

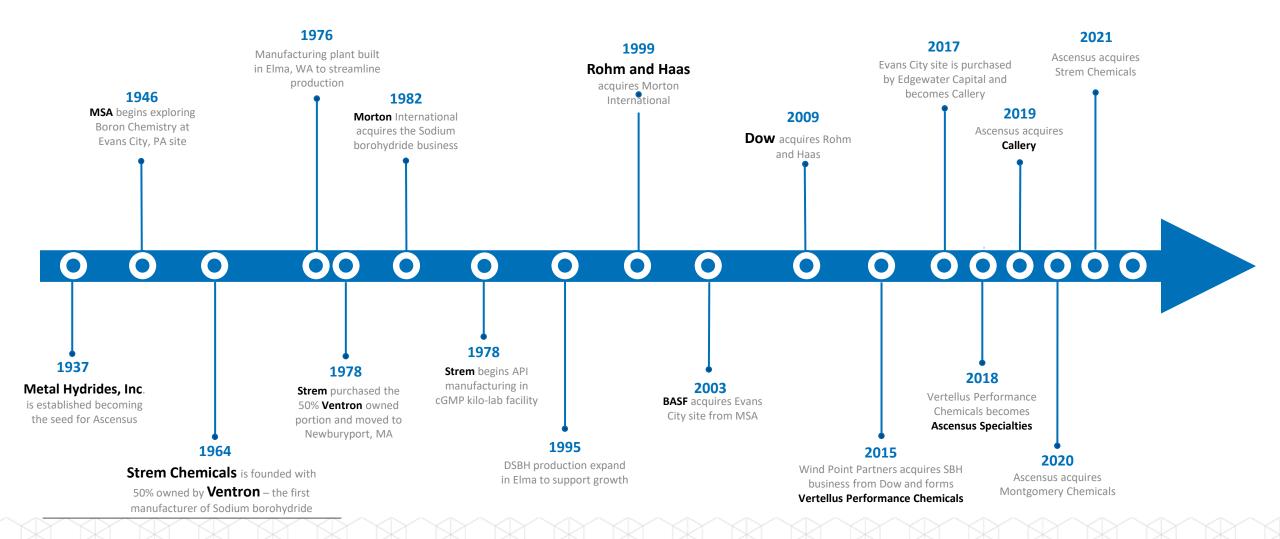
## Reliable Methods for Borohydride Reductions

Presenter: Nathan T. Allen PhD



### **Ascensus Specialties History**

#### Specialty Chemicals for over 80 years



### **Our Products**



#### Specialty Reagents that Matter

#### Borohydrides

Typical applications are in Life Sciences, Specialty Markets, and Pulp & Paper

#### **Strem Catalog**

Offering more than 6,000 specialty chemicals with an emphasis on metals, inorganics, organometallics, and nanomaterials for R&D and commercial applications

#### **Boranes**

Typical applications are in Life Sciences and Specialty Markets

#### **Thin Film Deposition**

Our portfolio includes 500+ MOCVD, CVD, and ALD precursors and bubblers/cylinders for microelectronics applications.

#### **Other Specialty Chemicals**

Portfolio includes TMB, NaK & K Metal. Typical applications are in Specialty Markets

#### APIs

Offering Cisplatin, Dexmedetomidine hydrochloride, and many more. Our Active Drug Master Files (DMFs) are maintained in over 20 countries.

#### **Specialty Alcoholates**

Typical applications are in Life Sciences and Specialty Markets

#### Catalysis

Portfolio includes thousands of catalysts and ligands such as Buchwald ligands and precatalysts, photocatalysts, metathesis catalysts, and biocatalysts

#### ASCENSUS PORTFOLIO

We offer a broad portfolio to ensure we capture all our customer's needs. From catalog sales to commercial scale, we're the partner that delivers specialty reagents that matter.

