Regio - and Stereochemical Study of a \( S_N2'' \) Nucleophilic Substitution:

**Piperidinolysis of Hexa-1,3-dien-5-yl Dichlorobenzoates.**

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**Introduction**

Bimolecular nucleophilic substitutions with \( \alpha-\chi \) rearrangement have raised controversies for decades\(^1\), bearing out the interest shown by scientists in this process from both synthetic\(^2\) and mechanistic\(^3\) points of view.

The well documented bibliography deals essentially with three themes:

1 - the regiochemistry of the reaction, i.e. the competition between \( S_N2 \) and \( S_N2' \) processes for a given substrate,

2 - the stereochemistry of \( S_N2' \) processes,

3 - the chronology of bond breaking with the leaving group and bond forming with the nucleophile, i.e. the concerted character of the substitution reaction. This last theme may also include the molecularity of the process. In the formal definition of \( S_N2' \) reactions it is taken equal to 2, implying second-order kinetics for usual non-solvolytic experimental conditions.

It has been shown that in most cases the \( S_N2 \) process is largely more favored than the \( S_N2' \) process for a given allylic substrate\(^4\) but also that in some cases the latter process can become predominant because of electronic influences and/or steric hindrance.

For instance substitution of 2-methyl-1,1,1-trichloro-prop-2-ene by sodium thiophenoxide in ethanol gives 64% of rearranged product\(^5\) probably due to the electron-withdrawing effect of the chlorine atoms.
Steric hindrance can also favor the formation of rearranged product as in the substitution of 2,2-dimethyl-3-chloro-pent-4-ene by sodium ethoxide, which affords 100% of (4,4-dimethylpent-2-en-1-yl) - ethylether. Most of the studies reported in the literature have been carried out with acyclic substrates with the exception of cyclohexenyl esters studies\(^{2a,e,f}\) the structure of which can be written:

\[
\begin{align*}
\text{C} & \quad \text{CH} & \quad \text{CH} \\
R_1 & \quad R_2 & \quad X
\end{align*}
\]

Where the leaving group X has generally been Cl, and R\(_1\) and R\(_2\) have been hydrocarbon substituents.

\[
\begin{align*}
\text{C} & \quad \text{CH} & \quad \text{CH} & \quad \text{CH} & \quad \text{CH}_2 \\
\alpha & \quad \beta & \quad \chi & \quad \delta & \quad \varepsilon \\
R_1 & \quad R_2 & \quad X
\end{align*}
\]

In the present work we extended the study by using a vinylogous mechanistic probe of the type: Which offers:

1. The existence of three reaction sites (\(\alpha\), \(\chi\) and \(\varepsilon\)) making theoretically possible the competition between \(S_N2\), \(S_N2'\) and \(S_N2''\) substitution processes.

2. The existence of (\(\beta\), \(\chi\)) - E and - Z isomers having different steric hindrances around the reaction sites, which may provide further information about the three processes.

As for the choice of the leaving group, we decide to use dichlorobenzoates since they are easily displaceable and the position of the chlorine atoms on the benzene ring allows modification of the steric and/or electronic factors which influence the reactivity of the various reaction sites.

A series of six dichlorobenzoates of hexadienyl was chosen:

- (E) - and (Z) - O - (2, 6 - dichlorobenzoyl) hexa - 1,3 - dien - 5 - ols \(1E\) and \(1Z\)
- (E) - and (Z) - O - (2, 4 - dichlorobenzoyl) hexa - 1,3 - dien - 5 - ols \(2E\) and \(2Z\)
- (E) - and (Z) - O - (3, 5 - dichlorobenzoyl) hexa - 1,3 - dien - 5 - ols \(3E\) and \(3Z\)

and piperidine was used as nucleophile under solvolytic conditions because several examples of this system have been already described in the literature for the study of \(\alpha\) - \(\chi\) rearrangements.\(^2\)
Regionchemical Study

We shall first examine the nature of the products formed in the reaction and the possible mechanisms explaining their formation, then the regiochemical features of the piperidinolysis of the substrates will be presented and discussed.

In order to determine the structural factors influencing the competition between the various processes, the solvolysis of the six chlorobenzoates was carried out under the same reaction conditions, i.e. in refluxing piperidine (bp = 106°C) until completion of the reaction (disappearance of starting material monitored by TLC). The results are summarised in Tables 1 and 2.

Table 1. Piperidinolysis of hexadienyl 2, 6 - 2, 4 - and 3, 5 - dichlorobenzoates at 106°C: product ratios.

