Dietary Supplements

Outline:
1. Natural products found in dietary supplements
2. Yohimbine syntheses:
   a) van Tamelen (1958)
   b) Stork (1972)
   c) Kuehne (1991)
   d) Aube (1994)
3. Huperzine A syntheses:
   a) Kozikowski (1989)
   b) Fukuyama (2009)
   c) Herzon (2011)
   d) White (2013)
4. Betaines in catalysis
   Corey forskolin synthesis
5. Vitamin chemistry:
   a) Vitamin D- C-H oxidations
   b) Vitamin C common transformations
6. Polyphenols syntheses
   a) Synthetic strategies
   b) Quadrugarin A (2006)
   c) Hopeahainol/Hopeanol A (2009)
7. Cannabinoid - supplement?
   Non-synthesis bonus - macronutrients

Some natural products that are key ingredients in dietary supplements:

- **Creatine**
  - Bodybuilding.com Foundation Series Micronized Creatine, 500 g, $9.99
  - 500 g, $110

- **Yohimbine**
  - Twinlab Yohimbe Fuel 80, 100 Capsules
  - ~400 mg, $9.15
  - 400 mg, $24.16 (HCl)

- **Carnitine (betaine)**
  - Bodybuilding.com Foundation Series L-Carnitine, 500 mg, $0.267
  - 500 mg, $18.95

- **Forskolin**
  - Livelong Nutrition 1.5 g, $16.7
  - 10 mg, $174

- **Huperzine A**
  - Source Naturals 12 mg, $10
  - 1 mg, $191

- **Sesamin**
  - 1 g, $0.33 maybe mixture
  - 5 mg, $330

- **DHEA**
  - 1.5 g, $4
  - 10 g, $11

- **Biotin**
  - 300 mg, $5
  - 500 mg, $40

- **Evdolamine**
  - 1 g, $1.04
  - 250 mg, $108.5

- **Ginkgoide B**
  - really cheap, mixture
  - 10 mg, $155

- **Fucosaxanthin**
  - 1 g, $2.14
  - 10 mg, $134
Dietary Supplements

Yohimbine Synthesis
van Tamelen, JACS 1958, 5006. (ref. to Woodward reserpine)

Kuehne. JOC 1991, 2701.

Aube, JACS 1994, 9009

Stork, JACS 1972, 5109

Wenkert, JACS 1982, 2244

Pyridinium reduction, Pictet-Spangler
Brown, TL 2000, 5627
Sugar SM, Pictet-Spangler
Jacobsen, OL 2008, 745
Asymmetric Pictet-Spangler, DA
Hiemstra, JOC 2011, 8907
Asymmetric Pictet-Spangler, DA
Dietary Supplements

Hang Chu

What it does:
- Improve memory/mental function
- Treatment for myasthenia gravis
- Potential treatment for Alzheimer's
- Toxicity:
  - Mild cholinergic effects

Some reviews of huperzine A products:
- ☑️ ☑️ ☑️ ☑️ ☑️ Works for me
- ☑️ ☑️ ☑️ ☑️ ☑️ Works for me
- ☑️ ☑️ ☑️ ☑️ ☑️ I think it improves memory but it sure gives you crazy dreams
- ☑️ ☑️ ☑️ ☑️ ☑️ Short term memory improvement, check. Vivid dreams, check.
- ☑️ ☑️ ☑️ ☑️ ☑️ Mold Sensitivity - CAUTION!!!!

Kozikowski, JACS 1989, 4116

OPRD 2012, 635

AcOCH₂CO OAc

Pd

12 steps

16 steps

huperzine A

4 steps

93% Mel

HCl, acetone; KH (OME)₂CO 74% 2 steps

CHO

TMG

93%

Herzon, Chem. Sci. 2011, 2251

Br PhMe₂SiLi Cul, then

LHMDS, TsCN

NC SiMe₂Ph

Pd(PBu)₂ NaOtfBu

TIOH; then

H₂O₂, TBAF

(5:1 dr)

71-76%, 3 steps

ElPPh₃Br

LHMDS, Et₂O

rt.

Burgess

NC Me Me H NOC

PIFA, MeOH then TMSI

H₂O

Me

Me

Me

Me

Me

Me

huperzine A

White, OL 2013, 882

hv, CH₂Cl₂

1. KHMDS

TIPSCI,

2. TMS₃

PhIO

(58%)

Ming

Magnus GM

73% Me

OTIPS

N₃

then

SePh

Me

Me

If Br instead of SePh.

Fukuyama, OL 2009, 5354

KHMDS

18-crown-6

THF

0 °C

TBAF, THF

80%

2 steps

Me

Me

H OMe

Me

Me

AlMe₃ 69%

Me

Me

Me

Me

Me

Me

HF

90%

1. TsOH

H₂NCO₂Me

PhH, 37%

2. TMSI

Mech.

17 steps from A
Dietary Supplements

Betaines (BEET-eh-en) Isolated from beets
What it does:
- Supports immune functions
- Maintains intestinal functions
- Boosts strength
Toxicity:
- none?