3

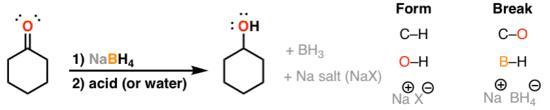




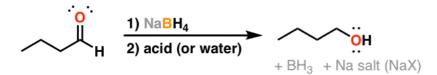
### Sodium Borohydride

#### **Classic Education**

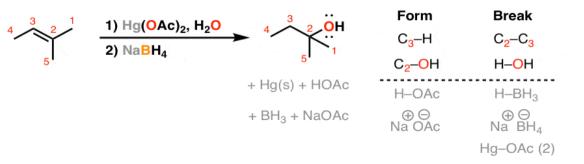
Example 1: Reduction of ketones



Example 2: Reduction of aldehydes



Example 3: In the second step of the oxymercuration reaction



https://www.masterorganicchemistry.com/2011/08/12/reagent-friday-sodium-borohydride-nabh4/



### Wide Application of Borohydride Chemistry

Generic	358 drugs, 1692 conditions	Antidepr essant Steroid Antidepr Hyperte Heart Disease Allergy	Antibiotic HIV Migraine Diabetes Expector Insomnia Obesity Cancer Herpes Hyperlipi demia
Mature	Cancer Diabetes Heart Antiviral Asthma ED Bipolar Gastro Opioids Other*	Obesity	
Launch	Cancer	Pain Multiple Influenza Hormone Octavitis	Neurologic Constipation Hypertension
Development	Tourette Cancer Cystic Cancer Antiviral	Diabetes COPD Cancer Antibiotics Opioids Antipsychotic Psychiatric	HIV Cancer Diagnostics Atopic Dermatitis

Single API 2-5 APIs

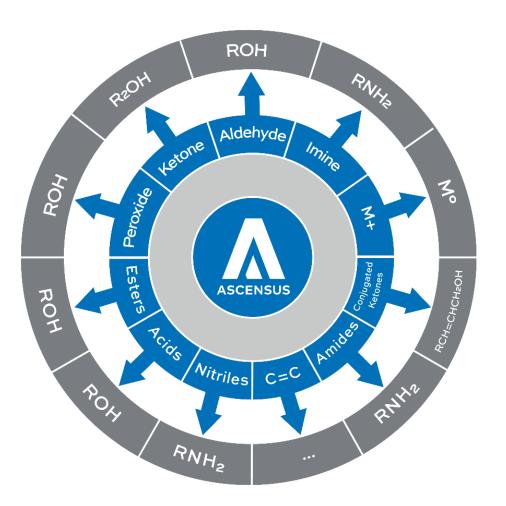
2-5 APIs 5+ APIs

\* Represents 25 additional API's



### **Borohydride-Based Transformations**

Reality is far more complicated



- 374k Reactions listed in CAS
- ► 55k References
- ▶ Begins in 1940's



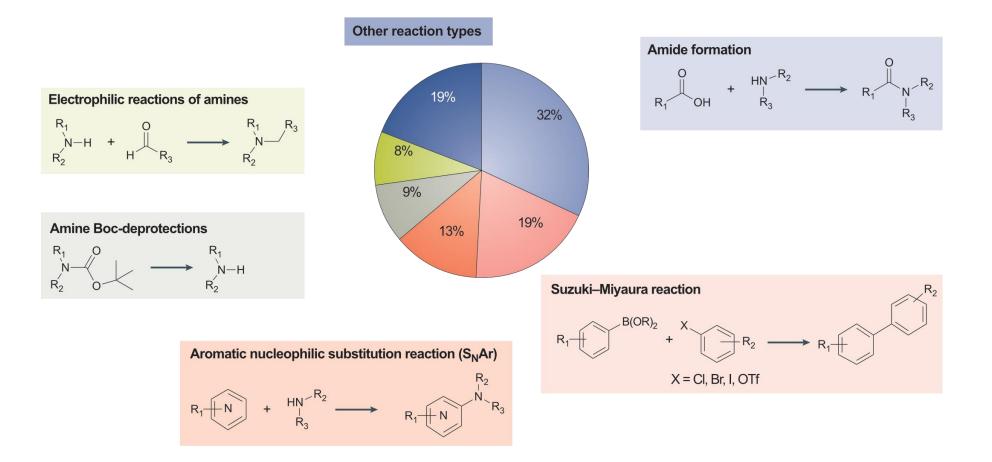
### Levels of Believability in Chemistry

