Total Synthesis of (-)-Pepluanol B: Conformational Control of the Eight-Membered-Ring System

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- Pepluacetal and Pepluanol A-D are family of *Euphorbia diterpenoids*
- These five diterpenoids were isolated from the plant *E. peplus* in 2016
- Effective inhibitory activity for asthma, type-1 diabetes, multiple sclerosis
- Pepluanol B (3) comprises unique fused polycyclic skeletons with six to eight stereogenic centers


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Total synthesis presentation
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Retrosynthetic Analysis of the (-)-Pepluanol B

[Chemical Structures and Reactions Diagram]
Step 1

1) 5 mol% Pd(OAc)$_2$, Pb(OAc)$_4$
AcOH, 1.5 d, rt
2) NaOH, MeOH
70% over 2 steps

(±)-10

Step 2: acetate to alcohol

MeOH + $\text{O}^-$ OH $\leftrightarrow$ MeO$^-$ + H$_2$O

R-OH
Step 4 mechanism: Swern Oxidation

Steps 5-7: Eschenmoser methylenation
Step 8: double bond isomerization

Steps 9 and 10
Step 16 mechanism: Ley–Griffith oxidation
Step 18

Step 19: PMB deprotection
Step 21

17 \[\text{TMMN, Ac}_2\text{O, DMF} \rightarrow 18 \quad 96^\circ\text{C, 75\%}\]

18 \[\text{20 mol\% RhCl}_3\cdot 3\text{H}_2\text{O} \rightarrow 19 \quad 52\%\]
Step 23

Step 24

- NBS, pyridine, then DMP, 95%
- LDA, Mel, 72%
backwards addition

Step 27

27) Zn-Cu. Et₂OH, sat. NH₄Cl, 93%

28) TMMN, Ac₂O, DMF, 95 °C, 93%

29) RhCl₃·3H₂O, 20 mol%, 60% brsm

(−)-Pepluanol B, 3

94% ee

[α]D²⁵ = -90.0 (c 0.1 MeOH)

lit. [α]D²⁵ = -29.8 (c 0.1 MeOH)