A Unified Approach for the Enantioselective Synthesis of the Brominated Chamigrene Sesquiterpenes

Reporter: Huanping Xie
Checker: Xiang Gao
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- Asymmetric total synthesis of elatol (高凹顶藻醇)
- A unified approach for the brominated chamigrene sesquiterpenes
- Summary
Assistant Professor in Stanford University.

- Selective halogenation of organic molecules: chemo-, regio-, and enantioselective dihalogenation and halo-functionalization reaction.
- Practical total synthesis of natural products, construction of unusual lipids with unanswered questions.

Education:
B.A., 2004, Columbia University, Prof. James Leighton;
Ph.D., 2009, The Scripps Research Institute, Prof. Phil S. Baran.

Research experience:
NIH Postdoctoral Fellow, 2009-2012, Harvard University, Prof. Eric Jacobsen;
Terman Fellow, 2013-2016, Stanford University.

Noah Z. Burns
Introduction

Brominated chamigrene sesquiterpenes

1: Bromocyclohexane motif >300 natural products
2: Br-Chamigrene sesquiterpenes >50 natural products

3: (-)-α-Br-Chamigrene
4: (+)-β-Br-Chamigrene
5: Rhodolauradiol
6: (+)-Elatol

Structure of elatol

- Densely functionalized;
- **A ring** bears three stereocenters:
  - including an all-carbon quaternary stereocenter, which is vicinal to a second, nonstereogenic quaternary carbon;
- **B ring** contains a fully substituted chlorinated olefin.
Retrosynthetic analysis

Synthesis of carbonate for ADA reaction

Asymmetric Decarboxylative Allylation
**Conditions:**
(a) HCO$_2$H, Pd(OAc)$_2$ (10 mol %), 15 (12.5 mol %), MS 4 Å, benzene, 40 °C;
(b) Pd(dmdba)$_2$ (10 mol %), 15 (13 mol %), benzene, 40 °C.

Possible reasons for low yield:
- ✗ Slow oxidative addition
- ✗ Slow decarboxylation
- ★ Slow allylation

Control experiments

>99% conversion
99:1 Protonation:Allylation by $^1$H NMR

X = Cl, 13
X = H, 16

X = Cl, 17
X = H, 18

>99% conversion by $^1$H NMR
Synthesis of carbonate for ADA reaction


\[
\begin{align*}
\text{Org. Lett.} & \quad 2007, \quad 9, \quad 2529.
\end{align*}
\]
Synthesis of elatol

\[ (+)-9 \xrightarrow{\text{Grubbs II, 97\% yield}} (+)-8 \xrightarrow{i-\text{BuO}} (+)-Laurencenone B \]

\[ \text{Br}_2, 48\% \text{ HBr (aq)}, \text{AcOH, 23 \degree C} \]

\[ 8:1 \text{ dr} \xrightarrow{\text{DIBAL-H, THF, -78-60 \degree C}} \]

\[ (+)-Elatol (6) \]

32\% yield, (two steps)
Synthesis of the chamigrene sesquiterpenes

Retroynthetic analysis

Enantioenriched Dihalide Solvolysis

Synthesis of bromocyclohexane motif

Asymmetric Bromochlorination

(R,S)-V (20 mol%) NBS, CI Ti(OiPr)_3

(66%, 94% ee)
scale = 4.4 g

1) Tf_2O, 2,6-lut.
2) L-selectride
3) Ac_2O, Et_3N, DMAP

46% yield (3 steps)

K_2CO_3, HFIP
(54%, 90% ee)
scale = 1.4 g
96% enantiospecificity

Synthesis of the chamigrene sesquiterpenes

29 → a) SOCl₂, Et₃N → 62% yield (2 steps)
    + b) RuCl₃, NaIO₄ → 30 → c) DBU → 31

32 → Me₂AlCl → 52% yield

33 + 34 → 12% yield
Synthesis of the chamigrene sesquiterpenes

33

\[ \text{Mg}^0, \text{TiCl}_4, \text{THF, CH}_2\text{Cl}_2 \]

\[ \text{MeMe} \]

\[ \text{d} \]

\[ \text{Br} \]

\[ \text{Cl} \]

\[ \text{Mg} \]

\[ \text{THF} \]

\[ \text{22} \]

\[ \text{e) SeO}_2 (42\%) \]

\[ \text{f) IBX (87\%)} \]

\[ \text{33} \]

\[ \text{O} \]

\[ \text{MeMe} \]

\[ \text{MeMe} \]

\[ \text{Me} \]

\[ \text{Br} \]

\[ \text{22} \]

\[ \text{20: (-)-Dactylone} \]