Level of R&D	Reported in	Typical Scale	Typical Yields Reported	Typical Reliability
Graduate Student	Lower Organic Chemistry Journals	milligram to gram	80-100%	Well, maybe
Researcher	Process R&D Journals	gram to kilogram	60-90%	It worked, but the project likely died or was a hobby
Lab Researcher	Patents	milligram to gram	50-90%	Their best unoptimized attempt
Process Chemist	Regulatory Documents	kilogram to MT	50-95%	Reality +/- generous error margins
Process Chemist/Engineer	Non-public Technical Conversations	100s kg to MT	50-90%	The Actual Fact



### **Medicinal Chemistry Toolbox**

#### 5 Reactions make up 80% of the Process Steps

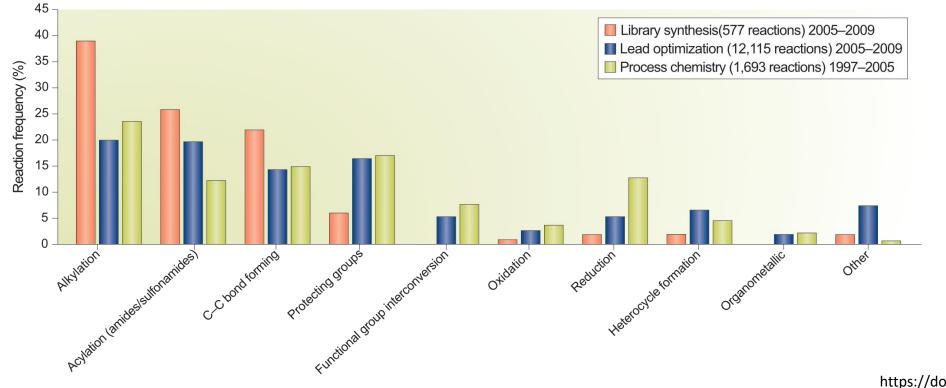


#### https://doi.org/10.1038/nrd.2018.116



### **Process Chemistry**

Even more conservative



#### https://doi.org/10.1038/nrd.2018.116



### Synthetic Transformations at Scale

11



- ▶ Ketone Reductions
- ▶ Reductive Aminations
- ► Ester Reductions
- ▶ Carboxylic Acids
- ▶ Deoxygenation
- ► Hydrogenations
- ▶ Flow Chemistry

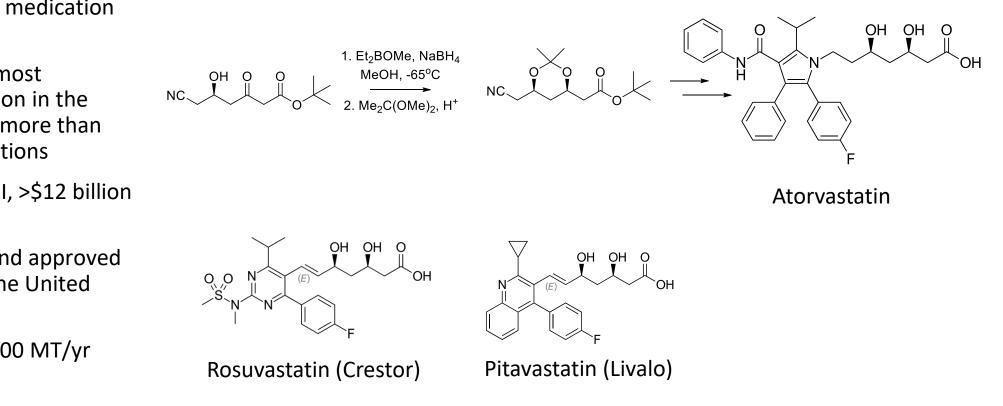




- Statin medication used to prevent cardiovascular disease
- World's best-selling medication of all time
- In 2019, it was the most prescribed medication in the United States, with more than 112 million prescriptions
- ► First \$10+ billion API, >\$12 billion in sales in 2005
- Patented in 1986, and approved for medical use in the United States in 1996
- ▶ Peak API volume >200 MT/yr

