Synthesis of Vitamin D (Calciferol)

Vitamin D - A Pluripotent Steroid Hormone

- Hormonally active metabolite of vitamin D
- Responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, modulating body defenses against microbial invaders by stimulating the innate immune system
- Application/potential application: rickets, renal osteodystrophy, osteoporosis, psoriasis, leukemia, breast cancer, prostate cancer, AIDS, CVD and Alzheimer’s disease

1α,25-dihydroxyvitamin D₃

rickets-symptom: absence of provisional calcification zone; cupping; rosary bead

Interaction network of VDR - Nuclear hormone receptor. Transcription factor

Metabolic pathway of vitamin D₃

7-Dehydrocholesterol (7-DHC)

General synthetic approach to 1α,25-dihydroxyvitamin D₃

Liver → 25-hydroxylase → 25-Hydroxyvitamin D₃ → Kidney → CYP27B1 → 1, 25-Dihydroxyvitamin D₃
Synthesis of Vitamin D (Calciferol)

**Method A: Photochemical Ring Opening**
Photochemical conversion of 7-DHC derivatives to previtamin D

![Reactions and structures](image)


***Introduction of the hydroxy group and Δ^7,8^-double bond***

![Reactions and structures](image)


**Method B: The Horner—Wittig Olefination**

![Reactions and structures](image)


The most practical approach to CD fragments is still the partial synthesis through D₃ degradation.

For synthesis of CD fragments, see appendix

**Diels-Alder Approach**

![Reactions and structures](image)

Synthesis of Vitamin D (Calciferol)

Binaphthol-Titanium promoted Diels-Alder Cycloaddition

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Michael addition-triflation

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me}
\end{align*}
\]


Other Synthesis

J. Org. Chem. 2002, 1580: Chiral pool, starting from (S)-carvone
Org. Lett. 2011, 86: Chiral pool, starting from (R)-carvone

Method C: Seco-A-Ring Tandem Palladium-Catalyzed Cyclization

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me}
\end{align*}
\]

Trost, J. Am. Chem. Soc. 1992, 9836
Synthesis of Vitamin D (Calciferol)

**Kinetic resolution of the racemic allylic alcohol**

\[
\text{H}_2\text{CO-CHO} + \text{Mg} ightarrow \text{H}_2\text{CO-CHO} + \text{MgBr} \
\text{1) CF}_3\text{CO}_2\text{H} \rightarrow \text{H}_2\text{CO-CHO} + \text{MgBr} \cdot 61\%
\]

**Catalytic enantioselective aldol reaction**

\[
\text{O}_\text{H} + \text{CH}_2\text{CHCHO} + \text{LDA} \rightarrow \text{O}_\text{H} + \text{CH}_2\text{CHCHO} + \text{nBuOH} \cdot 50\%
\]

**Noyori asymmetric hydrogenation**

\[
\text{Cl}_\text{CO}_2\text{Et} + \text{H}_2 + \text{RuCl}_2[(R)-BINA] \rightarrow \text{Cl}_\text{CO}_2\text{Et} + \text{Me}_3\text{Al} \cdot 96\%
\]

**Other similar disconnection strategies**

1. \([\text{PdCl}_2(\text{Ph}_3\text{P})_2], \text{K}_3\text{PO}_4\) \
2. \(\text{nBu}_4\text{NF}\)

**Trost, Tetrahedron Lett. 1994, 8119**

**Vandewalle, Synlett, 1999, 1435**
Synthesis of Vitamin D (Calciferol)

**Method D: A Plus CD Cross-Coupling Approaches**

Method D: A Plus CD Cross-Coupling Approaches

"Classic" carvone approach

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O₂, NaOH</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>1) O₃, MeOH</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>2) p-NO₂C₆H₄COCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) LiCH₂CO₂H</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>2) Pd(PPh₃)₄</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quinic acid approach

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO₂C₂OH</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>1) TBSCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) PhOC(S)Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₂N₂</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Alternative carvone approach

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₃/O₂, MeOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaHCO₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph₃P, NaHCO₃, DMAP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Desmaele, Tetrahedron Lett. 1985, 4941

Okamura, Tetrahedron Lett. 1987, 4947


Mourino, Tetrahedron Lett. 1988, 1203

Mourino, Tetrahedron Lett. 1986, 1523

Mourino, Tetrahedron. 1991, 3485

Srikrishna, Tetrahedron Lett. 2000, 3177
Synthesis of Vitamin D (Calciferol)

Method E: Mazur's Cyclovitamin D Solvolysis Approach

Wilson's Initial Approach

1) TSOH
2) hv

Wilson's New Approach

Wilson, Tetrahedron Lett. 1991, 2339

Wilson, Tetrahedron Lett. 1984, 3151

Wilson, Tetrahedron Lett. 1984, 3147

Wilson, Tetrahedron Lett. 1991, 2339
Synthesis of Vitamin D (Calciferol)

Alternative procedure for the intramolecular cyclopropanation

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad 1) \text{NB} \\
\text{Ph} = \text{CO}_2\text{NB} & \quad 2) \text{Phi(OAc)}_2 \\
\text{Cu}(\text{I})\text{Cl} & \quad 80\% \\
\text{Moriarty, } \text{Tetrahedron Lett.} \ 1993, \ 4129 \\
\text{Moriarty, } \text{J. Am. Chem. Soc.} \ 1989, \ 6443
\end{align*}
\]