<table>
<thead>
<tr>
<th>DCB</th>
<th>t (hour)</th>
<th>S-OH %</th>
<th>(β, χ)-E S-amine %</th>
<th>P-amine %</th>
<th>S-OH %</th>
<th>(β, χ)-Z S-amine %</th>
<th>P-amine %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6</td>
<td>20</td>
<td>6.4</td>
<td>67.6d</td>
<td>26d</td>
<td>17.6</td>
<td>28.4</td>
<td>54</td>
</tr>
<tr>
<td>2,4</td>
<td>48</td>
<td>24d</td>
<td>42.5e</td>
<td>33.5e</td>
<td>17</td>
<td>11.3</td>
<td>71.7</td>
</tr>
<tr>
<td>3,5</td>
<td>96</td>
<td>34.5</td>
<td>43.7</td>
<td>21.8</td>
<td>57.8</td>
<td>12.5</td>
<td>29.7</td>
</tr>
</tbody>
</table>

aDCB = dichlorobenzoate
breaction time corresponding to the disappearance of the starting material (TLC).
cratios were constant versus reaction time
dthe yield of amines (VPC with triethyleneglycol dimethylether as internal standard was 60 % after 96 h.
eextrapolated values for t = 0 (see Figure 1)

Table 2. Piperidinolysis of hexadienyl dichlorobenzoates: amine ratios

<table>
<thead>
<tr>
<th>DCB</th>
<th>(β, χ)-E</th>
<th>(β, χ)-Z</th>
<th>ΔA%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-amine %</td>
<td>P-amine %</td>
<td>S-amine %</td>
</tr>
<tr>
<td>2,6</td>
<td>72</td>
<td>28</td>
<td>34.5</td>
</tr>
<tr>
<td>2,4</td>
<td>56a</td>
<td>44a</td>
<td>13.6</td>
</tr>
<tr>
<td>3,5</td>
<td>66.7</td>
<td>33.3</td>
<td>29.6</td>
</tr>
</tbody>
</table>

aextrapolated values for t = 0 (see Figure 1)
bdifference of P-amine ratios for (E) and (Z) substrates
Three major products were isolated by preparative VPC and characterised (see experimental):

a- N-(hexa-1,3-dien-5-yl)piperidine 4 (which will be referred to as S-amine) probably resulting from a $S_N2$ substitution mechanism and retaining the E or Z configuration of the $\beta$, $\gamma$ double bond:

![Chemical structure of S-amine](image)

b- (2E, 4E)-N-(hexa-2,4-dien-1-yl) piperidine 5 (which will be referred to as P-amine) probably resulting from $S_N2''$ process.

![Chemical structure of P-amine](image)

In all cases, the configuration was exclusively (2E, 4E) as determined by NMR spectroscopy; in the $^1H$ NMR spectrum the coupling constant $J_{2,3} = 15$ Hz, indicating a trans relationship between H-2 and H-3, and in the $^{13}C$ NMR spectrum $\delta C-6 = 17.9$ ppm which is well in the range of the values reported for a E configuration of the C$_4$ - C$_5$ bond ($\delta C \approx 13$ ppm for a Z configuration).

A similar result was obtained when 3-chloro-but-1-ene was treated with an alcohol under solvolytic conditions: rearranged primary ethers were almost exclusively with a E configuration.$^{1b}$ Both results can be attributed to the conformation of the state where CH$_3$-1 is nearly antiperiplanar with the $\pi$-system, as already shown by stereochemical studies of the $S_N2'$ process.$^{2d,g}$
c - hexa-1,3-dien-5-ol 6 (E or Z, which will be referred to as S-OH) the formation of which can be due to aminolysis of the starting ester, commencing with a nucleophilic attack by piperidine at the ester carbonyl of the leaving group.

It is worthwhile to mention that in all our experiments, the formation of amines resulting from S_{N}2' process was never observed.

The data summarised in Table 1 show that 3,5-dichlorobenzoates are the most susceptible to nucleophilic attack at the carbonyl ester affording 34.5% of 6E from 3E and 57.8% of 6Z from 3Z.

Product ratios were constant vs time except in the case of (E)- 2,4-dichlorobenzoate 2E (Figure 1). This result can be interpreted by the concurrence of a S_{N}Ar process leading to (E)-O-(2-chloro-4-N-piperidino-1-benzoyl) hexa-1,3-dien-5-ol 7E:
This compound was isolated in 68 % yield by flash chromatography after complete disappearance of the starting material (t = 48 h). It reacts slowly with piperidine (15 % yield in amines after 96 h ; Table 3) and probably affords more P-amine than the starting 2,4-dichlorobenzoate. This difference is probably due to the strong electron-donating effect of the nitrogen atom to the benzene ring, which modifies the electron density of the various reaction sites.

This, in order to compare the reactivity of the six substrates it seemed pertinent to us to extrapolate the amine ratio for t = 0 (Figure 1).

![Figure 1. Amine ratio vs time for 2E.](image)
S-Amine is predominantly formed from (E)-isomers whereas (Z)-isomers afford mainly P-amine. The difference in P-amine (or S-amine) ratios for both types of isomers is nearly independent of the leaving group (Table 2: $\Delta A = 10 \pm 3\%$).