### Atorvastatin

Lipitor (Warner-Lambert/Pfizer)

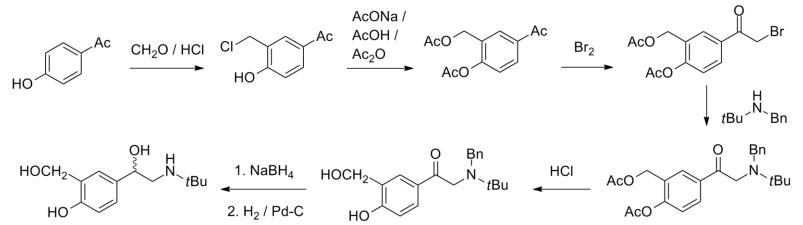


### Salbutamol

#### Albuterol, Accuneb, Proair, Proventil and Ventolin



- Bronchodilator; β2 adrenergic receptor agonist
- Patented in 1966 in Britain and became commercially available in the UK in 1969
- ► The original route developed in 1966 at Allen and Hanburys Ltd (UK, GB1838367) still practiced.
- Approved in the United States in 1982

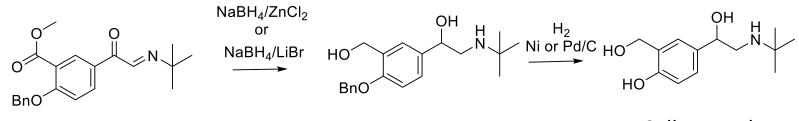




### Salbutamol

#### **Other Routes**

- ▶ Removes deprotection step
- Utilizes activated borohydride chemistry
- ► Typical ethereal solvents
- Could also be accomplished with MeOH and heat



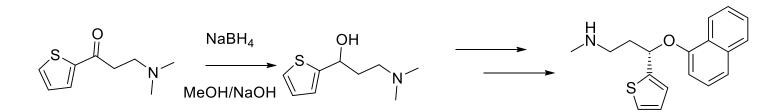
Salbutamol



### Duloxetine

#### Cymbalta, Drizalma Sprinkle, Irenka (Eli Lily)

- Used to treat major depressive disorder, generalized anxiety disorder, fibromyalgia, and neuropathic pain
- Developed by Eli Lily in 1986 (Patent US4956388A)
- 26th most-commonly prescribed medication in the United States, with more than 23 million prescriptions
- Borohydride reduction 89% at 100 kg batch size (78% in original patent)



Duloxetine





### Sumatriptan

Imitrex (Glaxo)

Patented in 1982 and approved for medical use in 1991 1) H<sub>2</sub>, 5% Pd/C, aq. HCl HCI ``<u>s</u>´ 0 0 50°C, 2 h ,S,´ O 98th most-commonly ►  $_{>}NH_{2}$ 2) NaNO<sub>2</sub>, conc. HCl, -5 °C  $NO_2$ prescribed medication in 3) Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, aq. NaOH, *i*-PrOH, -5 °C the United States, with 53% more than 7 million prescriptions OMe 1)  $NH_2$ 37% aq. HCHO, NaBH<sub>4</sub> On the World Health MeO ► Н Organization's List of EtOH, aq HCI, RT o´`o °`S∖́ ÓO MeOH, Na<sub>2</sub>HPO<sub>4</sub>, H<sub>2</sub>O, RT **Essential Medicines** 2) Na<sub>2</sub>HPO<sub>4</sub>, reflux, 4h (buffer reaction pH 8 to 10) 53% 87% **BASF Synthesis** ► WO2001034561A1 Sumatriptan Similar process step used in ► Almotriptan and Zolmitriptan

