Asymmetric synthesis via nor-ephedrine derived 2-alkenyloxazolidines

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Abstract - The stereochemistry of the acid catalysed cyclization between N-protected norephedrine and \( \alpha,\beta \)-unsaturated dimethyl acetal to give 2-alkenyloxazolidines is described. Such heterocycles, on the basis of their different formation and reactivity behaviour, are classified as electron rich or electron poor olefinic appendages. The mechanism and the factors determining the kinetic preference for the \( \text{cis} \) C-2/C-5 isomer is discussed. Experimental evidence together with theoretical considerations provide a reasonable rationalization for the observed selectivity of the conjugate addition. The addition of cuprates, \( \text{KClO}_3 \), \( \text{NaOCH}_2\text{C}_6\text{H}_5 \), and \( (\text{CH}_3)_2\text{C} = \text{P} (\text{C}_6\text{H}_5)_3 \), to \( \alpha,\beta \)-unsaturated esters, ketones and aldehydes with a chiral oxazolidine in \( \gamma \) position, occur with high stereoselectivity and yield. The corresponding adducts provide a useful tool for manipulation to more complex structures.

INTRODUCTION

The chiral masking of an \( \alpha,\beta \)-unsaturated aldehyde may be easily achieved through the incorporation of the carbonylic carbon into the C-2 of a suitable chiral oxazolidinic ring (ref.1,2). The newly generated allylic center, when stereochemically obtained, can in turn direct useful asymmetric transformations at the vicinal olefinic carbon. The chiral auxiliary may easily be split off in a second stage thus releasing the free carbonylic function. The availability of both the chiral auxiliary antipodes with their recycling, and high values of asymmetric induction and chemical yields are the obvious features which give synthetic value to the above approach. Such 2-alkenyloxazolidines, on the basis of their different formation and reactivity behavior, are best classified as type \( \text{I} \) and type \( \text{II} \) oxazolidines, bearing electron rich or poor olefinic appendages respectively (Scheme 1).

For instance type \( \text{I} \) and type \( \text{II} \) oxazolidines are both obtained from either benzyloxy carbonyl-nor-ephedrine (CBZ-nor-ephedrine) or tosyl-nor-ephedrine (TS-nor-ephedrine) and the corresponding dimethyl acetics of some \( \alpha,\beta \)-unsaturated aldehydes (ref. 3). These newly designed heterocycles feature perfect water and silica-gel stability and high degree of asymmetric induction in their formation (vide infra); furthermore they can be easily obtained as pure diastereomers.

STEREOCHEMISTRY OF THE CYCLIZATION

The cyclization between the N-protected nor-ephedrines 1 A-C and the dimethyl acetics 2 a-d, in the presence of pyridinium tosylate as acidic catalyst, required several hours refluxing in benzene. The expected 2-alkenyloxazolidines 3 with a constant preference for the \( \text{cis} \) isomer were obtained (Scheme 1; Table 1).

Table I. Stereoselectivity of cyclization to 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>EWG</th>
<th>R</th>
<th>c/t</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CBZ</td>
<td>CO Me</td>
<td>94/6</td>
<td>3Aa</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>TS</td>
<td>CO Me</td>
<td>( \geq 95/5 )</td>
<td>3Ba</td>
<td>85</td>
</tr>
<tr>
<td>3a</td>
<td>CBZ</td>
<td>CHO</td>
<td>( \geq 95/5 )</td>
<td>3Ab</td>
<td>90</td>
</tr>
<tr>
<td>4*</td>
<td>TS</td>
<td>CHO</td>
<td>( \geq 95/5 )</td>
<td>3Bb</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>CBZ</td>
<td>Me</td>
<td>92/8</td>
<td>3Ac</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>CBZ</td>
<td>( \text{BnOCH}_2 )</td>
<td>85/15</td>
<td>3Ad</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>TS</td>
<td>Me</td>
<td>( \geq 95/5 )</td>
<td>3Bc</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>CO Me</td>
<td>CO Me</td>
<td>( \geq 95/5 )</td>
<td>3Ca</td>
<td>87</td>
</tr>
</tbody>
</table>

*After treatment of the dimethyl acetal with Amberlyst 15 in aqueous acetone.