This difference can be related to the structural features of these isomers as shown below:

For (Z)-isomers s-trans and s-cis conformers present a strong steric hindrance in the case of a S$_{N}2$ process and S$_{N}2''$ is largely favored. In the case of (E)-isomers a nucleophile encounters a slight steric hindrance for S$_{N}2$ substitution, which appears to be the predominant process.

Finally the nature of the leaving group also has an influence on the product ratios, but any attempt to relate some physico-chemical data to these ratios was unsuccessful. The only relation between displacement facility and pK$_A$ of the dichlorobenzoic acids is in the time of disappearance of the starting materials: the better the leaving group (small pK$_A$) the faster the reaction, as shown in Table 3.

<table>
<thead>
<tr>
<th>Acid</th>
<th>pK$_A$ (H2O)</th>
<th>t (disappearance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-dichlorobenzoic</td>
<td>1.6</td>
<td>20 h</td>
</tr>
<tr>
<td>2,4-dichlorobenzoic</td>
<td>2.7</td>
<td>48 h</td>
</tr>
<tr>
<td>3,5-dichlorobenzoic</td>
<td>3.5</td>
<td>96 h</td>
</tr>
</tbody>
</table>
It is also to be noted that the « worst » leaving group leads to the highest ratio S-OH (Table 1).

Finally, the ratios of the reaction products formed during the piperidinolysis of the six hexa-1,3-dien-5-yl (E and Z) 2,6 - 2,4 - and 3,5-dichlorobenzoates were determined and the relevant regiochemical features were the following:

1 - in no case S_N2’ reaction products were observed;

2 - the better the leaving group - as excepted from the corresponding acid pK_A - the faster the reaction and the higher the yield in ε-rearranged (2E, 4E)-N-(hexa-2,4-dien-1-yl) piperidine. The worst leaving group leads to the slowest reaction and the highest yield in hexa-1,3-dien-5-ol ;

3 - the configuration of the β-γ double bond seems to be the commanding factor for the preferential formation of the ε-rearranged amine ;

4 - a parallel reaction path was established with the (E)-2,4-dichlorobenzoate leading to the same final products via an intermediate 7E resulting from a S_NAr on the starting material.

**Stereochemical study**

Among the compounds studied it was shown that (Z)-hexa-1,3-dien-yl 2,6 - and 2,4 - dichlorobenzoates afforded the highest ratio of ε - rearranged amines (respectively 54 % and 72 %).

When we started the stereochemical study our aim was twofold:

(i) to determine whether the ε - rearranged amine could retain the chiral character of the starting material if the latter was bearing a prochiral C-1 ;

(ii) to examine, in case of chiral transfer, if the observed configuration of the amine could be predict using Woodward-Hoffmann rules.

For this purpose optically active (1Z, 3Z)-hexa-1,3-dien-[1^-2H1]-5-yl 2,6 and 2,4 - dichlorobenzoates, respectively 1_d and 2_d, were prepared and submitted to solvolysis in refluxing piperidine (bp 106 °C). The configuration and the optical purity of both esters were determined by correlation with the known (S)-(+-)-hexan-2-ol^{12} (see experimental and Table 4).

**Table 4 : Piperidinolysis of 1 and 2 ;**

optical purity and configuration of obtained 5_d.
starting product & optical purity$^a$ & optical purity$^a$ of product 5d & configuration of product 5d \\
--- & --- & --- & --- \\
1d & 63.5% & 50% & (S)-(−) \\
2d & 40% & 14% & (R)-(＋) \\

$^a$corrected for fully deuterated compound.

Chiral (2E,4E)-N(hexa-2,4-dien-[1-^2H_1]-1-yl)piperidine 5d was the only ε-rearranged product isolated (preparative VPC). Its configuration and optical purity in both piperidinolyses were determined by correlation with the data obtained for the corresponding saturated amine 6 (see experimental and Table 4).

Woodward-Hoffmann rules enable the stereochemistry of a concerted process to be predicted, using the symmetry of molecular frontier-orbitals.$^{13}$ Another way of expressing the rules using the notion of parity was proposed by Mathieu.$^{14}$ It is based upon the number of electron - pairs involved in the transformation and it relates the stereochemistry of the process to the odd or even character of this number (see Table 5).

<table>
<thead>
<tr>
<th>Table 5 : Symmetry rules :</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of electron - pairs</td>
</tr>
<tr>
<td>2n</td>
</tr>
<tr>
<td>2n + 1</td>
</tr>
</tbody>
</table>

When applying these rules to a $S_N2$ mechanism, which involves two electron-pairs, the process is antarafacial and a Walden inversion usually takes place.

In order to get some information of the stereochemistry of the unrearranged amine obtained in 28 % yield the piperidinolysis of 2d (1Z,3Z)-N ( hexa-1,3-dien-[1-^2H_1]-5-yl) piperidine 4d was isolated by CPV.

