The Type II Intramolecular Diels-Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes

Taxol

Esperamicin A₁ aglycone

CP-264,114

Cerorubenic acid

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Bredt’s Rule vs Bridged alkene

Bredt's Rule

Bredt's rule is an empirical observation in organic chemistry that states that a double bond can not be placed at the bridgehead of a bridged ring system, unless the rings are large enough.

ex. norbornene

Forbidden norbornene isomers

Bredt, J., Liebig's Ann. Chem., 1924, 437, 1

Prelog, Fawcett...: Establishing Boundaries (Anti-bredt alkene)

Prelog, V., JCS, 1950, 420
**Introduction: Intramolecular Diels-Alder**

Type I: Tether is attached at 4-position of diene.

Type II: Tether is attached at 3-position of diene.

i) Bridged products rarely observed.
   (tether must be > 9 atoms)
ii) Fused products usually have 3 or 4 atom tether.

Type II Intramolecular Diels-Alder

Accidental discovery during a mechanistic study of the Cope rearrangement.
# Development of the Scope of the Reaction

## Activated Dienophiles

Table 2. Gas-phase thermolysis of three-atom-bridged triene esters and ketones

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions $^{[a]}$</th>
<th>Product</th>
<th>Yield [%] $^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>420°C, 23 s</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>395°C, 18 s</td>
<td>13</td>
<td>72</td>
</tr>
<tr>
<td>(E)-14</td>
<td>318°C, 18 s</td>
<td>15</td>
<td>76</td>
</tr>
<tr>
<td>(E)-14</td>
<td>365°C, 12 s</td>
<td>15 $^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>390°C, 12 s</td>
<td>17</td>
<td>30</td>
</tr>
</tbody>
</table>

$^{[a]}$ Atmospheric pressure, N$_2$ carrier gas; thermolysis temperature and contact time are given.  
$^{[b]}$ Determined by GC, percentages based upon starting material remaining after thermolysis.  
$^{[c]}$ The Z isomer underwent isomerization to the E isomer under the thermolysis conditions. The cycloaddition product was identical with that obtained from (E)-14.

## Lewis Acid Catalyst

Table 5. Lewis acid catalyzed type 2 IMDA reactions

<table>
<thead>
<tr>
<th>Starting triene</th>
<th>Conditions $^{[a]}$</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>4 h, 21°C</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>27</td>
<td>2 h, 21°C</td>
<td>28</td>
<td>75</td>
</tr>
<tr>
<td>29</td>
<td>1 h, 21°C</td>
<td>30</td>
<td>71</td>
</tr>
<tr>
<td>29</td>
<td>&lt;5 min, 21°C</td>
<td>31</td>
<td>70</td>
</tr>
<tr>
<td>31</td>
<td>12 h, 21°C</td>
<td>32</td>
<td>85</td>
</tr>
<tr>
<td>33</td>
<td>12 h, 21°C</td>
<td>34</td>
<td>85</td>
</tr>
</tbody>
</table>

$^{[a]}$ In CH$_2$Cl$_2$ with Et$_2$AlCl as Lewis acid; thermolysis temperature and reaction time are given.

Acetylenic and Allenic Dienophiles

Scheme 5. Kanematsu’s approach to tricyclic compounds using an allene dienophile. CSA = camphorsulfonic acid, PDC = pyridinium dichromate.

Masked Dienes and Dienophiles

![Chemical structures and reactions](image)

Scheme 7. Synthesis of advanced taxusin intermediate 76.\[33\]

### Hetero Diels-Alder Reactions

#### Table 7. Intramolecular acyl iminium Diels–Alder cycloadditions.

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions[a]</th>
<th>Products</th>
<th>Yields [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>80a</td>
<td>250°C, 2 min</td>
<td>81a</td>
<td>29</td>
</tr>
<tr>
<td>80b</td>
<td>200°C, 2 h</td>
<td>81b</td>
<td>82</td>
</tr>
<tr>
<td>80c</td>
<td>215°C, 2 h</td>
<td>81c</td>
<td>76</td>
</tr>
</tbody>
</table>

[a] Reactions were performed in xylenes at 0.01M. [b] Yields refer to isolated products after chromatography.

Regio- and Stereochemical Control

Scheme 11. Pericyclic umpolung applied to the synthesis of methyl 3-oxocyclohexanecarboxylate (115). The course of the normal Diels–Alder reaction is shown above. TBAF = tetrabutylammonium fluoride, m-CPBA = meta-chloroperoxybenzoic acid.

Scheme 12. Stereoselectivity of the type 2 IMDA reaction.

Disposable Tethers between Diene and Dienophile

Scheme 14. A disposable vinyl ether linker in the type 2 IMDA reaction.


