2.30 (2H, m, $C_5$-H×2), 1.60 (2H, m, $C_{1'}$-H×2), 1.25 (18H, broad s, $C_{2'}$-$C_{10'}$-H), 0.84 (3H, t, J=6.5 Hz, $C_{11'}$-H×3); $^{13}$C NMR (50 MHz, $CDCl_3$): δ (ppm): 164.7 ($C_2$), 145.1 ($C_4$), 121.3 ($C_3$), 78.0 ($C_6$), 34.8 ($C_5$), 31.8 ($C_{1'}$), 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.2, 24.75, 22.6 ($C_{2'}$-$C_{10'}$), 14.1 ($C_{11'}$); mass (IC $NH_3$): m/z: 270 (M+18), 253 ($MH^+$); mass (electrospray): m/z: 275.1 (M+23); $[\alpha]_D$=−44.1 (c=1, $CHCl_3$); high resolution mass spectrum, calcd for $C_{18}H_{28}NaO_2$: 275.1987; found: 275.1991.

### 3.6. *Kinetic resolution of racemic lactone **2** by cycloaddition with oxazoline* N*-oxide (1*R*)-**1***

This procedure is typical for cycloadditions between oxazoline *N*-oxide **1** and lactone **2**.

Calcium carbonate (0.2 g, 0.2 mmol) and powdered 4 Å molecular sieves (0.2 g) were flame-dried and cooled under an argon atmosphere. (1*R*)-Hydroxylamino isoborneol hydrochloride **7**[2] (0.206 g, 0.93 mmol) was added and the solids were suspended in dry toluene (10 mL). Trimethylorthoformate (0.4 mL, 0.37 mmol, 4 equiv.) was added with a syringe, and the white suspension was vigorously stirred at 45°C (oil bath temperature) for 4 h. The racemic lactone **2** was then added in one portion, and the temperature raised to 80°C. The reaction mixture was stirred for 12 h, then cooled to room temperature and filtered through a short pad of Celite. The filtrate was concentrated in vacuo and the residue purified by column chromatography (25% diethyl ether/heptane) to give a mixture of cycloadducts **8a** and/or *ent*-**8b** and recovered lactone **2**. The ratio of products was determined by integration of characteristic protons in each structure (**8a**: $C_{5b}$-H: 5.76 ppm; *ent*-**8b**: $C_{5b}$: 5.36 ppm; **2**: $C_3$-H: 5.98 ppm; $C_4$-H: 6.86

ppm). A second purification by chromatography (15% diethyl ether/heptane) allowed separation of each cycloadduct from the recovered lactone.

*3.7. (1a*R,*3*R,*5a*S,*5b*S,*6b*S,*7*R,*10*R,*10a*R*)-4-Oxa-5-oxo-3-undecyl-7,10,10-trimethyl-5,8-methano-perhydro-benzo[*d*]isoxazolo[3,2-*b*]benzoxazole* ***8a***

$R_f$: 0.28 (50% diethyl ether/heptane); IR (film): ν ($cm^{-1}$): 3400, 3025, 2900, 1723, 1410, 1260, 885, 735; $^1$H NMR (250 MHz, $CDCl_3$): δ (ppm): 5.76 (1H, d, J=1.5, $C_{5b}$-H), 4.70 (1H, dt, J=8.2 and 7.8, $C_{1a}$-H), 4.10 (1H, m, $C_3$-H), 3.91 (1H, d, J=7.6, $C_{6a}$-H), 3.24 (1H, d, J=7.6, $C_{10a}$-H), 2.98 (1H, dd, J=8.4 and 1.5, $C_{5a}$-H), 2.20 (2H, ddd, J=14.1, 8.2 and 1.5, $C_2$-H×2), 2.04 (1H, d, J=4.3, $C_{10}$-H) 1.67 (2H, m, $C_9$-H×2), 1.37 (2H, m, $C_8$-Hx2), 1.21 (20H, broad s, $CH_2$×10), 0.93–0.74 (12H, 3s and partially obscured t, $CH_3$×4); $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 169.6 (CO), 99.6 ($C_{5b}$), 88.9 ($C_{6a}$), 76.0 ($C_{1a}$), 74.3 ($C_{10a}$), 72.0 ($C_3$), 51.9 ($C_{5a}$), 48.8 ($C_{10}$), 48.4 ($C_{11}$), 45.9 ($C_7$), 34.7 ($C_2$), 31.8 ($C_8$), 25.4 ($C_9$), 32.2, 31.5, 29.53, 29.52, 29.4, 29.3, 29.25, 29.23, 24.8, 22.6 ($CH_2$×10), 22.1, 19.1, 14.0, 10.6 ($CH_3$×4); mass (electrospray): m/z: 470.2 (M+23); $[\alpha]_D$=−61.0 (c=1, $CHCl_3$); high resolution mass spectrum, calcd for $C_{27}H_{45}NNaO_4$ (M+Na): 470.3246; found: 470.3247.

*3.8. (1a*S,*3*S,*5a*R,*5b*S,*6b*S,*7*R,*10*R,*10a*R*)-4-Oxa-5-oxo-3-undecyl-7,10,10-trimethyl-5,8-methano-perhydro-benzo[*d*]isoxazolo[3,2-*b*]benzoxazole* ent-***8b***

$R_f$: 0.22 (50% diethyl ether/heptane); IR (film): ν ($cm^{-1}$): 3370, 2920, 2840, 1720, 1450, 1360, 1255, 1170, 1085, 730; $^1$H NMR (250 MHz, $CDCl_3$): δ (ppm): 5.36 (1H, d, J=2.7, $C_{5b}$-H), 4.67 (1H, dt, J=7.6 and 2.7, $C_{1a}$-H), 4.45 (1H, m, $C_3$-H), 4.01 (1H, d, J=7.6, $C_{6a}$-H), 3.20 (1H, d, J=7.6, $C_{10a}$-H), 3.19 (1H, dd, J=7.6 and 2.7, $C_{5a}$-H), 2.28 (2H, m, C$H_2$-$C_3$), 2.28 (2H, m, C$H_2$-$CH_2$-$C_3$), 2.02 (1H, d, J=4.3, $C_{10}$-H), 1.80 (2H, m, $C_2$-Hx2), 1.67 (2H, m, $C_9$-Hx2), 1.37 (2H, m, $C_8$-H×2), 1.21 (12H, broad s, $CH_2$×6), 0.93–0.74 (12H, 3s and partially obscured t, $CH_3$×4); $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 169.4 (CO), 102.1 ($C_{5b}$), 88.5 ($C_{6a}$), 75.2 ($C_{1a}$), 73.3 ($C_{10a}$), 72.2 ($C_3$), 52.5 ($C_{5a}$), 48.7 ($C_{10}$), 48.2 ($C_{11}$), 46.1 ($C_7$), 34.9 ($C_2$), 31.8 ($C_8$), 25.2 ($C_9$), 30.5, 29.5, 29.4, 29.3, 29.2, 24.7, 22.6; mass (CI $NH_3$): m/z: 448 ($MH^+$.); electrospray: m/z: 470.3 (M+23); $[\alpha]_D$=−54.3 (c=1, $CHCl_3$); high resolution mass spectrum, calcd for $C_{27}H_{45}NNaO_4$ (M+Na): 470.3246; found: 470.3246.

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