It was found to be optically active and its configuration and optical purity were determined by correlation with the data obtained for the corresponding saturated amine 4′d.
(see experimental). As expected, a total Walden inversion occurred and as far as we know this is the first example reported in the case of an acyclic dienic system.

When applying these rules to a $S_N^{2''}$ process, which involves four electron - pairs, an anti stereochemistry is predicted as illustrated below:

Taking into account the double bonds configuration of the starting products $1_d$ and $2_d$ and that of $\varepsilon$-rearranged amine $5_d$, the latter should have S configuration:

Our experiments showed that the amine formed from $1_d$ has the predicted configuration and that the anti process takes place with nearly 90 % stereospecificity.

Surprisingly, amine $5_d$ formed from $2_d$ was predominately with an R configuration.

Although 2,6 - dichlorobenzoate is a better leaving group than the corresponding 2,4 - it is not reasonable to envisage a carbocation intermediate, because such a pathway would lead to essentially racemized products, which is not the case.
Alternatively it is possible to envision a mechanism involving two competitive processes: (i) the expected S_N2" nucleophilic substitution; (ii) a preliminary S_Ni" rearrangement of the starting 2,6-dichlorobenzoate followed by a classical S_N2 substitution on the rearranged ester, which would be the predominant process.

Dienic rearrangement of the starting ester 2_d also involves 4 electron-pairs and according to the rules mentioned above, should take place with an anti stereochemistry, leading to the formation of (2E, 4E)-hexa 2,4-dien-[1^2H_1]-1-yl 2,6 - dichlorobenzoate 2'_d:

A space - filling model shows that the reaction is possible:
This rearrangement is analogous to a [1,7] sigmatropic rearrangement, which is known to take place in an antarafacial manner:\textsuperscript{15}

Subsequent nucleophilic substitution by piperidine would afford (R)-(+) 5\textsubscript{d} as observed in our experiment:
The presence of such a rearranged ester had already been mentioned in solvolytic studies with acyclic allylic p-nitrobenzoates\textsuperscript{16} and cyclohexenyl dichlorobenzoates.\textsuperscript{17} Although in our experiment compound 4\textsubscript{a} was not detected during the reaction, its formation cannot completely be ruled out since it would probably undergo a very fast substitution by piperidine as already reported for primary allylic substrates.

The observed discrepancy between esters 1\textsubscript{d} and 2\textsubscript{d} might be due to the strong steric repulsions, existing between C1-2 and C1-6 and the rest of the molecule in ester 2'\textsubscript{d} which probably account for the ease of the arrangement, suggesting that the driving force of the rearrangement is probably the release of these constraints. If a similar rearrangement occurs with 1\textsubscript{d}, it is negligible when compared to the predominant S\textsubscript{N}2\textsuperscript{"} process.

It is to be noted that in spite of the complexity of the system, every rearranged compound has a stereochemistry in agreement with that predicted by symmetry rules, even when the process is a sequence of two reactions, which both obey the aforementioned rules.

Our results corroborate those reported by various authors\textsuperscript{18, 19} for the stereochemistry of S\textsubscript{E}2\textsuperscript{"} electrophilic substitutions on dienylsilanes. Such a reaction which also involved four electron - pair in the process (three from the substrates and one form the Lewis acid catalyst, which is always necessary for this type of reaction) was also found to take place with an anti stereochemistry as predicted by symmetry rules.

Finally, the very fact that the stereochemistry of the rearranged product is in agreement with the prediction allowed by the symmetry rules, implies that in the activated complex the reacting species are not far from their fundamental state.

This, in our judgement, is a very strong indication that the bimolecular nucleophilic substitution with \(\alpha\)-\(\epsilon\) rearrangement is a concerted process.

**Experimental section**

**General methods.**
IR spectra were recorded on a Unicam SP3 - 300 spectrophotometer. \(^1\)H NMR were recorded in CDC\textsubscript{13} using Me\textsubscript{4}Si as internal standard at 300 MHz with Brucker apparatus operating in the FT mode. Gas chromatographic analysis was carried out on a Girdel 75 FD2 instrument equipped with flame ionisation detectors and fitted with a 20 % Carbowax 20M on 60-80 mesh
Chromosorb W AW DMCS (2 m x 0.375 in.). Analytical TLC was performed on precoated alumina plates (E. Merck silica gel 60F_{254}). For flash chromatography E. Merck silica gel (230 - 400) mesh was used.