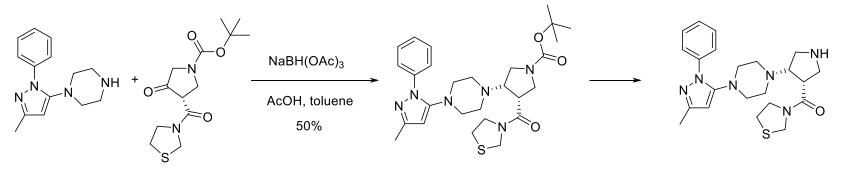


#### Tenelia (Mitsubishi Tanabe Pharma and Daiichi Sankyo)



ASCENSUS

- ▶ Patent W02012099915
- ► Ascensus STAB is used, but could easily be made in situ



Teneligliptin



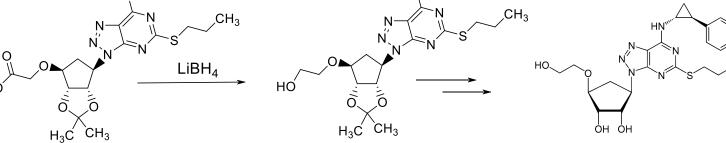
Ticagrelor

Brilinta, Brilique (AstraZeneca)

- Prevention of stroke, heart ► attack
- Approved in USA 2011, EU ► 2010
- 216th most prescribed ► medication in the United States, with more than 2.3 million prescriptions
- Alternative is DiBAI-H ► Reduction
- Options for LiBr/NaBH<sub>4</sub> or ► LiBH<sub>4</sub>
- Solvents: THF, Diglyme, ► MeOH, EtOH



Ticagrelor



OR

MeO

OR

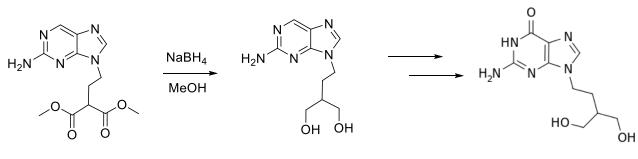




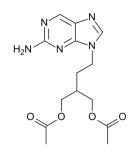
### Famciclovir / Penciclovir

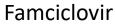
Denavir, Vectavir, Fenivir and Famvir (Novartis)

- Antiviral drug used for the treatment of various herpesvirus
- Patented in 1983 and approved for medical use in 1994
- Famciclovir is a prodrug of penciclovir with improved oral bioavailability



Penciclovir



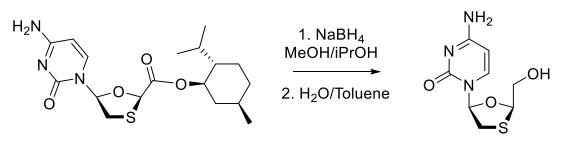




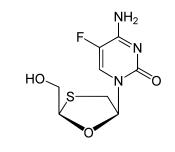
### Lamivudine

Epivir, Epivir-HBV, Zeffix, others (Glaxo)