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The absolute configuration at C-2 of 3Ab and 3Ac has been determined via N.O.E. difference measurements, and that of oxazolidine 3Ba by X-ray diffraction (ref.4).

The ring closure secures to proceed through an oxonium ion which in turn can cyclize via a 5-endo-trig process (ref.5).

We believe that the kinetic preference for the cis oxazolidine is due to steric hindrance factors during the formation and the cyclization of the transient oxonium ion (ref.4).

It is worth noting that the cis isomer is favoured by kinetic as well as thermodynamic conditions (ref.4,6).

**ASYMMETRIC ELECTROPHILIC CONJUGATE ADDITION**

The catalytic osmium tetroxide dihydroxylation of (2S)-2-alkenyl oxazolidines of type I 3Ac, 3Ad afforded the diols synα and synβ with a diastereomeric excess of about 55-60%.

In contrast with the electron rich alkenes, the type II oxazolidine 3 Aa shows the opposite diastereoface preference either by OsO₄ (46% e.e.) or KMnO₄ dihydroxylation (60% e.e.) (ref.7) (Table 2; Scheme 2).

<table>
<thead>
<tr>
<th>Oxazolidine</th>
<th>OsO₄ (4/5; yield%)</th>
<th>KMnO₄ (4/5; yield%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Aa</td>
<td>1/27; 95</td>
<td>1/4; 60</td>
</tr>
<tr>
<td>3Ac</td>
<td>3.4/1; 76</td>
<td>-; -</td>
</tr>
<tr>
<td>3Ad</td>
<td>3.5/1; 88</td>
<td>-; -</td>
</tr>
</tbody>
</table>

**Scheme 2**

Ketalization of the pure diols 4, CBZ removal by standard hydrogenation and subsequent mild acidic hydrolysis released the desired optically pure aldehydes together with L-norephedrine hydrochloride (ref.7).

Since the mechanism of osmylation is not well defined (ref.8), the factors determining reaction selectivity are particularly difficult to evaluate.

A rationalisation of the results can be attempted on the basis of the known models for osmylation (ref.9, 11).

From this point of view, the 3,4-anti selectivity shown by E-enoate with an allylic alcohol or ether can be explained assuming that reaction takes place preferentially through transition structure A.

This structure, which features an S-cis conformational arrangement between the olefinic linkage and the allylic C-O bond is indeed suggested by Stork to be more stable than B (ref.9) because of favorable interaction between the system and an unshared electron pair on the γ-oxygen (Fig.1).
It is interesting to know that models A and B correspond to the most stable transition structures proposed by Houk for electrophilic attacks to double bonds on the basis of hyperconjugative effect considerations (ref.10). In accordance to Houk, the σ-acceptor (OR) would occupy "inside" or "outside" positions and the best σ-donor would be "anti" to the electrophile to facilitate olefin HOMO - electrophile LUMO interactions. Structure A and B should represent the best transition states for allylic ether E-enoates hydroxylations.

Presumably, in the case of type II oxazolidine 3Aa, steric reasons favour structure B' over A' as shown in Fig. 1 where B' structure rationalizes the most significant transition structure.

The diastereofacial preference observed in the dihydroxylation of 2-alkenyl oxazolidines without electron withdrawing groups may be rationalized in terms of product like intermediate C for R= Me or CH2OCH2Ph (Fig. 2) according to the model proposed by Vedejs (ref.12).

In effect the scarce importance of σ-antaromatic interactions has been tested by Vedejs by comparing the osmylation of substrates having bulky donors vs. bulky acceptors. However the face selectivity does not depend on σ-acceptor/donor but only on the olefin geometry.

Therefore the osmylation transition states will have the C-2 hydrogen in the most demanding environment and this depends on olefin geometry. For E-alkenes, steric requirements of osmium ligands are dominant and conformations with C-2 hydrogen near osmium are preferred.