**Hexa-1,3-dien-5-yl dichlorobenzoates** were prepared as shown in Scheme I.

\[
\begin{align*}
H-C=\equiv-C & \rightarrow H-C=\equiv-C\text{MgBr} & b & \rightarrow CH_3-CH=\equiv-CH-CHOH-C=\equiv-C-H & c & \rightarrow \\
CH_3-CHOH-CH=\equiv-C=\equiv-C-H & \text{(E/Z mixture)} & d,e & \rightarrow \\
CH_3-CH(ODCB)-CH=\equiv-C=\equiv-C-H & \text{(E or Z)} & f & \rightarrow CH_3-CH(ODCB)-CH=\equiv-C=\equiv=CH_2
\end{align*}
\]

\(a)\ C_2H_5MgBr/THF/0^\circ C^8; \quad b)\ CH_3-CH=\equiv-CH-CHO/THF \text{ and hydrolysis}^9 (75 \% \text{ yield}) ; \quad c)\ \text{Paratoluuenesulfonic acid }/H_2O^{10}; \quad d)\ \text{gas chromatographic separation on a 20 }\%\ \text{Carbowax 20M on 60 - 80 mesh Chromosorb W NAW column (2 m x 0.375 in.) at 90 }\circ C (26 \% \text{ yield for E alcohol; 5.5 }\% \text{ yield for Z alcohol}) ; \quad e)\ 2,6-, 2,4- \text{ or 3,5- dichlorobenzoyl chloride (DCB1)/pyridine}^2 (80 \% \text{ yield}) ; \quad f)\ H_2/Lindlar Pd/THF (85 \% \text{ yield}).

*(E)-2,6-dichlorobenzoate* (1E) was characterised as follows: IR (cm\(^{-1}\)) 1730 (C = O), 1580, 1550, 780 (1, 2, 6 trisubstitued benzene); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.31 (m, 3H, aromatic H) 6.28 (m, 2H, H-2, H-3, \(J_{1E,2}=15.6\ \text{Hz, } J_{1Z,2}=11.5\ \text{Hz}\), 5.7 (m, 2H, H-4, H-5, \(J_{5,6}=7.8\ \text{Hz}\) ), 5.2 (dd, 1H, H-1E, \(J_{1E,1Z}=2\ \text{Hz}\), 5.12 (dd, 1H, H-1Z), 1.5 (d, 3H, H-6);

*(E)-2,4 Dichlorobenzoate* (2E) was characterised as follows: IR (cm\(^{-1}\)) 1730 (C = O), 1580, 1550, 870, 830 (1, 2, 4 trisubstituted benzene); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.80 (d, 1H, aromatic H-6', \(J_{5',6}=7.8\ \text{Hz}\) ), 7.65 (d, 1H, H-3', \(J_{3',5}=2.5\ \text{Hz}\), 7.30 (dd, 1H, H-5'), 6.26 (m, 2H, H-2, H-3, \(J_{1E,2}=17\ \text{Hz, } J_{1Z,2}=10.6\ \text{Hz}\), 5.73 (dd, 1H, H-4, \(J_{4,5}=7.6\ \text{Hz}\), 5.62 (m, 1H, H-5, \(J_{5,6}=8\ \text{Hz}\), 5.20 (dd, 1H, H-1E, \(J_{1E,1Z}=2.3\ \text{Hz}\), 4.76 (dd, 1H, H-1Z), 1.47 (d, 3H, H-6);

*(E)-3,5-dichlorobenzoate* (3E) was characterised as follows: IR (cm\(^{-1}\)) 1730 (C = O), 1580, 1550, 880 (1, 3, 5 trisubstituted benzene); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.86 (d, 2H, H-2', H-6', \(J_{5',6}=2\ \text{Hz}\), 7.48 (t, 1H, H-4'), 6.27 (m, 2H, H-2, H-3, \(J_{1E,2}=14.6\ \text{Hz, } J_{1Z,2}=11.4\ \text{Hz, } J_{3,4}=14.5\ \text{Hz}\), 5.75 (dd, 1H, H-4, \(J_{4,5}=6.8\ \text{Hz}\), 5.63 (m, 1H, H-5, \(J_{5,6}=6.4\ \text{Hz}\), 5.24 (dd,
1H, H-E, J_{1E, 1Z}=1.9 Hz), 5.13 (dd, 1H, H-1Z), 1.40 (dd, 3H, H-6); HRMS m/e for C_{13}H_{12}Cl_2O_2 calcd 270.02156, found 256.02170;

**(Z)-2,6-dichlorobenzoate (1Z)** was characterised as follows: $^1$H NMR (CDCl$_3$) $\delta$ 7.28 - 7.17 (m, 3H, aromatic H) 6.80 (ddddd, 1H, H-2, J_{1E, 2}=21.3 Hz, J_{1Z, 2}=11.1 Hz, J_{2, 4}=16.7 Hz, J_{2, 4}=1.1 Hz), 6.08 (m, 2H, H-3, H-4, J_{3, 4}=10.2 Hz, J_{4, 5}=9.9 Hz), 5.49 (m, 1H, H-5, J_{5, 6}=6.5 Hz), 5.33 (dd, 1H, H-1E, J_{1E, 1Z}=1.3 Hz), 5.27 (dd, 1H, H-1Z), 1.45 (dd, 3H, H-6); HRMS m/e calcd for C_{13}H_{12}Cl_2O_2, 270.02156, found 270.02120;