34

\[ \text{h) MeLi, CeCl}_3 \]

\[ \text{i) SOCl}_2, \text{Et}_3\text{N} \]

\[ \text{MeMe} \]

\[ \text{Br} \]

\[ \text{34} \]

\[ \text{Me} \]

\[ \text{3: (-)-\(\alpha\)-Br-chamigrene} \]

\[ \text{4: (-)-ent-\(\beta\)-Br-chamigrene} \]

\[ \text{1.5:1 (4/3)} \]

\[ \text{78\% overall) \]
Synthesis of the chamigrene sesquiterpenes

20: (−)-Dactylone

21: (+)-Aplydactone
### Irradiation induced [2+2] cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>hv</th>
<th>t</th>
<th>Conv. [%]/(Yield [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>254 nm</td>
<td>15 min</td>
<td>100/(7&lt;sup&gt;[a]&lt;/sup&gt;)</td>
</tr>
<tr>
<td>2</td>
<td>benzene</td>
<td>350 nm</td>
<td>20 h</td>
<td>85/(85)</td>
</tr>
<tr>
<td>3</td>
<td>benzene</td>
<td>350 nm</td>
<td>36 h</td>
<td>100/(98&lt;sup&gt;[b]&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Yield based on 1H NMR with 1,4-dinitrobenzene as an internal standard. <sup>[b]</sup> Yield of the isolated product.
Summary

- 9 Steps, 11% overall yield
- Asymmetric allylation
- Ring-closing metathesis


- 22 and its three analogues
- Asymmetric dihalide solvolysis
- D-A reaction

Of the roughly 300 natural products containing a bromocyclohexane motif 1 that have been isolated and structurally characterized, more than 50 are represented by the brominated chamigrene sesquiterpenes 2. Most members of this family differ in their level of saturation, halogenation, and oxygenation. The structural variety within the halogenated chamigrenes is complemented by diverse biological activities, including antibacterial, antifungal, antiviral, anthelmintic, and anticancer effects.
To date, the total synthesis of (+)-elatol (6) by Stoltz, Grubbs, and co-workers constitutes the only catalytic enantioselective synthesis of a member of the halogenated chamigrene sesquiterpenes. A general catalytic enantioselective approach for the synthesis of this class of molecules has yet to be reported. Along these lines, we set out to develop a strategy that would enable the rapid construction of the spirocyclic core and thus facilitate elaboration to structurally disparate members of this family of small molecules for further chemical and biological investigations.
The enantioselective total synthesis of (-)-α- and (-)-ent-β-bromo-chamigrene, and (+)-aplydactone was enabled by the gram-scale enantiospecific solvolytic cyclization of an enantiomerically enriched bromochloride. Access to this interhalogenated motif was enabled by the highly chemo-, diastereo-, and enantioselective titanium-based bromochlorination of allylic alcohol 10. This study highlights a highly general approach to the halogenated chamigrene sesquiterpenes, and we anticipate that it will find use in the synthesis of additional members of this class. Studies along those lines as well as a comprehensive investigation into the solvolytic cyclization of enantiomerically enriched dihalides are in progress and will be reported in due course.
Fluorinated PHOX in allylation

## Reaction optimization

![Chemical structures and reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%) 36+37</th>
<th>36:37</th>
<th>Ee (36), Ee (37) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 mol % II, CH$_2$Cl$_2$, r.t.</td>
<td>88</td>
<td>1:2</td>
<td>6, 8</td>
</tr>
<tr>
<td>2</td>
<td>50 mol % III, CH$_2$Cl$_2$, r.t.</td>
<td>73</td>
<td>1:2</td>
<td>12, 6</td>
</tr>
<tr>
<td>3</td>
<td>50 mol % IV, CH$_2$Cl$_2$, r.t.</td>
<td>89</td>
<td>1:1</td>
<td>17, 0</td>
</tr>
<tr>
<td>4</td>
<td>50 mol % V, CH$_2$Cl$_2$, r.t.</td>
<td>67</td>
<td>1:1</td>
<td>63, 6</td>
</tr>
<tr>
<td>5</td>
<td>50 mol % V, hexanes, r.t.</td>
<td>70</td>
<td>8:1</td>
<td>94, 52</td>
</tr>
<tr>
<td>6</td>
<td>50 mol % V, hexanes, -20 °C</td>
<td>80</td>
<td>20:1</td>
<td>98, -</td>
</tr>
<tr>
<td>7</td>
<td>10 mol % V, hexanes, -20 °C</td>
<td>88</td>
<td>20:1</td>
<td>94, -</td>
</tr>
</tbody>
</table>

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Mechanism of methylenation

**Tebbe’s reagent**

\[ \text{Cp}_2\text{TiCl}_2 + 2 \text{Al(CH}_3)_3 \rightarrow \text{Cp}_2\text{TiH} \rightarrow \text{CH}_4 + \text{Cp}_2\text{Ti=CH}_2 \]

\[ \text{Cl-Al(CH}_3)_2 \quad \leftrightarrow \quad \text{Cl-Al(CH}_3)_2 + \text{Cp}_2\text{Ti=CH}_2 \]

\[ \text{Cp}_2\text{Ti=CH}_2 \quad \rightarrow \quad \text{Cp}_2\text{TiCH}_2 \quad \rightarrow \quad \text{R}R^1 \quad + \quad \text{Cp}_2\text{Ti=O} \]

**CH}_2\text{Cl}_2 Activation Promoted by MgTi-Bimetallic Complexes**

\[ \text{TiCl}_4 \quad \xrightarrow{\text{Mg}} \quad \text{(THF)}\text{n-TiMgCl}_x \quad \rightarrow \quad \text{Cl-Ti-Mg} \quad \text{THF} \quad \text{Cl}_2\text{Cl}_2 \]

Thanks for your kind attention!