(+)-3-Carene, an efficient chiral pool for the diastereoselective synthesis of $\beta$-lactams†

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Abstract
Design and synthesis of chiral acids, a ketene precursor, and imines from easily available (+)-3-carene, a bicyclic monoterpene, and their efficient use for the diastereoselective synthesis of $\beta$-lactams via Staudinger reaction has been discussed. A very high diastereoselectivity (90:10) in $\beta$-lactam formation was observed when an imine derived from a sterically demanding bicyclo[3.1.0]hexenyl aldehyde (4) was used.

Keywords: (+)-3-Carene, ketene, imines, Staudinger reaction, $\beta$-lactam.

1. Introduction
Antibiotics belonging to the families of penicillins, cephalosporins, cephemycins, nocardicins and monobactams have in common a $\beta$-lactam ring moiety.1 Chiral $\beta$-lactams besides their clinical importance have also proven to be very useful synths for the various non-$\beta$-lactam derivatives such as pyrrolidones,2 natural and non-natural $\alpha$-amino acids,3 peptides,4 nonprotein amino acids,5 $\alpha$-hydroxy-$\beta$-amino acids,6 an intermediate for taxol side chain.

Among the various methods reported for the construction of $\beta$-lactam ring, Staudinger reaction (ketene-imine cycloaddition reaction) has found wide acceptance in stereoselective synthesis of $\beta$-lactams.7,8 The organized transition state of cycloaddition reaction offers diverse options to design suitable partners of ketene and imine so that the product stereoselectivity can be efficiently controlled. The presence of a chiral centre at the adjacent sites of the reacting groups can dictate the preference for a particular diastereomer.8 Ideally, there are three sites where a chirality-directing group can be located: (a) the ketene ($R_1^1$, I), (b) the aldehyde component ($R_2$) of the imine (II), and (c) the amine component ($R_3$) of the imine (II) (Scheme 1).

\[ I + II \rightarrow III + IV + V + VI \]

Scheme 1.

† Dedicated to Prof. S. C. Bhattacharyya.
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Various chiral acid derivatives, as ketene precursors, and chiral imines have been reported to effect moderate to very high diastereoselectivity in $\beta$-lactam ring construction via asymmetric Staudinger reaction.\textsuperscript{8–10} A formal 2+2 cycloaddition requires a close approach of a reacting partner to attain an organized transition state and steric interaction among the substituents should be heightened as a result of proximity. It was surmised that stereoface-discrimination should be possible with a considerable bulky substituent. (+)-3-Carene, a bicyclic monoterpen, is an inexpensive natural product abundantly available from Indian turpentine oil. The ketenes or imines derived from (+)-3-carene retains the imposing gem-dimethyl group in the fused cyclopropane ring, which can effectively shield one face of the molecule from reagent approach. This account describes an efficient use of (+)-3-carene-derived ketenes as well as imines for the diastereoselective synthesis of $\beta$-lactams.

2. Synthesis of $\beta$-lactams using (+)-3-carene-derived imines

It has been argued, and even theoretically corroborated, that if the aldehyde component has a chiral $\alpha$-carbon with a hetero-atom attached to it, high diastereoselectivity in the cycloaddition reaction is assured. In the course of our studies, we observed a highly diastereoselective cycloaddition where the selectivity is controlled by a sterically demanding, bicyclic aldehyde component.\textsuperscript{11} Significantly, the nearest chiral centre was located at the $\beta$-carbon from the aldehyde group. The bicyclic aldehyde, 3,6,6-trimethylbicyclo[3.1.0]hex-2-ene-2-aldehyde (4),\textsuperscript{12} was obtained from optically pure (+)-3-carene (1) by a reported procedure (Scheme 2).

\begin{equation}
\text{i) a) H}_2\text{O}_2/\text{HCOOH; b) NaOH; ii) NaIO}_4/\text{acetone:H}_2\text{O; iii) piperidine/\text{AcOH:C}_6\text{H}_6, reflux, 5 h.}
\end{equation}

Scheme 2.