ASYMMETRIC NUCLEOPHILIC CONJUGATE ADDITION

The addition of nucleophile reagents to conjugated olefins bearing an allylic stereocenter is a problem which has been receiving considerable attention from both theoretical and experimental points of view (ref.4,13,14).

The study of conjugate additions to type II oxazolidines, expected for electronic reasons to take place at C-1', thus appeared of particular interest.

ADDITION OF CUPRATE REAGENTS

We reported in recent communications (ref.4,14) that cuprate reagents cleanly add to oxazolidine cis-3Aa with excellent regio- and stereo-selectivity (diastereomeric ratio > 95:5) to give, in good yields, esters 6a-6d (Scheme 3; Table 3).

Scheme 3

Table 3. Diastereoselection and yield of cuprate addition to 3.

<table>
<thead>
<tr>
<th>Oxazol.</th>
<th>Cuprate reagent</th>
<th>T°C</th>
<th>Product</th>
<th>Diast. ratio</th>
<th>Config.</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Aa</td>
<td>Me2CuLi</td>
<td>-25</td>
<td>6a</td>
<td>95:5</td>
<td>S</td>
<td>70</td>
</tr>
<tr>
<td>3Aa</td>
<td>Me2CuLi/Me3SiCl</td>
<td>-78</td>
<td>6a</td>
<td>95:5</td>
<td>S</td>
<td>72</td>
</tr>
<tr>
<td>3Aa</td>
<td>Bu2CuLi</td>
<td>-25</td>
<td>6b</td>
<td>95:5</td>
<td>S</td>
<td>70</td>
</tr>
<tr>
<td>3Aa</td>
<td>(CH2=CH)2CuLi</td>
<td>-50/-25</td>
<td>6c</td>
<td>95:5</td>
<td>R</td>
<td>75</td>
</tr>
<tr>
<td>3Aa</td>
<td>(CH2=CH-CH2)2CuLi</td>
<td>-78/ R.T. 6d</td>
<td>89:11</td>
<td>S</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>3Ab</td>
<td>Me2CuLi/Me3SiCl</td>
<td>-78</td>
<td>6e</td>
<td>95:5</td>
<td>S</td>
<td>77</td>
</tr>
<tr>
<td>3Ab</td>
<td>Bu2CuLi/Me3SiCl</td>
<td>-78</td>
<td>6f</td>
<td>88:12</td>
<td>S</td>
<td>65</td>
</tr>
<tr>
<td>3 Ae</td>
<td>Me2CuLi/Me3SiCl</td>
<td>-78</td>
<td>6g</td>
<td>95:5</td>
<td>S</td>
<td>80</td>
</tr>
<tr>
<td>3 Ae</td>
<td>Bu2CuLi/Me3SiCl</td>
<td>-78</td>
<td>6h</td>
<td>95:5</td>
<td>S</td>
<td>80</td>
</tr>
</tbody>
</table>
The same stereoselectivity is also observed by adding cuprate reagents to oxazolidine cis containing an aldehyde or a ketone instead of a carbomethoxy group conjugated to the double bond.

The \( \alpha,\beta \)-unsaturated aldehyde 3Ab (ref.20) can be easily prepared on a large scale from one of the two commercially available N-CBZ-norephedrine enantiomers (i.e. 1R,2S) and fumaraldehyde bis dimethylacetal (ref.22) in the presence of pyridinium tosylate in benzene solution, followed by treatment with Amberlyst-15 in aqueous-acetone (Scheme 1).

The \( \alpha,\beta \)-unsaturated ketone 3Ac is prepared from 3Ab through condensation with methyl magnesium iodide and subsequent oxidation with pyridinium dichromate. However with \( \alpha,\beta \)-unsaturated aldehyde or ketone oxazolidines it is necessary to add TMSCl to obtain good yields (ref.15) (Scheme 3).

Although the mechanism of organocopper conjugate addition is still an open question, convincing recent evidence shows the reversible formation of a cuprate-substrate \((d-\pi)^+\) complex and a Cu \(\beta\)-adduct in the initial step (ref.16, 17).