Additional synthetic approaches

Julia olefination

\[
\begin{align*}
\text{Me} & \quad \text{R} \\
\text{Ts} & \quad \text{TBSO}\_\text{OTBS} \\
\text{Me} & \quad \text{R} \\
\text{Me} & \quad \text{Me} \\
\text{TBSO}\_\text{OTBS} & \quad \text{TBSO}\_\text{OTBS} \\
\text{H} & \quad \text{H} \\
\text{1) } \text{EtMgBr} & \quad 76\%
\end{align*}
\]

\[
\begin{align*}
\text{NaH} & \quad (\text{EtO})_2\text{P(O)}\text{Cl} \\
\text{60}\% & \quad \text{Me} \quad \text{R} \\
\text{Ts} & \quad \text{TBSO}\_\text{OTBS} \\
\text{Me} & \quad \text{Me} \\
\text{Ts} & \quad \text{TBSO}\_\text{OTBS} \\
\text{TBSO}\_\text{OTBS} & \quad \text{TBSO}\_\text{OTBS} \\
\text{H} & \quad \text{H} \\
\text{Lythgoe, } \text{J. Chem. Soc., Perkin Trans.} \ 1980, \ 1405
\end{align*}
\]

NHK reaction

\[
\begin{align*}
\text{Me} & \quad \text{R} \\
\text{OHC} & \quad \text{TBSO}\_\text{OTBS} \\
\text{CrCl}_2 & \quad \text{Me} \quad \text{R} \\
\text{Me} & \quad \text{Me} \\
\text{OHC} & \quad \text{H} \\
\text{TBSO}\_\text{OTBS} & \quad \text{TBSO}\_\text{OTBS} \\
\text{H} & \quad \text{H} \\
\text{HO} & \quad \text{HO} \\
\text{NH} & \quad \text{NH}
\end{align*}
\]

1) CuSO\text{4} on silica gel
2) HF/MeOH/THF

90\%

Jieyu Gu

Baran Group Meeting
10/13/18


Why vitamin D synthesis still worth studying?

- Calcitriol regulates numerous cellular pathways that could have a role in determining cancer risk and prognosis. It inhibits the proliferation and stimulates the differentiation of normal as well as malignant cells. - Front. Physiol., 2014, 122; Nature reviews cancer, 2014, 342

- \{1,25(OH)\text{2}D\text{3}\} induces DCs. Researchers have found that a short treatment with 1,25(OH)\text{2}D\text{3} induces tolerance to fully mismatched mouse islet allografts. - Journal of cellular biochemistry, 2003, 227

- In innate immune responses, activation of Toll-like receptors (TLRs) triggers direct antimicrobial activity against intracellular bacteria. It is reported that TLR activation of human macrophages up-regulated expression of the vitamin D receptor and the vitamin D-1--hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular Mycobacterium tuberculosis. - Science, 2006, 1770

- It has been shown that diminished levels of vitamin D induce immune-mediated symptoms in animal models of autoimmune diseases and is a risk factor for various brain diseases. - Psychoneuroendocrinology, 2009, S265

- Clinical studies have generally demonstrated an independent association between vitamin D deficiency and various manifestations of degenerative cardiovascular disease including vascular calcification. - Circulation research, 2014, 379

- Analogues: find molecules with clear dissociation between the beneficial effect and adverse calcemic side effects (e.g., hypercalcemia and hypercalciuria)
Synthesis of Vitamin D (Calciferol)

Appendix I

Synthesis of CD fragment
Synthesis of Inhoffen-Lythgoe Diol Derivatives

\[
\text{BzO} \quad \text{EtO} \quad \text{OEt} \\
\text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2
\]

1) KOH then CH₂N₂
2) tBuOK then TsOH
43%

\[
\text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2
\]

1) NaOCH₃
2) H₂C=CN(CH₃)₂OCH₃
72%

\[
\text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2
\]

1) CH₃MgBr
2) NaOH
75%

\[
\text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2 \quad \text{Me}\text{Me}\text{Me}_2
\]

Fujimoto. J. Am. Chem. Soc. 1951, 1856


Synthesis of Grundmann’s Ketone Derivatives

\[
\text{Me} \quad \text{Et} \quad \text{S} \\
\text{Me} \quad \text{Me} \quad \text{O}
\]

1) (CH₂O)n, BF₃•Et₂O
2) H₂, PdO₂
3) KOH
60%

Johnson. J. Am. Chem. Soc. 1984, 1138

1) LDA
2) BF₃•Et₂O
3) LiAlH₄
4) PCC


10/13/18

Baran Group Meeting
Synthesis of Vitamin D (Calciferol)

Appendix II

Approved Vitamin D derived drugs

- Calcipotriol
- Doxercalciferol
- Paricalcitol
- Tacalcitol
- Alfacalcidol
- Maxacalcitol

Anagolues after preclinical

Genomic mechanism of calcitriol action through the VDR

- Proliferation: Increase in p21 and p27 expression, Decrease in CDK4, cyclin D1, MYC, and RB expression
- Apoptosis: Increase in BAX, Decrease in BCL-2, Increased sensitivity to radiation and chemotherapy
- Differentiation: Myeloid leukemia cells differentiate into monocytes, Increased expression of differentiation factors such as c-myc, adhesion proteins, lipids, PSA, prostate differentiation factor and E-cadherin
- Inflammation: Inhibition of expression of COX2, IL-1, IL-6, IFN-γ, NFκB, IL-17, IL-18, and IL-19
- Invasion and metastasis: Increased expression of MMP3, plasminogen activator, matrix metalloproteinase-2, and E-cadherin
- Angiogenesis: Decreased expression of VEGF, IL-6, PSMA, and E-cadherin

Vitamin D metabolites and immune modulation

- Macrophage
- Dendritic Cell
- T Cell
- Endocrine Effect
- Autocrine Effect
- Paracrine Effect
- Modulation of Inflammatory and Innate Immune Response
- Tolerogenic Adaptive Immune Response