The aldehyde (4) on reaction with various amines in the presence of MgSO\textsubscript{4} offered the imines (5) in quantitative yield. These imines (5) on treatment with acid chlorides (6) in the presence of triethylamine at −78°C to room temperature gave diastereomeric mixture of only cis-$\beta$-lactams (7a–m & 8a–m) in very high isolated yield (Scheme 3, Table I.)

\begin{equation}
\text{i) R}_1\text{NH}_2/\text{CH}_2\text{Cl}_2/\text{MgSO}_4, \text{rt, 24 h; ii) Et}_3\text{N/CH}_2\text{Cl}_2, -78^\circ\text{C to rt, 12 h.}
\end{equation}

Scheme 3.
The absolute stereochemistry of the major diastereomer (7e) was ascertained by single-crystal X-ray analysis. The absolute configuration at C-3 and C-4 of the β-lactam was assigned as 3R,4S on the basis of known absolute configuration (1R,5S) of the bicyclic moiety. The absolute configuration of the other β-lactams was assigned by correlating 1H and 13C NMR, and HPLC analysis data with that of 7e.

The use of a chiral amine in combination with the chiral aldehyde (4) had marginal effect on the diastereoselective β-lactam ring formation. The imines (5c,d) derived from chiral α-phenylethylamines and bicyclic aldehyde (4) afforded a diastereomeric mixture of β-lactams (7j–m & 8j–m) in high isolated yield but the diastereoselectivity was largely unaffected (Table I).

A slight improvement in diastereoselectivity (96:4) was observed when phthalimidoacetyl chloride (6a) and imine (5c) derived from R- (+)-phenylethylamine was used (Table I, entry 10). However, diastereoselectivity was decreased when imines (5d) derived from S-(−)-phenylethylamine was used for the β-lactam formation (Table I, entry 12, 13).

We believe that the steric course of the reaction is determined by the steric bulk of the cyclopropyl ring with gem-dimethyl substituent as the ketene approaches the imine from the face opposite to the cyclopropane (Fig. 1). The imine can adopt two orientations, cisoid and transoid, with respect to the double bond. Analysis of the product stereochemistry indicates that the major product (7) results from the reaction between the cisoid imine and the ketene from the less hindered face (TS-1). The minor product (8) results from a similar reaction between the transoid imine and the ketene also approaching from the less hindered side (TS-2). Thus, the selectivity is a manifestation of kinetic control.

It should be noted that the steric bulk of the aldehyde was effective in inducing diastereoselectivity even though the nearest chiral centre was at the β carbon from the aldehyde end. We also examined the imines (11) derived from (+)-3-carene where the chiral centre is located at γ position in a bicyclo[4.1.0]heptane system for possible stereodifferentiation.

### Table I

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-Lactams (7 &amp; 8)</th>
<th>R1</th>
<th>R2</th>
<th>Yielda (%)</th>
<th>Ratiob of 7 &amp; 8</th>
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<td>90:10</td>
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<td>99</td>
<td>77:23</td>
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<tr>
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<td>c</td>
<td>PMP</td>
<td>BnO</td>
<td>92</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>PMP</td>
<td>AcO</td>
<td>76</td>
<td>85:15</td>
</tr>
<tr>
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<td>e</td>
<td>PMP</td>
<td>N3</td>
<td>66</td>
<td>86:14</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>Bn</td>
<td>PhthN</td>
<td>90</td>
<td>88:12</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>Bn</td>
<td>PhO</td>
<td>92</td>
<td>65:35</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>Bn</td>
<td>BnO</td>
<td>99</td>
<td>60:40</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>Bn</td>
<td>AcO</td>
<td>88</td>
<td>85:15</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>–CH(Me)Ph(R)</td>
<td>PhthN</td>
<td>92</td>
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</tr>
<tr>
<td>11</td>
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<td>–CH(Me)Ph(R)</td>
<td>PhO</td>
<td>65</td>
<td>63:37</td>
</tr>
<tr>
<td>12</td>
<td>l</td>
<td>–CH(Me)Ph(S)</td>
<td>PhthN</td>
<td>86</td>
<td>72:28</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>–CH(Me)Ph(S)</td>
<td>PhO</td>
<td>94</td>
<td>55:45</td>
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</table>

*a* Isolated yields of diastereomeric mixture. *b* Ratio of the diastereomers is determined by 1H NMR and HPLC analysis. *c* Prepared from N₃CH₂COOK and cyanuric chloride.
The bicyclic aldehyde, 4,7,7-trimethylbicyclo[4.1.0]hept-3-ene (10), was obtained by Swern oxidation\textsuperscript{14} of 3-hydroxymethyl-4,7,7-trimethyl[4.1.0]hept-3-ene, which was prepared from (+)-3-carene (1) under Prins reaction conditions\textsuperscript{15} followed by hydrolysis of acetate 9 (Scheme 4). The aldehyde on treatment with different amines yielded imines 11 in very good yields.