However, the presence of TMSCl in the reaction medium can irreversibly trap the latter intermediate thereby shifting the rate determining step from the reductive elimination level to the earlier \(d,\pi\) complexation stage (ref.13d). Cuprate additions to oxazolidines 3Aa, 3Ab, and 3Ac always occurred from the substrate \(S1\) face; moreover the same selectivity was observed regardless of the presence (5 mol equiv) or absence of TMSCl. It follows that the postulated kinetic \(\beta\)-adduct must be the more stable \((d-\pi\) complexation as r.d.s.) or the faster reacting diastereomer (reductive-elimination as r.d.s.).

Treatment of adducts 6a and 6b with HSCH\(\_\)CH\(\_\)SH/BF\textsubscript{3}Et\textsubscript{O} in \(\text{CH}_3\text{Cl}_2\) smoothly released the intact auxiliary together with the corresponding dithiolanes. Thioacetal hydrolysis (\(\text{CaCO}_3/\text{MeI}/\text{H}_2\text{O}\)) gave the corresponding \(\alpha\)-alkyl aldehydes thereby unveiling the constant \(S1\) face selectivity of the cuprate additions as well as the effectiveness of the deprotection steps (Scheme 3).

The stereochemical outcome of these additions can be interpreted in terms of stereoelectronically and/or sterically controlled kinetic \(\pi\)-face differentiation. The two staggered transition structures A and B were thus considered (Fig.3).

For nucleophilic attack on \(\pi\) bonds, electronegative allylic groups (A and B) prefer the anti conformation so that the withdrawal of electrons from the \(\pi\)-system can be maximized. The most electropositive group will prefer to be outside to minimize the donation of electrons to the perturbed system of the already electron-rich transition state. When the \(\sigma^*\) orbital is aligned anti to the forming bond, its overlap with the HOMO of the transition state, consisting of a mixture of the nucleophile HOMO and the carbonyl LUMO is maximized. This overlap of the substituent LUMO with the transition structure HOMO results in stabilization (ref.10c,19). On the other hand it is evident that H-2-ring interactions destabilize structure B.

Structure A, leading to the observed stereochemistry therefore appears to be the transition state fulfilling both stereoelectronic as well as steric requirements.

The configuration of the adducts obtained by adding dialkylolithium cuprates to \(\alpha,\beta\)-unsaturated aldehyde and ketone oxazolidines has been determined transforming the aldehyde adducts 6e and 6f into the corresponding methyl ketones 6g and 6h (1.\text{MeMgBr} 2.\text{PDC}) identical to the compounds obtained by the direct addition of cuprate to the \(\alpha,\beta\)-unsaturated ketone oxazolidine 3Ac. Aldehyde oxazolidines 6e and 6f have been in turn transformed into the corresponding methyl esters (1.\text{Ag}_2/\text{dioxane} 2.\text{CH}_2\text{N}_2) of known absolute configuration.

For synthetic purposes adduct 6e was transformed into the corresponding alcohol and protected as O-benzyl derivative 10. A straightforward non-destructive removal of the chiral auxiliary performed by treating with HSCH\(\_\)CH\(\_\)SH/BF\textsubscript{3}Et\textsubscript{O} in \(\text{CH}_3\text{Cl}_2\) smoothly released the intact auxiliary together with the corresponding dithiolane 11. Immediate submission of the crude

Fig.3. Proposed transition structures for nucleophilic addition to 3.
reaction mixture to standard thioacetal hydrolysis (CaCO₃/Mel/H₂O/Me₂CO) gave the known (S)-2-methyl-4-benzyloxybutanal 12 (e.e. > 0.99) already prepared by C.J. Sih and coworkers using three different enzymatic approaches (ref.23) (Scheme 4).

**Scheme 4**

![Chemical structure](attachment:image.png)

Derivatization and chiral auxiliary removal from oxazolidine 6e.

The direct treatment of oxazolidines 6g and 6h with HSCH₂CH₂SH/BF₃·Et₂O in CH₂Cl₂ released analogously the chiral auxiliary 1A together with the bis dithiolane 13a and 13b (Scheme 5).

