Total Synthesis of Ingenol

1. Introduction

Structural Features and Synthetic Challenges
1) Trans-fused bicyclo[4,4,1]undecane ring
2) Highly strained inside-outside intrabridgehead stereochemistry of the BC ring
3) cis-triol segment located on upper face

Comparison of Ingenol and Isoingenol

<table>
<thead>
<tr>
<th>Structure</th>
<th>Ingenol</th>
<th>Isoingenol</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Ingenol structure" /></td>
<td><img src="image2" alt="Isoingenol structure" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ΔErel (kcal/mol)</th>
<th>5.9</th>
<th>0</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>First total synthesis (yeah)</th>
<th>2002</th>
<th>1988 (Paquete, L. A.)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Biological activity</th>
<th>tumor promoting etc.</th>
<th>no activity</th>
</tr>
</thead>
</table>

2. What's In/Out chemistry?

3. Synthesis of Ingenane core

4. Tanino & Kuwajima’s total synthesis

5. Summary
Natural source
*Euphorbia Ingens* (Hecker, E. et al., Cancer Res. 1968, 28, 2338)

Bioactivity
Tumor promoting, antileukemic, and anti-HIV properties (activation of PKC)

Biosynthesis

Although no details are known, a 1,2-alkyl shift (ex. Wagner-Meerwein rearrangement) connects tiglanes to ingenanes.

History
1) Ingenol was isolated by Hecker, E. and co-workers in 1968

2) Zeckmeister, K. and co-workers determined its structure by X-ray crystallography in 1970

3) Synthetic approach to Ingenol

4) Total synthesis of Ingenol
   Winkler, J. D. .................................. 2002 (*J. am. Chem. Soc.*)

5) Synthetic Studies toward 13-Oxyingenol
   Kigoshi, H. ...................................... 2011 (*Org. Lett.*)

now (2011)
2. What's In/Out chemistry?

Angle Definition
C-H in : $0^\circ < \theta < 90^\circ$
C-H out : $90^\circ < \theta < 180^\circ$

Table 1. MM2 Calculated Steric Energies of Lowest Energy Conformations of Bicyclic Hydrocarbons (in kcal/mol)