The imines (11) on cycloaddition reactions with ketenes, generated in situ from acid chlorides (6) in the presence of triethylamine, gave almost 1:1 diastereomeric mixture of \( \beta \)-lactams (12 & 13) in moderate yields (Scheme 5, Table II).\textsuperscript{11b} The poor diastereoselectivity in \( \beta \)-lactam ring formation may be due to the presence of chiral centre further away (on \( \gamma \) carbon) from the reacting centre in the imines derived from bicyclo[4.1.0]heptenyl aldehyde (10).
(+) -3 -Carene as a ketene precursor

Encouraged by diastereoselectivity in \( \beta \)-lactam ring formation using sterically demanding chiral imines derived from (+)-3-carene, we decided to study the effect of chiral ketenes derived from (+)-3-carene. (+)-3-Carene on reaction with hydrogen peroxide in the presence of ethyl chloroformate and phosphate buffer yielded \( \alpha \)-carene oxide (14) in excellent yield. The oxide (14) was opened with alcohol in the presence of a catalytic amount of \( p \)-toluenesulphonic acid (PTSA) to give alkoxy alcohols (15a, b) in very high yield. The alcohols 15a, b on alkylation either with chloroacetic acid in the presence of NaH or ethyl bromoacetate followed by hydrolysis offered the chiral acids (16a, b) in good yield (Scheme 6).17

The chiral acid (16) on annulation reaction with imine (17a–f) in the presence of phenyl dichlorophosphate, an acid activator, and triethylamine at 0°C afforded a diastereomeric mixture of cis-\( \beta \)-lactams (18a–g & 19a–g) in 50–68% yield (Scheme 7, Table III).

The analysis of the crude reaction mixture by \( ^1 \)H NMR showed the presence of only two diastereomers in the maximum ratio of 67:33 (Table III, Entry 3). These diastereomers were separated by crystallization from acetone/pet. ether.17 An improvement in the yield (65%) of
diastereomeric mixture of \( \beta \)-lactams (18a & 19a) with a similar diastereomeric ratio (60:40) was observed when cycloaddition reaction of acid 16a with imine 17a was carried out by our newly developed methodology\(^{18}\) using triphosgene as an acid activator.

The \( \beta \)-disposition of cyclopropane ring with gem-dimethyl group and \( \alpha \)-orientation of alkoxy acid side chain in acid 16 did not provide necessary steric requirement for facial discrimination during the ketene–imine cycloaddition, which resulted in poor diastereoselectivity. Therefore, we decided to see the effect of chiral ketene precursor with \( \beta \)-orientation of both alkoxy acid side chain at tertiary carbon and cyclopropane ring, on diastereoselectivity in \( \beta \)-lactam formation. The starting acids (21a, b) were prepared from 15b by protection of secondary alcohol as methyl ether (20a) or acetate (20b) followed by oxidation of allylic side chain (Scheme 8).

\[
\begin{align*}
\text{15b} & \quad \text{i) NaH/Mel/C,H, 0°C to rt, 9 h or (b) AcCl/py/CH,Cl, 0°C to rt, 6 h; ii) RuCl/NaIO/CH, CN:CCl,H,O (2:2:1), 0°C, 4 h.} \\
& \quad \text{Scheme 8.}
\end{align*}
\]

The acid 21a, b on cycloaddition reaction with imine (17a) in the presence of triethylamine and phenyl dichlorophosphate offered diastereomeric mixture (60:40) of only cis-\( \beta \)-lactams (22a, b & 23a, c) in 60–65% yield (Scheme 9).\(^{19}\) However, no improvement in the diastereoselectivity was observed by inter-changing the positions of acid and alkoxy groups.

\[
\begin{align*}
\text{21a R = Me} & \quad \text{21b R = Ac} \\
\text{22a R = Me} & \quad \text{22b R = Ac} \\
\text{23a R = Me} & \quad \text{23b R = Ac}
\end{align*}
\]

\[
\begin{align*}
& \quad \text{i) Et,N/CH,Cl/PhOP(O)Cl, 0°C to rt, 15 h.} \\
& \quad \text{Scheme 9.}
\end{align*}
\]
2.2. Synthesis of 3-hydroxy-cis-β-lactams via (+)-3-carene-derived ketene precursor

It has been reported that a suitably protected 3-hydroxy-β-lactam can serve as a synthetic equivalent for phenylisoserine side chain of taxol. A direct coupling of protected 3-hydroxy-4-phenyl-β-lactam with 10-baccatin III has also been used for the synthesis of taxol. We have utilized (+)-3-carene-derived acids efficiently for the synthesis of 3-hydroxy-β-lactams via Staudinger reaction.