**Scheme 5**

![Chemical structure](attachment:image.png)

The usual deprotection step (CaCO₃/Mel/H₂O/Me₂CO) gave 2-methyl-4-oxopentanal 14a and 2n-butyl-4-oxopentanal 14b (Scheme 5).

Unfortunately when the acceptor was trisubstituted such as compound 15a and 15b any attempt of conjugate addition (R₂CuLi, R₂CuBF₃ in Et₂O or THF, -78/-25°C, also in the presence of TMSCl 1-18h) failed.

![Chemical structure](attachment:image.png)

**ADDITION OF POTASSIUM HYPOCHLORITE**

Various nucleophilic epoxidation conditions (sodium hypochlorite in aqueous pyridine, alkaline hydrogen peroxide, potassium tert-butyl peroxide) were tried working with the α,β-unsaturated aldehyde 3Bb.

**Scheme 6**

![Chemical structure](attachment:image.png)

Epoxidation of oxazolidine 3Bb and chiral auxiliary removal.
The best results were obtained using potassium hypochlorite in aqueous THF; the epoxidation was complete after 1.5 hr at 0 deg. C, but the mixture was stirred two additional hours at room temperature to oxidize the epoxy aldehyde 16 to epoxy acid 17, obtained in 90% yield as a single isomer (>20:1 by 2H NMR spectroscopy) (ref. 20) (Scheme 6). The stereochemical outcome of this epoxidation can be rationalized using the same transition structure models A and B (Fig. 3) utilized to explain the π-face differentiation shown by cuprate reagents.

Trans epoxy acid was then treated with 23% aqueous ammonia solution at 70 deg. C for 3 hr to give regio- and stereospecifically, the anti α-amino-β-hydroxy acid in quantitative yield as a single isomer (>50:1 by 2H NMR spectroscopy). The anti configuration was proved by conversion of the α-amino-β-hydroxy acid into the cis oxazolidinone 22 (a. COCl₂, KOH, H₂O; b. CH₃CN; c. BOC₂O) characterized by a coupling constant J₂₁ = 8.9 Hz. Isomerization of cis under alkaline conditions (KOH, MeOH, reflux) followed by standard derivatization (a. CH₃CN; b. BOC₂O) gave complete conversion (>100:1) into the trans oxazolidinone 24 characterized by a coupling constant J₂₁ = 2.9 Hz.

\[
\text{21 } \text{R} = \text{H} \\
\text{22 } \text{R} = \text{BOC} \\
\text{23 } \text{R} = \text{H} \\
\text{24 } \text{R} = \text{BOC}
\]

Anti α-amino-β-hydroxy acid was then transformed into the N-CBZ derivative 19 (CBZ₂O, Shotton-Baumann) which was treated with diazomethane to give after flash chromatography, ethyl ester 20 in 64% overall yield from α,β-unsaturated aldehyde 38 with no intermediate purification (91% average yield per step).

The chiral oxazolidine was then removed by treatment of N-CBZ-α-amino-β-hydroxy ethyl ester 20 with ethanedithiol and BF₃·Et₂O in methylene chloride to give 25 (67%; 90% recovery of optically pure N-tosyl nor ephedrine) which was protected as TBDMS ether (TBDMS-OTf, lutidine, CH₂Cl₂, 80%) (Scheme 6).

Dithiolane 26 was then hydrolysed (CH₃I, CaCO₃, acetone-H₂O) to give the target aldehyde 27 in 80% yield. The aldehyde function of the last derivative provide a useful handle for manipulation to more complex structures, allowing potential access into a range of optically pure multifunctional α-amino-β-hydroxy acids, especially those of unusual, non-protein or unnatural types which are not easily accessible by fermentation.

The absolute configuration and the optical purity of aldehyde 27 were confirmed by reduction to the corresponding alcohol 28 (NaBH₄, MeOH, H₂O 85%), hydrolysis of the silyl ether to the vicinal diol 29 (HF, CH₃CN, H₂O, 85%) and ketal formation (acetone, 2,2-dimethoxypropane, p-TsOH, 90%) (Scheme 6). The ketal 30 shows the same optical rotation as that reported for the compound previously synthesized by Moriwake and coworkers from D-tartaric acid (ref. 21).

