**Synthesis of Substituted 1,4-Dienes by Direct Alkylation of Allylic Alcohols**

**Total Synthesis and Structure Elucidation of (+)-Phorbasin C**

**Total Synthesis of Lehualide B by Allylic Alcohol-Alkyne Reductive Cross-Coupling**

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1996
BS Chemistry
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PhD Chemistry - William Roush
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Current Methods for Allylic Alkylation

**Copper-Catalyzed Asymmetric Allylic Substitution**

\[
\text{PhCH=CHCl} \xrightarrow{\text{MeMgBr, CuBr (3 mol %) \ ligand (3.3 mol %)}} \text{PhCH=CHMe} \quad 96\% \text{ ee}
\]

(+)-naproxen, 93% ee


**Coupling of Alkynes with Allylic Alcohols to Generate Unsaturated Ketones**

\[
\text{Ph-} \equiv \equiv \text{Ph} + \text{MeO-} \equiv \equiv \text{Me} \xrightarrow{\text{10 mol % catalyst}} \text{Ph-} \equiv \equiv \text{MeO-} \equiv \equiv \text{Me} \quad 50\%
\]

catalyst = [Ru]-Cl


**Iridium-Catalyzed Allylation of Enamines**

\[
\text{MeO}_2\text{CO-} \equiv \equiv \text{Ph} + \text{Ph-} \equiv \equiv \text{N} \xrightarrow{\text{1. 5 mol % ligand}} \text{Ph-} \equiv \equiv \text{N} \xrightarrow{\text{2. NaOAc/AcOH, H}_2\text{O}} \text{Ph-} \equiv \equiv \text{Ph}
\]

76% 99:1 branched to linear 96% ee

Methods for Synthesis of Skipped Dienes

Olefination Reactions for the Generation of 1,4-Dienes

\[
\text{CH}_2=\text{C} \left(\text{Me}\right)\text{Me} + \text{PhNNNN} \xrightarrow{\text{LiHMDS, DME}} \text{Li}\text{Me}\text{Me} \text{Me} \xrightarrow{-78 \degree C} \text{Me} \text{Me} \text{Me} \text{Me}
\]

73%, Z:E = 98:2


Synthesis of Z,Z-Skipped Dienes

\[
\text{C}_9\text{H}_9\text{I} \xrightarrow{1. \text{2 EtMgBr, THF}, 2. \text{CuCN}} \text{C}_9\text{H}_9\text{C}_5\text{H}_9\text{CO}_2\text{H}
\]

60%


Thermal Rearrangements of Vinylcyclopropanes

\[
\text{R}_3\text{Si} \xrightarrow{\text{toluene}, 110 \degree C} \text{R}_3\text{Si}\text{H}_2\text{H}_2\text{H}
\]

96%

Synthesis of Substituted 1,4-Dienes by Allylic Alkylation

1. $\text{CITi(OiPr)}_3$, $\text{C}_3\text{H}_9\text{MgCl}$, toluene, -78 to -35 °C
2. add allylic alkoxide

Both 5- and 6-membered rings could be utilized

Exocyclic alkenes were tolerated

C-C bond formation occurs in a suprafacial manner across the allyl system

Tertiary alcohols could be used to generate trisubstituted alkenes

Reactions with stereodefined allylic alcohols proceed with minimal stereochemical erosion

$er = 97:3$

$er = 96:4$

$dr \geq 20:1$
Coupling of Acyclic Allylic Alcohols and Alkynes

1. \( \text{CITi(OiPr)}_3, \text{C}_5\text{H}_9\text{MgCl, toluene, -78 to -35 °C} \)

2. add allylic alkoxide

**primary allylic alcohols couple efficiently with more substituted coupling partners**

**substitution can be introduced on neighboring methylene utilizing substituted tertiary allylic alcohols**

**tetrasubstituted olefins can be prepared using this method**

**secondary allylic alcohols generate an additional stereodefined double bond, but with no stereoselection for the unsubstituted case**

**1,1-disubstituted alcohols produce 1,4 dienes with a stereodefined trisubstituted \( Z \) olefin**
Additional Scope of Coupling Reaction

1. ClTi(OiPr)_3, C_5H_9MgCl, toluene -78 to -35 °C
2. add allylic alkoxide

PhCH=CH + PhTMS \rightarrow \text{unsymmetrical alkynes couple regioselectively}

\text{neighboring unsaturation in allylic alcohol is tolerated}

R_1 = \text{Me}, R_2 = \text{H}, 59\%, E:Z = 8:1
R_1 = \text{H}, R_2 = \text{Me}, 67\%, E:Z = 1:1

Z-disubstituted olefins couple with higher selectivity than E-olefins

control by minimization of A1,2 strain

control by minimization of A1,3 strain
The lehualides are a family of pyrone-containing natural products isolated from a Hawaiian sponge *Plakortis* sp.

Lehualide B shows nanomolar inhibition of IGROV-ET ovarian cancer cell proliferation, while its isomer lehualide A was inactive.

The lehualides share structural similarities with the peiricidins, which are inhibitors of mitochondrial electron-transport chain Complex I.