<table>
<thead>
<tr>
<th>bicyclic hydrocarbon</th>
<th>out,out</th>
<th>in,out</th>
<th>in,in</th>
</tr>
</thead>
<tbody>
<tr>
<td>bicyclo[3.2.2]nonane</td>
<td>24.25</td>
<td>81.43</td>
<td></td>
</tr>
<tr>
<td>bicyclo[3.3.1]nonane</td>
<td>18.26</td>
<td>64.43</td>
<td></td>
</tr>
<tr>
<td>bicyclo[4.2.1]nonane</td>
<td>24.36</td>
<td>68.04</td>
<td></td>
</tr>
<tr>
<td>bicyclo[5.1.1]nonane</td>
<td>46.75</td>
<td>87.44</td>
<td></td>
</tr>
<tr>
<td>bicyclo[3.3.2]decane</td>
<td>29.95</td>
<td>66.78</td>
<td>130.17</td>
</tr>
<tr>
<td>bicyclo[4.2.2]decane</td>
<td>29.60</td>
<td>67.14</td>
<td></td>
</tr>
<tr>
<td>bicyclo[5.2.1]decane</td>
<td>30.10</td>
<td>50.90</td>
<td></td>
</tr>
<tr>
<td>bicyclo[4.3.1]decane</td>
<td>24.20</td>
<td>48.30</td>
<td></td>
</tr>
<tr>
<td>bicyclo[3.3.3]undecane</td>
<td>37.28</td>
<td>70.17$^b$</td>
<td>119.57</td>
</tr>
<tr>
<td>bicyclo[4.3.2]undecane</td>
<td>37.26</td>
<td>56.15</td>
<td>107.83</td>
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<tr>
<td>bicyclo[5.2.2]undecane</td>
<td>38.22</td>
<td>53.96</td>
<td></td>
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<td>bicyclo[4.4.1]undecane</td>
<td>27.19</td>
<td>37.52</td>
<td>62.23</td>
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<tr>
<td>bicyclo[5.3.1]undecane</td>
<td>26.19</td>
<td>37.52</td>
<td>63.93</td>
</tr>
<tr>
<td>bicyclo[4.3.3]dodecane</td>
<td>48.60</td>
<td>55.80</td>
<td>93.45</td>
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<tr>
<td>bicyclo[4.4.2]dodecane</td>
<td>44.09</td>
<td>51.43</td>
<td>84.68</td>
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<tr>
<td>bicyclo[5.3.2]dodecane</td>
<td>43.75</td>
<td>48.47</td>
<td>86.46</td>
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<tr>
<td>bicyclo[5.4.1]dodecane</td>
<td>32.98</td>
<td>33.99</td>
<td>48.02</td>
</tr>
<tr>
<td>bicyclo[6.3.1]dodecane$^c$</td>
<td>43.43</td>
<td>50.53</td>
<td></td>
</tr>
<tr>
<td>bicyclo[4.3.3]tridecane</td>
<td>58.35</td>
<td>54.81</td>
<td>82.43</td>
</tr>
<tr>
<td>bicyclo[5.3.3]tridecane</td>
<td>56.46</td>
<td>52.43</td>
<td>78.20</td>
</tr>
<tr>
<td>bicyclo[5.4.2]tridecane</td>
<td>48.00</td>
<td>46.51</td>
<td>67.33</td>
</tr>
<tr>
<td>bicyclo[5.5.1]tridecane</td>
<td>36.55</td>
<td>37.45</td>
<td>41.55</td>
</tr>
<tr>
<td>bicyclo[7.3.1]tridecane$^c$</td>
<td>32.50</td>
<td>31.34</td>
<td></td>
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<tr>
<td>bicyclo[4.4.4]tetradecane</td>
<td>68.66</td>
<td>56.45</td>
<td>71.92</td>
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<td>bicyclo[5.4.3]tetradecane</td>
<td>63.21</td>
<td>53.01</td>
<td>69.21</td>
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<tr>
<td>bicyclo[5.5.2]tetradecane</td>
<td>53.43</td>
<td>48.84</td>
<td>55.97</td>
</tr>
<tr>
<td>bicyclo[6.5.1]tetradecane</td>
<td>42.16</td>
<td>40.18</td>
<td>42.44</td>
</tr>
<tr>
<td>bicyclo[5.4.4]pentadecane</td>
<td>64.86</td>
<td>55.03</td>
<td>63.61</td>
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<tr>
<td>bicyclo[6.6.1]pentadecane</td>
<td>48.36</td>
<td>44.06</td>
<td>46.35</td>
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<tr>
<td>bicyclo[7.5.1]pentadecane</td>
<td>41.83</td>
<td>41.78</td>
<td>41.48</td>
</tr>
<tr>
<td>bicyclo[5.5.4]hexadecane</td>
<td>63.79</td>
<td>54.77</td>
<td>57.08</td>
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<tr>
<td>bicyclo[5.5.5]heptadecane</td>
<td>60.83</td>
<td>54.16</td>
<td>49.78</td>
</tr>
<tr>
<td>bicyclo[6.5.5]octadecane</td>
<td>57.88</td>
<td>50.81</td>
<td>45.61</td>
</tr>
<tr>
<td>bicyclo[6.6.6]eicosane</td>
<td>47.42</td>
<td>43.62</td>
<td>36.4</td>
</tr>
</tbody>
</table>

$^a$ All data is taken from reference 36 unless otherwise stated.
$^b$ Calculation by present authors.
$^c$ Data from ref 77.

out,out-isomers are strongly preferred for smaller bicyclic system

in,out-isomers become the most stable

in,in-isomers is most stable

Due to nonbinding interactions between methylene groups in the bridges, out,out-isomer is itself usually severely strained.
Amines

1,4-diazabicyclo-[2,2,2]-octane (DABCO, 41)
1,5-diazabicyclo-[3,3,3]-undecane (43)
1,6-diazabicyclo-[4,4,4]-tetradecane (10)

Transannular interactions involving inside functionally

By Barton-McCombie deoxygenation of in/out-substrate, unusual rearrangement was discovered.

\[ \text{in/out} \rightarrow \text{out/out} \]
Application of in/out chemistry

Proton is strongly caught, and not detached.