The complementary syn α-amino-β-hydroxy acid series was easily accessible through the oxazolidinone chemistry described above. Anti α-amino-β-hydroxy acid was converted into the cis-oxazolidinone 21 (a. COCl₂, KOH, H₂O; b. CH₃CN; c. BOC₂O) 75% overall yield from α,β-unsaturated aldehyde used as starting material) which was completely isomerized to trans oxazolidinone (KOH, MeOH, reflux) and saponified (KOH, MeOH, H₂O) to give the syn α-amino-β-hydroxy acid oxazolidine 31. Treatment of this compound with CBZ₂O under Shotton-Baumann conditions followed by diazomethane gave, after flash chromatography, ethyl ester 32 in 70% overall yield from cis oxazolidinone without intermediate purification.

**Scheme 7**

Conversion of anti α-amino-β-hydroxy to syn α-amino-β-hydroxy oxazolidine ester and removal of chiral auxiliary.
The target syn aldehyde 35 was easily prepared from 32 through the same sequence of reactions described above for the anti series (a. ethanedithiol, BF₃·Et₂O; b. TBDMS-OTf, lutidine, c. CH₂I₂, CaCO₃, acetone-H₂O) (Scheme 7).

In conclusion type II norephedrine-derived oxazolidine with R=CHO has proven to be a useful and versatile synthon for the synthesis of both syn and anti enantiomerically pure functionalized α-amino-β-hydroxy acids and derivatives.

**ADDITION OF SODIUM BENZYLATE**

In the last decade the synthesis of many natural products, particularly macrolide and ionophore antibiotics was essentially realized through enantioselective and diastereoselective aldol reactions (ref. 24). 2-Alkenyl norephedrine-derived oxazolidines give the opportunity to realize different strategies of obtaining aldol type chirons useful for assembling consecutive asymmetric carbon atoms along an open chain skeleton. On the basis of the experimental evidence before described, we took advantage of using oxazolidine 3 Ae and 36 respectively, available in both enantiomeric forms, as Michael acceptors of the nucleophilic benzyloxy anion for the synthesis of chiral 2-benzyloxy-4-oxopentanal 37 and 3-benzyloxy succinic aldehydic acid benzyl ester 38.

Of course the resulting β-benzyl ether would serve as readily removable protecting group for the derived hydroxyl function. Benzylester 36 was prepared from the corresponding acid 39 (BnBr/CH₂CN/n-Bu,NHSO₄ on the K salt) in its turn obtained through its oxidation of aldehyde 3 Ab (t-BuOH/Me₂C=CHMe/NaClO₂) (ref. 25) (Scheme 8).

**Scheme 8**

Benzylate addition to oxazolidines 36 and 3 Ae and chiral auxiliary removal.

Oxazolidines 3 Ae and 36 add sodium and lithium benzylate in benzyl alcohol to give respectively 40 and 41 with high stereoselectivity and yield although 3 Ac requires THF as cosolvent (PhCH₂OH/THF 2:1) to avoid the solidification at -50°C of the reaction mixture (Scheme 8) (Table 4).

**Table 4. Benzylate addition to oxazolidines 36 and 3 Ae.**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Oxazolidine</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield%</th>
<th>Diastereoisomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH₂OLi</td>
<td>36</td>
<td>PhCH₂OH</td>
<td>25</td>
<td>36</td>
<td>30</td>
<td>&gt; 95/5</td>
</tr>
<tr>
<td>PhCH₂ONa</td>
<td>36</td>
<td>PhCH₂OH</td>
<td>25</td>
<td>18</td>
<td>65</td>
<td>&gt; 95/5</td>
</tr>
<tr>
<td>PhCH₂ONa</td>
<td>36</td>
<td>PhCH₂OH</td>
<td>-5</td>
<td>24</td>
<td>35</td>
<td>&gt; 95/5</td>
</tr>
<tr>
<td>PhCH₂ONa</td>
<td>3 Ae</td>
<td>PhCH₂OH/THF</td>
<td>-50</td>
<td>18</td>
<td>98</td>
<td>&gt; 95/5</td>
</tr>
<tr>
<td>PhCH₂ONa</td>
<td>3 Ae</td>
<td>PhCH₂OH/THF</td>
<td>-50</td>
<td>18</td>
<td>98</td>
<td>&gt; 95/5</td>
</tr>
</tbody>
</table>