There are no stereocenters in lehualide B, but it possesses a synthetically challenging skipped diene with two trisubstituted alkenes.
Retrosynthetic Analysis of Lehualide B

Lehualide B

Reductive Cross-Coupling

Claisen rearrangement and \( \text{H}_2\text{C} = \text{C(Me)}\text{MgCl} \)
Synthesis of Allylic Alcohol Coupling Precursor

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{Phl(OAc)}_2, \text{BF}_3 \cdot \text{OEt}_2} \quad \text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{MeOH}} \quad 70\%
\]

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{LDA (2.2 equiv), MeCONMe}} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad 24\% \text{ over two steps}
\]

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{mCPBA, then } \text{NET}_3} \quad 94\%
\]

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{LiHMDS, then } \text{MeCSePh}} \quad 78\%
\]

\[
1. \text{Hg(OOCOCF}_3) \quad \xrightarrow{\text{MeOH}} \quad 90\%
2. \text{Toluene, 150 °C}
\]

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{Claisen rearrangement}} \quad \text{E:Z = 10:1}
\]

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{THF, -78 to -25 °C}} \quad 59\%
\]

\[
\text{Me}_2\text{C} = \text{O} \quad \xrightarrow{\text{THF, -78 to -25 °C}} \quad 59\%
\]
**Reductive Coupling Endgame of Lehualide B**

LiHMDS (2.5 equiv) THF, -78 °C

pyrone was masked as dianion to prevent reactivity at the carbonyl group

natural product was obtained in a 50% yield from reductive coupling, but relative ratio of regioisomers was only 1.3:1

*lehualide B*
Reductive Coupling Endgame of Lehualide B

LiHMDS (2.5 equiv) THF, -78 °C

TMS—≡—Me

CITi(OiPr)_3, c-C_5H_9MgCl toluene, -78 to -40 °C 61%

1. NIS, ClCH_2CN:EtOAc (2:1), 93%
2. BnZnBr, Pd(PPh_3)_4 THF, rt, 68%

Z:E = 7:1

E:Z ≥ 20:1 rs ≥ 20:1
The phorbasins are a class of diterpenes isolated from the Australian marine sponge *Phorbas* sp. Structurally related to carvotacetone monoterpenes and carvone. The phorbasins demonstrate growth inhibitory activity against Gram positive bacteria such as *Staphylococcus aureus* and *Micrococcus luteus*, as well as selective growth inhibition of several human cancer cell lines (e.g., A549 lung adenocarcinoma, HT29 colorectal adenocarcinoma). The relative stereochemistry of all of the phorbasin family members at C11 is undefined, while the absolute stereochemistry was assigned based on analysis of the CD spectra.
Retrosynthetic Analysis of (+)-Phorbasin C

**Phorbasin C**

**Suzuki-Miyaura Cross-Coupling**

**Reductive Cross-Coupling**

**2R or 2S**
Synthesis of Vinyl Iodide Coupling Partner

1. nBuLi, THF
2. Ti(OiPr)_4
3. c-C_5H_9MgCl, Et_2O

Me=\equiv\text{TMS}\quad\text{Me}\geq 20:1

Radical dehalogenation

1. VO(acac)_2, TBHP
2. (COCI)_2, DMSO
3. Ph_3P=CH_2, THF

Me=\equiv\text{TMS}\quad\text{dr} \geq 20:1

Swern oxidation and Witting olefination

1. Pd(PPh_3)_4
2. Ac_2O, pyridine
3. DMAP, CH_2Cl_2

Me=\equiv\text{TMS}\quad\text{dr} \geq 20:1

90% over two steps

1. NIS, CH_3CN, 77%
2. TFA, H_2O, THF
3. IBX, DMSO

Me=\equiv\text{TMS}\quad\text{AcO\quad\text{AcO}}

75% over two steps

1. Sc(OTf)_3
2. MeOH, H_2O

Me=\equiv\text{TMS}\quad\text{Me}\geq 20:1

80%
Synthesis of Vinyl Iodide Coupling Partner

1. DMSO, (COCl)_2, Et_3N, CH_2Cl_2
2. KHMDS, DME

OTHP

\( \text{MeOH, CH}_2\text{Cl}_2 \)

1. PTSA, MeOH, CH_2Cl_2
2. DMP, CH_2Cl_2, H_2O
3. CrCl_2, CH_3, THF

44% over three steps

\( E:Z \geq 20:1 \)

Takai olefination

51% over two steps

\( E:Z \geq 20:1 \)

Julia-Kocienski olefination

Mechanism of Modified Julia-Kocienski Olefination
Endgame of Synthesis and Structure Confirmation

\[ \text{Pd}(\text{PPh}_3)_4, \text{Ti}_2\text{CO}_3, \text{THF}, \text{H}_2\text{O} \]

\[ \text{Suzuki-Miyaura cross-coupling} \]

\[ [\alpha]^{20}_D +124 \, (c \, 0.18 \, \text{MeOH}) \]

\[ [\alpha]^{22}_D -131 \, (c \, 0.18 \, \text{MeOH}) \]

**phorbasin C**