**(Z)-2,4-dichlorobenzoate (2Z)** was characterised as follows: $^1$H NMR (CDCl$_3$) $\delta$ 7.29 (m, 3H, aromatic H) 6.76 (m, 1H, H-2, J_{1E, 2}=19.7 Hz, J_{1Z, 2}=10.6 Hz, J_{2, 3}=16.1 Hz), 6.11 (m, 2H, H-3, H-4, J_{3, 4}=10.2 Hz, J_{4, 5}=9.7 Hz), 5.52 (m, 1H, H-5, J_{5, 6}=6.7 Hz), 5.29 (dd, 1H, H-1E, J_{1E, 1Z}=1.8 Hz), 5.04 (dd, 1H, H-1Z), 1.46 (dd, 3H, H-6);

**(Z)-3,5-dichlorobenzoate (3Z)** was characterised as follows: $^1$H NMR (CDCl$_3$) $\delta$ 7.82 (d, 2H, H-2', H-6'), J_{2', 4}=2 Hz), 7.47 (t, 1H, H-4'), 6.79 (m, 1H, H-2, J_{1E, 2}=20.7 Hz, J_{1Z, 2}=10.6 Hz, J_{2, 3}=16.4 Hz), 6.07 (m, 2H, H-3, H-4, J_{3, 4}=10 Hz, J_{4, 5}=9.6 Hz), 5.51 (m, 1H, H-5, J_{5, 6}=6.8 Hz), 5.30 (dd, 1H, H-1E, J_{1E, 1Z}=1.4 Hz), 5.25 (dd, 1H, H-1Z), 1.45 (d, 3H, H-6);

**(E)-N-(hexa-1,3-dien-5-yl) piperidine (4E)** was characterised as follows: $^1$H NMR (CDCl$_3$) $\delta$ 6.34 (m, 1H, H-2, J_{1E, 2}=17 Hz, J_{1Z, 2}=10.5 Hz), 6.08 (dd, 1H, H-3, J_{3, 4}=15.2 Hz), 5.70 (dd, 2H, H-4, J_{4, 5}=7 Hz), 5.15 (dd, 1H, H-1E, J_{1E, 1Z}=1.7 Hz), 5.03 (dd, 1H, H-1Z), 2.96 (m, 1H, H-5, J_{5, 6}=7 Hz), 2.45 (m, 4H, H-7, H-11), 1.54 (m, 4H, H-8, H-10), 1.43 (m, 2H, H-9), 1.17 (d, 3H, H-6); MS (m/e) : 81 (M$^+$ - C$_5$H$_{10}$N), 84 (C$_5$H$_{10}$N$^+$), 150 (M$^+$ - CH$_3$), 165 (M$^+$).

**(Z)-N-(Hexa-1,3-dien-5-yl) piperidine (4Z)** was isolated by preparative VPC and hydrogenated on Raney nickel. The retention time of the saturated amine (VPC) was found identical to that of N - (2 - hexyl) piperidine obtained by reaction of 2 - hexyl tosylate with piperidine. Anal. Calcd for C$_{11}$H$_{23}$N (saturated amine) : C, 78.11 ; H, 8.28 ; N, 13.61. Found: C, 78.02 ; H, 8.33, N, 13.54.
(2E, 4E)-N-hexa-2,4-dien-1-yl) piperidine (5) was characterised as follows: $^1$H NMR (CDCl$_3$) $\delta$ 6.07 (m, 2H, H-3, H-4, $J_{2, 3}$=15 Hz) 5.64 (m, 2H, H-2, H-5), 2.95 (d, 2H, H-1, $J_{1, 2}$=7.5 Hz), 2.35 (bs, 4H, H-7, H-11), 1.74 (d, 3H, H-6, $J_{5, 6}$=6.5 Hz), 1.58 (m, 4H, H-8, H-10), 1.43 (m, 2H, H-9). $^{13}$C NMR (CDCl$_3$) $\delta$ 133.1 C-4, 131.1 C-3, 128.5 C-2, 127.6 C-5, 127.6 C-2, 61.5 C-1, 54.4 C-7 and C-11, 25.9 C-8 and C-10, 24.3 C-9, 17.9 C-6; HRMS, m/e for C$_{11}$H$_{19}$N calcd 165.15180, found 165.15210.

(E) -hexa-1,3-dien-5-ol (6E) was characterised as follows: IR (cm$^{-1}$) : 3300 (OH), 1600 (C=C), 945 (=C-H); $^1$H NMR (CDCl$_3$) $\delta$ 6.33 (m, 1H, H-2, $J_{1E, 2}$=10 Hz, $J_{1Z, 2}$=17 Hz, $J_{2, 3}$=10.3Hz), 6.18 (dd, 1H, H-3, $J_{3, 4}$=15 Hz), 5.74 (dd, 1H, H-4, $J_{4, 5}$=6.8 Hz), 5.2 (dd, 1H, H-1E, $J_{1E, 1Z}$=1.7 Hz), 5.03 (dd, 1H, H-1Z), 4.33 (m, 1H, H-5, $J_{5, 6}$=7 Hz), 1.27 (d, 3H, H-6).