Inside-monoprotonated ion could not be deprotonated easily.

| Table 1. Calculated (B3LYP/6-311+G**/B3LYP/6-31G*) PA and pK_a Values |
|---------------------------------|----------------|----------------|----------------|
| **diamine** | **gas-phase PA** (kJ mol\(^{-1}\)) | **pK_a** (H\(_2\)O)\(^a\) | **pK_a** (MeCN)\(^b\) | **\(\Delta E(i)\)** (kJ mol\(^{-1}\)) | **\(\Delta E(i)\)** (kJ mol\(^{-1}\)) |
| 4a | 1028 | 11.9 | 16.1 | | |
| 4b | 1089 | 20.1 | 23.2 | | |

\(^{a\text{ Relative to Me}_2\text{N}, pK_a = 9.81.}^{b\text{ Relative to Me}_2\text{N}, pK_a = 17.61.}\)

| Table 2. Calculated (B3LYP/6-311+G**/B3LYP/6-31G*) PA and pK_a Values for diastereomers of 15,16-dimethyl-15,16-diazatricyclo[9.3.1.1\(5,9\)]hexadecane |
|---------------------------------|----------------|----------------|----------------|
| **diamine** | **gas-phase PA** (kJ mol\(^{-1}\)) | **pK_a** (H\(_2\)O)\(^a\) | **pK_a** (MeCN)\(^b\) | **\(\Delta E(i)\)** (kJ mol\(^{-1}\)) | **\(\Delta E(i)\)** (kJ mol\(^{-1}\)) |
| syn-RRRR | 1105 | 23.6 | 30.4 | 43 | -23 |
| anti-RRRR | 1022 | 9.8 | 16.7 | 16 | 33 |
| Syn-RRRS | 1091 | 21.4 | 28.0 | 36 | -18 |
| Anti-RRRS | 1025 | 10.4 | 16.9 | 13 | 24 |
| Syn-RSRR | 1082 | 19.9 | 25.8 | 41 | -3 |
| Anti-RSRR | 1071 | 19.1 | 25.4 | 45 | 13 |
| Syn-RSSR | 1107 | 24.5 | 30.9 | 93 | 24 |
| Anti-RRSS | 1031 | 10.9 | 17.8 | 2 | 7 |
| Syn-RSSR | 1093 | 21.5 | 26.9 | 59 | 2 |
| anti-RSSR | 1014 | 9.5 | 16.1 | -1 | 22 |

\(^{a\text{ Relative to Me}_2\text{N}, pK_a = 9.81.}^{b\text{ Relative to Me}_2\text{N}, pK_a = 17.61.}\)
Enantioselective epoxidation by threitol-strapped Manganese porphyrin

Background


The "picnic-Basket" Strategy

Scheme 1. Strategy for catalysis by "picnic-basket" porphyrins.

1,5-dicyclohexylimidazole binds to the unhindered face of the manganese porphyrin


Table 3. % ee from the Asymmetric Epoxidation of 4-Chlorostyrene and cis-β-Methylstyrene Catalyzed by Manganese Threitol-Strapped Porphyrrins: Effect of Added Pyridine or 4-tert-Butylpyridine

<table>
<thead>
<tr>
<th>catalyst</th>
<th>blank N</th>
<th>N</th>
<th>blank N</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out/Out 7</td>
<td>36</td>
<td>17</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Out/In   8</td>
<td>55</td>
<td>34</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>In/In    9</td>
<td>58</td>
<td>32</td>
<td>58</td>
<td>59</td>
</tr>
</tbody>
</table>

In three catalyst, in/in - isomer 9 is the most effective asymmetric catalyst.

The function of the bridge is to pull the threitol rings closer to the center of the macrocycle.

Table I. Asymmetric Epoxidation of Aromatic Olefins with 9 (Yields are based upon iodosylbenzene.)