Betaines in catalysis
Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for
Asymmetric Mannich-Type Reaction of α-Nitrocarboxylates
JACS 2008, 10878.

\[
\begin{align*}
\text{Me}_3N & \overset{\text{O}}{\text{O}} \\
\text{trimethylglycine}
\end{align*}
\]

97% yield, 99% ee 4:1 dr

Chiral Ammonium Betaines as Ionic Nucleophilic Catalysts
ACIE 2010, 5567.

99% yield, 96% ee

What it does:
- Treats heart conditions (congestive cardiomyopathy)
- Asthma
- Maintains testosterone levels
- Supports lean muscles
- Supports fat loss
Toxicity:
- mostly safe, irritation?

Highlights of Corey forskolin synthesis
JACS 1988, 3672

Other applications of singlet oxygen see (GM SJ McKerrall 2011)
### Dietary Supplements

#### Vitamin chemistry

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Formula</th>
<th>Price</th>
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<tbody>
<tr>
<td>C (ascorbic acid)</td>
<td>$1.4/g</td>
<td></td>
</tr>
<tr>
<td>B2 (riboflavin)</td>
<td>$4.9/g</td>
<td></td>
</tr>
<tr>
<td>B7 (biotin)</td>
<td>$63.3/g</td>
<td></td>
</tr>
<tr>
<td>D (cholecalciferol)</td>
<td>$59.2/g</td>
<td></td>
</tr>
<tr>
<td>A (retinol)</td>
<td>$38.7/g</td>
<td></td>
</tr>
</tbody>
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#### Some Transformations of L-Ascorbic Acid

- **80-85%**
- DEAD, PPh₃, THF/DMF
- **64-77%**
- 2 eq. tBuOK, RBr, DMSO/THF

#### Methods

- 10 mol% CuMeSal
- Ascorbic acid
- DMF, 55°C
- 74 - 86%

- 1 mol% CuMeSal
- Ascorbic acid
- DMA
- 49-89%

- AA
  - **OL, 2009, 843**

- **JACS, 1995, 2381**

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*Hang Chu*

*Baran GM*

*6/27/15*
Dietary Supplements

**Polyphenols**

The Composition of a Typical Tea Beverage, % by Weight

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<th>Compound</th>
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<th>Black Tea</th>
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<td>30%</td>
<td>9%</td>
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<td>Theaflavines</td>
<td>4%</td>
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<td>Simple polyphenols</td>
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<td>5%</td>
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Representative (oligo/poly)phenol strategy

**Dietary Supplements**

**Polyphenols**

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**Representative (oligo/poly)phenol strategy**

**Quadrangularin A.**

**ACIE, 2006, 7771**

**Hopeahainol A/Hopeanol.**

**Nicolaou, 2009, 3440.**

**Lewis acids:**

- TiCl₄, SnCl₄
- TMSOTf, AgBF₄
- K₂[Be₄O(SiMe₃)₂]₂, Sc(OtBu)₃
- Yb(OtBu)₃

**TL 2006, 5298**

**Oligostilbenes**

- FeCl₃, acetone or AgOAc, MeOH
  - 97%
- Ti(NO₃)₃, MeOH
  - 30%
- HO

**Resveratrol OH trans-dehydrodimer**

- HO

**Resveratrol**

- HO

**Hopeahainol A**

- HO

**Hopeanol A**

- HO
Dietary Supplements

The total synthesis of cannabinoids
Synthesis from simple terpenes:

Macronutrients

Protein

Whey protein:
- a) concentrate
- Basic, cheap protein
- b) isolate
- Fast absorbing, more expensive
- c) hydrolysate
- Fastest absorbing, most expensive

Casein:
- Slow digesting, taken before bed

Milk protein:
- Contain both whey and casein, lower protein concentration by weight.

Natural Sources of protein

Dairy:
- Greek yogurt 23g/8oz.
- Cottage cheese 14g/1/2 cup.

Snacks:
- Peanut butter 8g/2tbsp.
- Mixed nuts 6g/2oz.

Produce/frozen food/ grains:
- Tofu 12g/3oz.
- Green peas 7g/1 cup
- Quinoa 8g/1 cup

Carbohydrates

Preferred sources of energy for any physical activity.
Insulin brings blood glucose to liver, muscle then fat.

The glycemic index: measurement of how quickly a carbohydrate is converted into glucose and enters the body.

High glycemic carbs:
- candy, potatoes, white bread
- honey, corn chips, white rice
- some fruits (cantaloupe, watermelon), some cereals (puffs), instant oatmeal

Moderate/low glycemic carbs:
- sweet potato, brown rice, nuts,
- legumes, oats, bran, dairy, fruits:
  (strawberries, cherries, apples, pruness),
- pasta (boiled), beans

Fats

Why eat fat?
1. Highly concentrated form of energy: 1g fat = 9 cal
2. Transport, store and absorb vitamins
3. Insulation/protection
4. Essential fatty acids
5. Makes food taste good

3/4th of avocado:
- 240 calories
- 13g carbs
- 22.1g fat
- 3g protein

Natural PB:
- 210 calories
- 6g carbs
- 16g fat
- 7g protein