Scheme 17. Elaboration of bridgehead vinyl silanes.
Enantioselective Intramolecular Diels-Alder

Organocatalytic Intramolecular Diels–Alder (IMDA)

1. amine catalyst 1 or 2

-cocatalysts =
 a = TFA
 b = HCl
 c = HClO₄

catalyst 1
catalyst 2

2. 20 mol% 2
 20 mol% p-TSA
 CHCl₃, 25 °C

65% yield
99:1 endo:exo, 98% ee (endo)

Stereoselective Elaboration

Addition to the Bridged Double Bond

Figure 7. Stereochemistry of the addition to bridgehead double bonds.

\[ \text{Pd/C, H}_2 \rightarrow 75\% \]
\[ \text{NaOEt, EtOH, 100\%} \]

147 \rightarrow 148 \rightarrow 151

149 \rightarrow 150 \rightarrow 152 \rightarrow 153, 70\%
Functionalization of the Bridged Ring System

Scheme 20. Stereoselective reduction of bicyclo[3.3.1] ketones to give alcohols. DIBALH = diisobutylaluminum hydride.

Scheme 21. Kinetic (K) versus thermodynamic control (T) in the alkylation of ketone 103. KHMDMS = potassium salt of hexamethyldisilazane, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

Bridged to Fused Ring Interchange

Scheme 24. Examples for bridged to fused ring interchange. PPTS = pyridinium para-toluenesulfonate.

Ring Expansion of Bridged Alkenes

Scheme 25. Ring expansion in bridgehead enol lactones (I) to cycloheptenones (III) via cyclopropane intermediates (II).

exo addition of dichlorocarbene
Applications in Natural Product Synthesis

Taxanes

the most celebrated member of the taxane family of natural products
treatment of ovarian cancer
enormous synthetic effort toward the total synthesis of Taxol
bridged tricyclopentadecene ring system with 11 stereocenters and protected oxygen substituents

Shea, K. J.,
Taxanes (Yadav)

Scheme 30. Synthesis of taxane core 208 according to Yadav and Ravishankar. imid. = imidazole.

Type II IMDA & Wittig rearrangement

Yadav, J. S.,
Taxanes (Phillips and Abell)

Taxanes

Scheme 32. Our synthesis of the functionalized taxane core 224. DME = dimethoxyethane, Bn = benzyl.

Shea, K. J.,
Taxanes

Scheme 34. Synthesis of taxane core 238 according to Winkler et al.

Scheme 35. Synthesis of cyclopropyl taxane derivative 244 according to Winkler et al.

Winkler, J. D.,
Applications in Natural Product Synthesis

Esperamicin

![Chemical structure of Esperamicin]

bicyclo[7,3,1]tridecane bridged core
enediyne structural unit
antitumor agent

Esperamicin A_1 aglycone

Scheme 37. Type 2 IMDA cycloaddition of polycyntyne 249. PMB = para-methylbenzoyl.

Scheme 38. Synthesis of esperamicin core 255 according to Schreiber et al.
Ms = methanesulfonyl, DDQ = dichlorodicyanobenzoquinone.

Shea, K. J.,
Total Synthesis of (+)-Adrenosterone

Scheme 43. Our enantioselective synthesis of (+)-adrenosterone (278).

Shea, K. J.,

Total Syntheses of Plocamium monoterpenes, ledol and ledene

insect antifeedant property
cyclohexane with 3 stereocenters and halogens

Scheme 44. Our synthesis of Plocamium monoterpene 280.

Scheme 45. Our synthesis of ledol (286) and ledene (287).

Shea, K. J.,
Total Synthesis of CP-264,114 (racemic)

cholersterol-lowering and anticancer agents
bicyclo[4,3,1]decene ring system

Nicolaou, K. C.,
Total Synthesis of CP-264,114 (asymmetric)

Nicolaou, K. C.,
Type II intramolecular Diels-Alder reaction
- provides bridgedhead alkenes
- access to other compounds through disposable tethers, bridged to fused interchange, and ring expansion
- the most useful synthetic method for forming 7, 8-membered rings embedded in the bicyclic structure
- used in natural product synthesis
Thank you
Quiz!

(26) 

35 \[\xrightarrow{\text{Et}_2\text{AlCl}, \text{CH}_2\text{Cl}_2, 21^\circ\text{C, 1 h, 90\%}}\] 36 \[4:1\] 37

(27) 

110 \[\xrightarrow{\text{toluene, 8 h, 190^\circ\text{C, 93\%}}}\] 111 \[3:7\] 112

(26) 

267 \[\xrightarrow{\text{EtAlCl}_2 (1 \text{ equiv}) \text{ py (0.1 equiv)}}\] 268

1) m-CPBA
2) TFAA, Et₃N

267 \[\xrightarrow{\text{CH}_2\text{Cl}_2, 0^\circ\text{C, 63\%}}\] 268

269
Quiz!