<table>
<thead>
<tr>
<th>substrate</th>
<th>reaction $T$, $^\circ$C</th>
<th>yield, %$^b$</th>
<th>ee, %$^c$</th>
<th>configuration$^d$</th>
<th>best reported ee, %$^r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clphenylethylene</td>
<td>25</td>
<td>86</td>
<td>69</td>
<td>$R(\pm)$</td>
<td>53$^f$</td>
</tr>
<tr>
<td>phenylethylene</td>
<td>25</td>
<td>82</td>
<td>70</td>
<td>$R(\pm)$</td>
<td>51$^f$</td>
</tr>
<tr>
<td>Clphenylethylene</td>
<td>25</td>
<td>65$^t$</td>
<td>79</td>
<td>($-\gamma)$</td>
<td>16$^r$</td>
</tr>
<tr>
<td>Clphenylethylene</td>
<td>25, 0</td>
<td>89, 76</td>
<td>77, 80</td>
<td>1$R,2S(\pm)$</td>
<td>92$^l$</td>
</tr>
<tr>
<td>Clphenylethylene</td>
<td>25, 0</td>
<td>85, 67</td>
<td>84, 87</td>
<td>1$R,2S(\pm)$</td>
<td>83$^l$</td>
</tr>
<tr>
<td>Clphenylethylene</td>
<td>25, 0</td>
<td>26, 88</td>
<td></td>
<td>1$R,2S(\pm)$</td>
<td></td>
</tr>
<tr>
<td>Clphenylethylene</td>
<td>25, 0</td>
<td>81, 21</td>
<td>1$S,2S(\pm)$</td>
<td>56$^l$</td>
<td></td>
</tr>
</tbody>
</table>
Lonepair inversion in simple trialkylphosphines require 29-36 kcal/mol, which corresponds to very slow process at room temperature. It is established that the species responsible for the two signals are in equilibrium. 31P NMR and 31P EXSY experiment established that the species resposible for the two signals are in equilibrium.

\( \text{strong peak: } \text{in,in-} \rightarrow \text{weak peak: } \text{out,out-} \)

**Figure 1.** 31P\(^1\)H NMR spectrum of 2 in [D\(_8\)]toluene at \(-80^\circ\)C (the arrows denote exchanging species; * and ** denote unknown and known impurities, respectively).
in,out-2 exhibited a single signal in the $^{31}\text{P}$ NMR spectrum at -50 °C. But at -90 °C, two signals were observed. This implies that a degenerate in,out/out,in homeomorphic isomerization is rapid on the NMR time scale.

Figure 2. Low-temperature $^{31}\text{P}[{^1}\text{H}]$ NMR spectra of in,out-2.
3. Synthesis of Ingenane core

**Winkler's route**

[2+2] photocycloaddition

**Funk's approach**

Ireland-Claisen rearrangement

Kigoshi, Wood's route

ring-closing olefin metathesis

Rigby's approach

[1,5]-hydrogen shift

**Winkler's route**

1. **11 steps**
   - **1**: (±)-Ingenol
   - **2**: [2+2] photocycloaddition
   - **3**: Retro-aldol fragmentation

**Funk's approach**

1. **5 steps**
   - **5**: (+)-3-carene
   - **6**: (-)-3-carene

2. **27 steps**
   - **7**: LDA (2 eq), HMPA
   - **8**: 1) HF, CH₃CN
   - **9**: 2) KOH

**Ireland-Claisen rearrangement**

DCC, DMAP 78% (3 steps)
Rigby’s approach

\[
\begin{align*}
\text{Cl} & \xrightarrow{\text{MgBr}} \text{13} \\
& \xrightarrow{\text{PhH, } \Delta} \text{14} \\
& \xrightarrow{\text{[6+4] cycloaddition}} \text{15} \\
& \xrightarrow{\text{8 steps}} \text{16} \\
& \xrightarrow{\text{Pd(OAc)}_2 (0.2 \text{ eq})} \text{PPh}_3, \text{Et}_3\text{N} \\
& \text{toluene, reflux} \\
& \xrightarrow{\text{80%}} \text{17} \\
& \xrightarrow{\text{KH, THF, 18-crown-6}} \text{18} \\
& \xrightarrow{0^\circ \text{C, 69%}} \text{17} \\
& \xrightarrow{\text{[1,5]-hydrogen shift}} \text{16}
\end{align*}
\]