(Z)-hexa-1,3-dien-5-ol (6Z) was isolated by VPC and hydrogenated on Raney nickel ans its retention time (VPC) and IR spectrum were found identical to those of commercially available hexan - 2 - ol.

O-(2-Chloro-4-N-piperidine-1-benzoyl) hexa-1,3-dien-5-ol (7E) was isolated by chromatography on silica gel using pentane as eluent and characterised as follows: HRMS, m/e for C$_{18}$H$_{22}$C1NO$_2$ calcd 319.13406, found 319.13370.

Optically active compounds.

Starting materials:

Optically active (1E,3Z)-hexa-1,3-dien-[1-$^2$H$_1$]-5-yl dichlorobenzoates 1d and 2d were prepared using the following sequence of reactions:

$\text{(CH}_3\text{)}_3\text{Si-CH} \xrightarrow{\text{a}} \text{(CH}_3\text{)}_3\text{Si (C} \equiv \text{C) }_2\text{Si (CH}_3\text{)}_3 \xrightarrow{\text{b}} \text{CH}_3\text{CO(C} \equiv \text{C)}_2\text{Si(CH}_3\text{)}_3 \xrightarrow{\text{c}} \text{CH}_3\text{C}^*\text{HOH(C} \equiv \text{C)}_2\text{Si(CH}_3\text{)}_3 \xrightarrow{\text{d}} \text{CH}_3\text{C}^*\text{H(OBDCB)-(C} \equiv \text{C)}_2\text{Si(CH}_3\text{)}_3 \xrightarrow{\text{e}} \text{CH}_3\text{C}^*\text{H(OBDCB)-C} \equiv \text{C-C} \equiv \text{C-D} \xrightarrow{\text{f}} \text{CH}_3\text{C}^*\text{H(OBDCB)-CH=CH-CH=CHD}$
a) CuCl/acetone/TMEDA\textsuperscript{20} (75 \% yield) ; b) CH\textsubscript{3}COCl/AlCl\textsubscript{3}/CH\textsubscript{2}Cl\textsubscript{2}/10 ° C\textsuperscript{21} (65 \% yield) ; c) S-Alpine-borane (Aldrich) /THF/20°C\textsuperscript{22} (yield 78 \%); d) 2,6-or 2,4-dichlorobenzoyle chloride (DBC1)/pyperidine\textsuperscript{23} (86 \% yield) ; e) KF/CH\textsubscript{3}OD/DCl/D\textsubscript{2}O/20°C \textsuperscript{24} (quantitative yield) ; f) H\textsubscript{2}/Lindar Pd/ THF (85 \% yield).

The optical purity esters 1 and 2 was determined by desilylation\textsuperscript{24} of optically active intermediate 1-trimethylsilyl hexa-1,3-diyn-5-ol followed by complete hydrogenation and comparison with the literature data for hexan-2-ol: 12 [\alpha]_D\textsubscript{20} 12.7 ° (C 11 ; EtOH). Optical rotations measured for hexan-2-ol were respectively 8.6 ° (63.5 \% optical purity) for 1\textsubscript{d} and 5.0 ° (40 \% optical purity) for 2\textsubscript{d}.

\textbf{(Z)-2,6-Dichlorobenzoate (1\textsubscript{d})} was characterised as follows: \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 7.28 - 7.17 (m, 3H, aromatic H), 6.80 (ddddd, 1H, H-2, J\textsubscript{1E,2}=21.3 Hz, J\textsubscript{1Z,2}=11.1 Hz, J\textsubscript{2,3}=16.7 Hz, J\textsubscript{2,4}=1.1 Hz), 6.08 (m, 2H, H-3, H-4, J\textsubscript{3,4}=10.2 Hz, J\textsubscript{4,5}=9.9 Hz), 5.49 (m, 1H, H-5, J\textsubscript{5,6}=6.5 Hz), 5.33 (dd, 0.4H, H-1E, J\textsubscript{1E,1Z}=1.3 Hz), 5.27 (dd, 1H, H-1Z), 1.45 (d, 3H, H-6).

\textbf{(Z)-2,4-Dichlorobenzoate (2\textsubscript{d})} was characterised as follows: \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 7.29 - 7.17 (m, 3H, aromatic H), 6.76 (m, 1H, H-2, J\textsubscript{1E,2}=19.7 Hz, J\textsubscript{1Z,2}=10.6 Hz, J\textsubscript{2,3}=16.1 Hz), 6.11 (m, 2H, H-3, H-4, J\textsubscript{3,4}=10.2 Hz, J\textsubscript{4,5}=9.7 Hz), 5.52 (m, 1H, H-5, J\textsubscript{5,6}=6.7 Hz), 5.29 (dd, 0.2H, H-1E, J\textsubscript{1E,1Z}=1.8 Hz), 5.04 (dd, 1H, H-1Z), 1.46 (d, 3H, H-6).