b. With the recovery of 36 (35%)
c. 2:1 ratio PhCH₂OH/THF

An attempt was made to effect benzyloxymercuration/demercuration (ref. 26) on 3 Ae and 36 to see whether it occurred with the same stereoselectivity. Unfortunately however it failed because at T<25 no reaction was observed and at higher temperature many products were obtained with partial decomposition of 3 Ae and 36. Coordination-directed mechanism of nucleophilic conjugate addition must be ruled out because neither the stereoselectivity nor the diastereoisomeric ratio is under the influence of the nature of counterion...
(Li⁺ or Na⁺) or of the presence of the crown ether. The configuration of 41 has been determined by correlation with the known lacton 42 (ref.27). So the treatment of 41 with HSCH₂CH₂SH/BF₃·EtO in CH₂Cl₂ smoothly released the intact auxiliary 1a together with the corresponding dithiolane. Standard thioacetal hydrolysis (CaCO₃/MeI/Acetone/H₂O) gave the 3(S)-benzyloxysuccinaldehydic acid benzylester 38. The reduction of 38 with NaCNBH₃ in AcOEt/AcOH 9:1 followed by treatment with PTSA in benzene overnight at room temperature gave the enantiomerically pure lacton 42 (Scheme 8). The stereochemistry of 40 was consequently determined transforming 41 into 40 (1. NaOH in aq. MeOH; 2. (COCl)₂; 3. Me₂CuLi). Unfortunately when the Michael acceptors were trisubstituted such as compounds 15a and 15b any attempt to add sodium or lithium benzylate failed. The stereochemical outcome of these additions, always occurring from the substrate Si face, can be rationalized using the transition structure models A and B (Fig.3) analogously to the other nucleophilic additions already described. For synthetic purposes 3Ae was converted into 37 by protecting the keto group as thioethylenketal 43 and deblocking oxazolidine ring as usual (HSCH₂CH₂SH/BF₃·EtO/CH₂Cl₂). The bis dithiolane 44, isolated by flash chromatography and subjected to standard hydrolysis (MeI/CaCO₃/acetonewater) afforded 12 (Scheme 9).

**Scheme 9**

![Image of chemical structures](image)

**Chiral auxiliary removal from oxazolidine 40.**

**ADDITION OF ISOPROPYLIDENETRIPHENYL PHOSPHORANE TO OXAZOLIDINE 3Aa**

Isopropylidenuenetrphenylphosphorane (45) adds to oxazolidine 3Aa with high stereoselectivity. This reaction constitutes a novel and enantioselective route to methyl trans (1R, 3R) 2,2-dimethyl-3-formylcyclopropanecarboxylate 46 (hemicaronic aldehyde), i.e. the target molecule in the synthesis of chrysanthemic acid 47 and its cis dibromo vinylanalog 48 component of natural pyrethrins and of deltamethrin, the most powerful commercially available insecticide (ref.28). Cyclopropanation of 3Aa has been achieved with 3 equiv. of 45 (generated from isopropyl triphenylphosphonium iodide and n-butyl lithium in benzene), the reaction being performed at 25°C for 12h. The adduct 49 is obtained in 70% yield as a single diastereoisomer. The usual chiral auxiliary removal (1. HSCH₂CH₂SH/BF₃·EtO/CH₂Cl₂ 2. CaCO₃/MeI/Acetonewater) gave the hemicaronic aldehyde 46 (70% overall yield) from which it is possible to prepare 47 and 48 (ref. 28) (Scheme 10).

**Scheme 10**

![Image of chemical structures](image)

**Cyclopropanation of oxazolidine 3Aa.**
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