Wood’s Route

\[
\begin{align*}
\text{19} & \xrightarrow{\text{BF}_3\cdot\text{OEt}_2} \text{20} \\
& \xrightarrow{\text{PhH, } \Delta} \text{21} \\
& \xrightarrow{\text{Ring-opening metathesis}} \text{22} \\
& \xrightarrow{\text{4 steps}} \text{23} \\
& \xrightarrow{\text{Ring-closing metathesis}} \text{25} \\
& \xrightarrow{\text{PhH, } \Delta} \text{24} \\
& \xrightarrow{17 \text{ steps}} \text{23}
\end{align*}
\]

Prepared in 10 steps from a chiral terpene

\[
\begin{align*}
\text{Mes} & \xrightarrow{\text{Ru cat.}} \text{25}
\end{align*}
\]

\[
\begin{array}{c}
\text{Ring-opening metathesis} \\
\text{Ring-closing metathesis}
\end{array}
\]

Ingenol
4. Tanino & Kuwajima's total synthesis of Ingenol

Synthetic strategy

6: Prepared in 4 steps

11 steps

14: Nicholas reaction

5 steps

15

18 steps

16: Pinacol rearrangement

17

OH

OMe

OTES

Br

OMe

OTES

CO2t-Bu

OH

OMe

OTES

OH

OMe

OTES

Br

OMe

OTES

OH

OMe

OTES

Br

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**Dicobalt hexacarbonyl complex**

(i) **Introduction**

Organocobalt compounds in organic synthesis have three characteristic reactions.
A) A high affinity to C-C π-bonds or C-N π-bonds.
B) A high affinity to carbonyl groups.
C) Easily tending to form square-planar bipyramidal six-coordination structures at the square-planar position, and to bond with one or two carbon atoms at axial position.

Nicholas reaction, Pauson-Khand reaction and [2+2+2] cyclization are based on character A. (Pauson-Khand reaction is also based on character B)

(ii) **Nicholas reaction (character A)**

The cation at the β-position of the cobalt is stabilized by dicobalt hexacarbonyl acetylene moiety.

Ref: Mayr et al., *JACS*, 1998, 120, 900
Model study of Nicholas reaction

CH$_2$Cl$_2$

1) Li, liq NH$_3$
   67% (2 steps)

2) CHBr$_3$, aq. NaOH
   Br$_2$
   71%

14

Me$_3$CuLi$_2$, Et$_2$O; MeI, 95%

TBHP, Ti(OrPr)$_4$

MS$_4$A, CH$_2$Cl$_2$

18

15
Construction of ABCD ring by pinacol rearrangement

1) \[ \text{tBuO(Me}_2\text{N)}_2\text{CH, DMF} \atop 100 \, ^\circ \text{C} \]
2) DIBAL, \( \text{CH}_2\text{Cl}_2, \text{MeI} \) THF, 98% (2 steps)
3) \[ \text{NaBH}_4, \text{EtOH}, 95\% \]

Introduction of hydroxyls for tetraol 28

1) \[ \text{DIBAL, CH}_2\text{Cl}_2 \]
2) \[ \text{TFAA, 2,6-lutidine DBU, CH}_2\text{Cl}_2, 83\% (2 steps) \]

1) \[ \text{TBAF, THF, 100\%} \]
2) \[ \text{PDC, CH}_2\text{Cl}_2, 97\% \]

Dead End

Retro-Aldol
By repeating 9 times of this sequence
5. Summary

Total synthesis of Ingenol
Winkler, J. D. [2+2]-photocycloaddition
  racemic total synthesis - 43 steps, 0.007% yield

Tanino, K. and Kuwajima, I. Nicholas reaction and pinacol rearrangement
  racemic total synthesis - 45 steps, 0.03% yield

Wood, J. L. ring-closing metathesis
  asymmetric synthesis - 35 steps, 0.002% yield