The keto acid with β alkoxy acid side chain was obtained from α-carene oxide (14) by the acid-catalyzed epoxide ring opening with ethylene glycol followed by Jones’ oxidation of the resulting diol 24 (Scheme 10).

The cycloaddition of ketene derived from acid 25 with various imines (17a,c–d,g) in the presence of phenyl dichlorophosphate and triethylamine yielded a diastereomeric mixture of only cis-β-lactams (26 and 27) with moderate selectivity (Scheme 11, Table IV). A maximum diastereoselectivity (70:30) was obtained when imine 17a was used for cycloaddition reaction. The major isomer 26a was obtained in optically pure form by single crystallization (benzene:pet. ether) in 47% yield.

Table IV

<table>
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<tr>
<th>Entry no.</th>
<th>Compounds</th>
<th>R¹</th>
<th>R²</th>
<th>Yield¹ (%)</th>
<th>Ratio² of 26 &amp; 27</th>
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<td>74</td>
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<td>PMP</td>
<td>79</td>
<td>56:44</td>
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<td>3</td>
<td>c</td>
<td>PMP</td>
<td>Styryl</td>
<td>69</td>
<td>53:47</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>Bn</td>
<td>Ph</td>
<td>47</td>
<td>61:39</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>Bn</td>
<td>Styryl</td>
<td>86</td>
<td>54:46</td>
</tr>
</tbody>
</table>

¹Isolated yield of mixture of diastereomers 26 & 27. ²The ratio of diastereomers is determined by 'H NMR and HPLC analysis.
The major diastereomer 26a on Baeyer–Villiger oxidation using m-chloroperoxybenzoic acid (m-CPBA) in dichloromethane gave (3R,4S)-3-hydroxy-4-phenyl-β-lactams (28) along with keto acid (29) (Scheme 12). The keto acid (29), obtained after the cleavage of the chiral auxiliary, is also an intermediate for the synthetic pyrethroids.23

![Scheme 12.](image)

The absolute stereochemistry of β-lactam (28a), obtained from β-lactam (26a), was found to be 3R,4S by comparing its rotation with the known 3-hydroxy-4-phenyl-β-lactams.24 Based on these results, the absolute stereochemistry of 3R,4S and 3S,4R was assigned to the other major β-lactams (26b–e) and minor β-lactams (27a–e), respectively, by comparing their spectral data with that of β-lactam 26a.

We were also interested to see the effect of inversion of the stereo centre carrying the acid side chain in the keto acid (25) on diastereoselectivity in β-lactam ring formation. The other keto acid (33) was prepared from β-carene oxide (31) by a similar reaction sequence as in Scheme 10. The carane diol (2) on monotosylation followed by treatment with base offered β-carene oxide (31) in good yield (Scheme 13).25

![Scheme 13.](image)

The reaction of keto acid (33) with imine (17a) under Staudinger reaction conditions using phenyl dichlorophosphate as an acid activator yielded a diastereomeric mixture of only cis-β-lactams (34 & 35) in the ratio of 60:40 in 70% yield (Scheme 14).17 However, the inversion of stereocentre at the tertiary carbon bearing acid side chain could not improve the diastereoselectivity in cycloaddition reaction.

![Scheme 14.](image)
We have also developed a complementary method for the synthesis of 3-hydroxy-β-lactams (28 and 41) via halo acids (37) derived from (+)-3-carene. The halo acids (37a,b) were prepared by NBS or NCS reaction with (+)-3-carene in the presence of ethylene glycol followed by Jones’ oxidation of halohydrins (36a,b) in moderate yield (Scheme 15). The halo acids (37a,b) were converted into corresponding acid chlorides (38a,b) in almost quantitative yields by thionyl chloride.

\[
\text{(+)-3-Carene (1)} \xrightarrow{i} 36a \quad X = \text{Br} \quad 36b \quad X = \text{Cl} \xrightarrow{\text{ii}} 37a \quad X = \text{Br} \quad 37b \quad X = \text{Cl} \xrightarrow{\text{iii}} 38a \quad X = \text{Br} \quad 38b \quad X = \text{Cl}
\]

\(i\) NBS or NCS/HOCH\text{2}CH\text{2}OH, 0°C, 4 h; \(ii\) Jones’ reagent, 0°C, 4 h and \(iii\) SOCl₂/Benzene, reflux, 3 h.