Solvolysis of 1\textsubscript{d} and 2\textsubscript{d} gave rise to amine 5\textsubscript{d} which was completely hydrogenated on platinum oxide in ethyl acetate. After filtration the saturated amine 5\textsubscript{d}' was isolated by VPC and its rotation was measured: 1.36 ° (c 6 ; AcOEt) from 1\textsubscript{d} and [\alpha]_D\textsubscript{546}\textsuperscript{20} 0.377 ° (c 5 ; AcOEt) from 2\textsubscript{d}. The optical purity was evaluated by comparison with the data obtained for amine 6 (see above) and found to be respectively 14 \% and 50 \%.

Amine 4\textsubscript{d}, which was also obtained in the solvolysis, was submitted to the same treatment, leading to the corresponding saturated amine 4\textsubscript{d}' : [\alpha]_D\textsubscript{20} 11.4 ° (c 3.5 ; AcOEt). The optical
purity was evaluated by comparison with the value measured for the 30 % optically pure 4’, and found to be equal to 41.2 %. This value is remarkably similar to that determined for the purity of the starting ester (40 %), implying thus a complete Walden inversion.

**Reference products :**

**(R)-(-)-N-(2-hexyl) piperidine (4’)** was prepared from hexan-2-ol by the tosylate/piperidinolysis sequence. Its rotation was \([ \alpha ]_D^{20} 8.3 ^\circ \) (c 4.6 ; AcOEt) when prepared from an alcohol with 30 % optical purity.

**(R)-(+) -N-(1-hex-[1\text{-}^2H\text{1}]-yl) piperidine (5’\text{d})** was prepared using the following sequence of reactions :

\[
\begin{align*}
\text{CH}_3\text{(CH}_2\text{)}_4\text{COCl} & \rightarrow \text{CH}_3\text{(CH}_2\text{)}_4\text{CD}_2\text{OH} \rightarrow \text{CH}_3\text{(CH}_2\text{)}_4\text{CDO} \\
\text{CH}_3\text{(CH}_2\text{)}_4\text{C}^*\text{HDOH} & \rightarrow \text{CH}_3\text{(CH}_2\text{)}_4\text{C}^*\text{HDOTs} \\
& \rightarrow \text{CH}_3\text{(CH}_2\text{)}_4\text{C}^*\text{HD-NC}_5\text{H}_{10}
\end{align*}
\]

\(5’\text{d}\)

\(a\) ) \text{LiAlH}_4/\text{Et}_2\text{O}^{25} \) (80\% yield) ; \(b\) ) \text{pyridinium bichromate/CH}_2\text{Cl}_2/\text{molecular sieves/15} ^\circ \text{C}^{26} \) (yield) ; \(c\) ) \text{baker's yeast/sucrose/20} ^\circ \text{C}/\text{40 h}^{27} \) (26 \% yield of pure alcohol) ; \(d\) ) \text{TsCl/pyridine/-15} ^\circ \text{C}^{28} \) (73 \% yield) ; \(e\) ) \text{piperidine/toluene/130} ^\circ \text{C}/\text{6 h}^{28} \) (48 \% yield of isolated product).

**(R)-(+) -N-(1-hex-[1\text{-}^2H\text{1}]-yl) piperidine (5’\text{d})** was characterised as follows: \(^1\text{H NMR (CDC13)} \delta 2.36 \) (t, 4H, H-7, H - 11), 2.33 \) (bt, 1H, H-1), 1.58, 1.45, 1.25 \) (m, 10H, H-2, H-3, H-4, H-5, H-9), 0.88 \) (t, 3H, H-6) ; \([ \alpha ]_D^{20} 1.86 ^\circ \) (neat ; 11), \([ \alpha ]_{540}^{20} 2.72 ^\circ \) (c 10 ; AcOEt) ; Anal. Calcd for C\text{11}H\text{22} DN : C, 77.57 ; H, 14.21 ; N, 8.22. Found C, 77.71 ; H, 14.12 ; N 8.12.

**(+) -Hexan-[1\text{-}^2H\text{1}]-1-ol (6’\text{d})** was characterised as follows : \(\text{IR cm}^{-1} \) (film) 3350 \) (OH), 2150 \) (C - D) ; Anal. Calcd for C\text{16}H\text{13DO} : C, 69.38 ; H, 14.65. Found : C, 69.45 ; H, 14.52 ; \([ \alpha ]_D^{20} 0.20 ^\circ \) (neat ; 11). The configuration of C - 1 and the optical purity of this compound
were determined by measuring the chemical shift of H - 1 in the corresponding (S)-(+) -
camphanate ester in the presence of Eu (dpm)$_3$. The configuration of alcohol $6d'$ was found
to be (S)-(+ ) and its optical purity to be nearly 100 %. 
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