Scheme 15.

The acid chloride (38a,b) on treatment with imines (17) in the presence of triethylamine at 0°C to room temperature gave a diastereomeric mixture of only cis-β-lactams (39a–f & 40a–f) in good yields (Scheme 16, Table V).17,26

\[
38a,b \quad \xrightarrow{i} \quad 39a-f \quad \xrightarrow{\text{ii}} \quad 40a-f
\]

\(i\) Et₃N/CH₂Cl₂, 0°C to rt, 15 h.

Scheme 16.

The diastereomers (39 and 40) were separated either by crystallization or column chromatography. The absolute stereochemistry of 3\(R\),4\(S\) and 3\(S\),4\(R\) were assigned to the major (39) and minor β-lactams (40), respectively, by single-crystal X-ray analysis of one of the isomers as well as by converting some of them to the known 3-hydroxy-β-lactams.

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Compounds (39 &amp; 40)</th>
<th>X</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (a) (%)</th>
<th>Ratio of 39 &amp; 40</th>
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<td>a</td>
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<td>Ph</td>
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<td>Styryl</td>
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<td>6</td>
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<td>Cl</td>
<td>PMP</td>
<td>Styryl</td>
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<td>60:40</td>
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\(a\) Isolated yield of mixture of diastereomers 39 & 40. \(b\) The ratio of diastereomers is determined by \(^1\)H NMR and HPLC analysis.
Table VI
Synthesis of 3-hydroxy-cis-β-lactams (28a,b & 41a–d) by zinc/acetic acid-mediated cleavage of halo ethers (39a,b & 40a–d)

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Product</th>
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<th>R²</th>
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<td>Ph</td>
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<td>3R, 4S</td>
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<td>28b</td>
<td>Ph</td>
<td>Ph</td>
<td>96</td>
<td>3R, 4S</td>
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<td>95</td>
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<td>41d</td>
<td>Ph</td>
<td>Ph</td>
<td>96</td>
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<td>PMP</td>
<td>98</td>
<td>3S, 4R</td>
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<tr>
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<td>41d</td>
<td>PMP</td>
<td>Styryl</td>
<td>96</td>
<td>3S, 4R</td>
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</table>

*Isolated yield of pure product.

The cleavage of the chiral auxiliary was effected by reacting pure diastereomers (39a,b & 40a–d) with zinc/acetic acid under reflux for 30 min to give corresponding enantiomerically pure 3-hydroxy-cis-β-lactams (28a,b & 41a–d) in almost quantitative yields (Scheme 17, Table VI).26

The (+)-3-carene formed in the reaction by cleavage of the chiral auxiliary was also isolated and characterized. The formation of 3-hydroxy-cis-β-lactams (28a,b & 41a–d) was confirmed from their spectral data. The absolute configuration of the β-lactams (28 & 41) was assigned as (3R,4S) and (3S,4R), respectively, by comparing their physical data as well as specific rotation with some of the compounds reported in the literature.22, 24, 29

Thus, this methodology provides an easy access for large-scale preparation of enantiopure 3-hydroxy-cis-β-lactams, one of which, 28a, is a key intermediate for taxol side chain.

Acknowledgement
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9. **Evans, D. A. and Sjogren, E. B.**

10. **Palomo, C., Aizpurua, J. M., Ganboa, I. and Oiarbide, M.**

11. a. **Jayaraman, M., Deshmukh, A. R. A. S. and Bhawal, B. M.**

   b. **Jayaraman, M., Srirajan, V., Deshmukh, A. R. A. S. and Bhawal, B. M.**

12. a. **Matsui, M., Yoshboka, H., Sakamoto, H., Yamada, Y. and Kitahara, T.**

   b. **Mitra, R. B., Kulkarni, G. H., Muliani, Z. and Khanna, P. N.**

   c. **Deshmukh, A. R. A. S.**

13. a. **Ojima, I. and Chen, H. C.**

   b. **Ojima, I., Chen, H. C. and Qiu, X.**

   c. **Alcaide, B., Dominguez, G., Escobar, G., Perreno, V. and Plumet, J.**

14. a. **Omura, K. and Swern, D.**

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15. a. Cocker, W. and Laud, H. St. J.
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23. a. Arlt, D., Jautelat, M. and Lantzsch, R.


27. Boguslavskaya, L. S.


29. Borer, B. C. and Balogh, D. W.