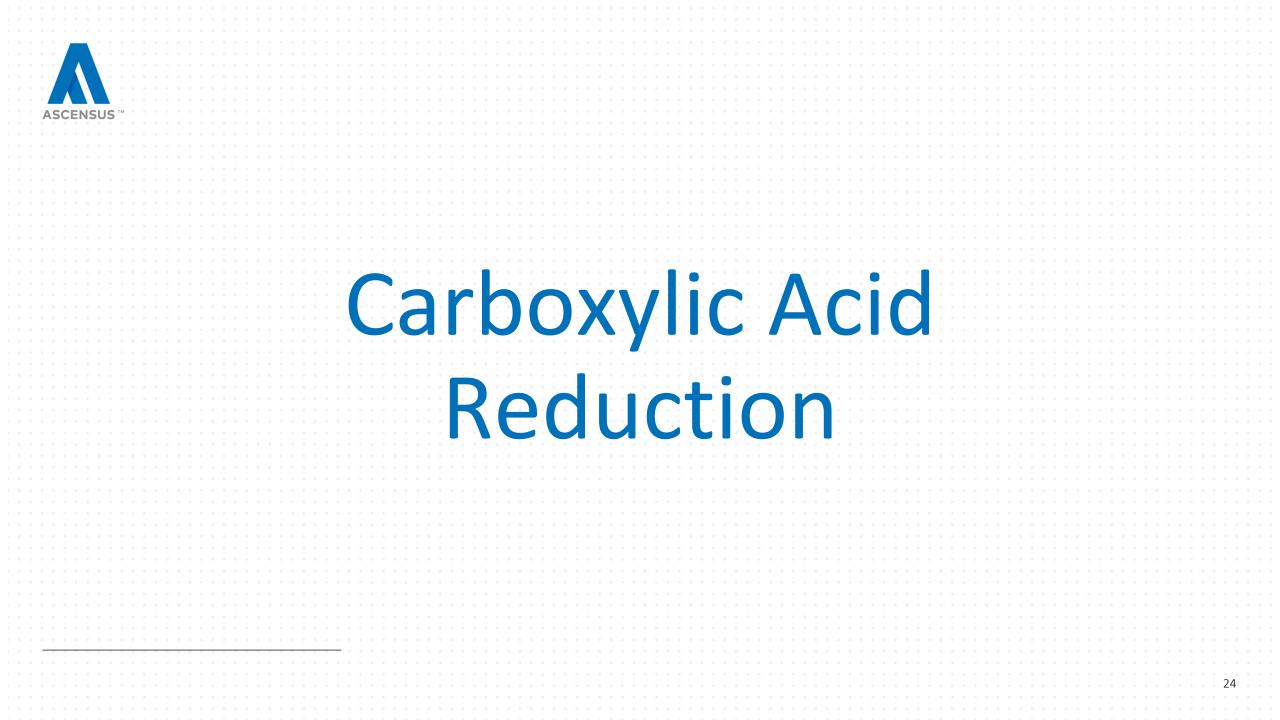
- 3TC, is an antiretroviral medication used to prevent and treat HIV/AIDS
- Patented in 1995 and approved for use in the United States in 1995
- On the World Health Organization's List of Essential Medicines
- ▶ Part of the ARV "drug cocktail"
- ► Has saved millions of lives
- Synthesis done at 500 kg batch size



Lamivudine



Emtricitabine

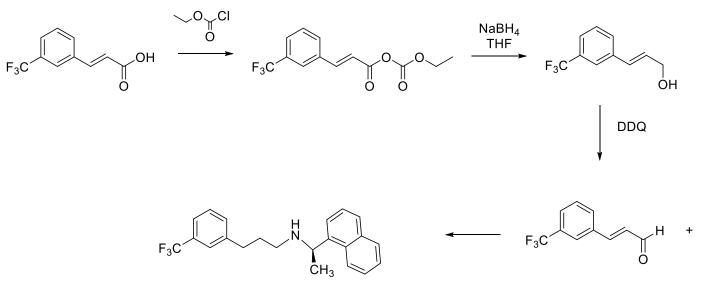




### Cinacalcet

#### Sensipar, Mimpara (Amgen)

- Used to treat secondary hyperparathyroidism, parathyroid carcinoma, and primary hyperparathyroidism
- ▶ Reduces calcium in blood
- In 2013, the 76th most prescribed medicine in the United States
- Originally developed by Amgen (NPS Pharma originated, patent US6211244B1)



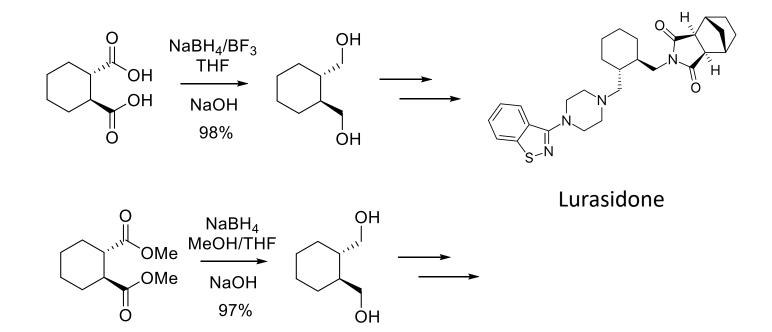
Cinacalcet

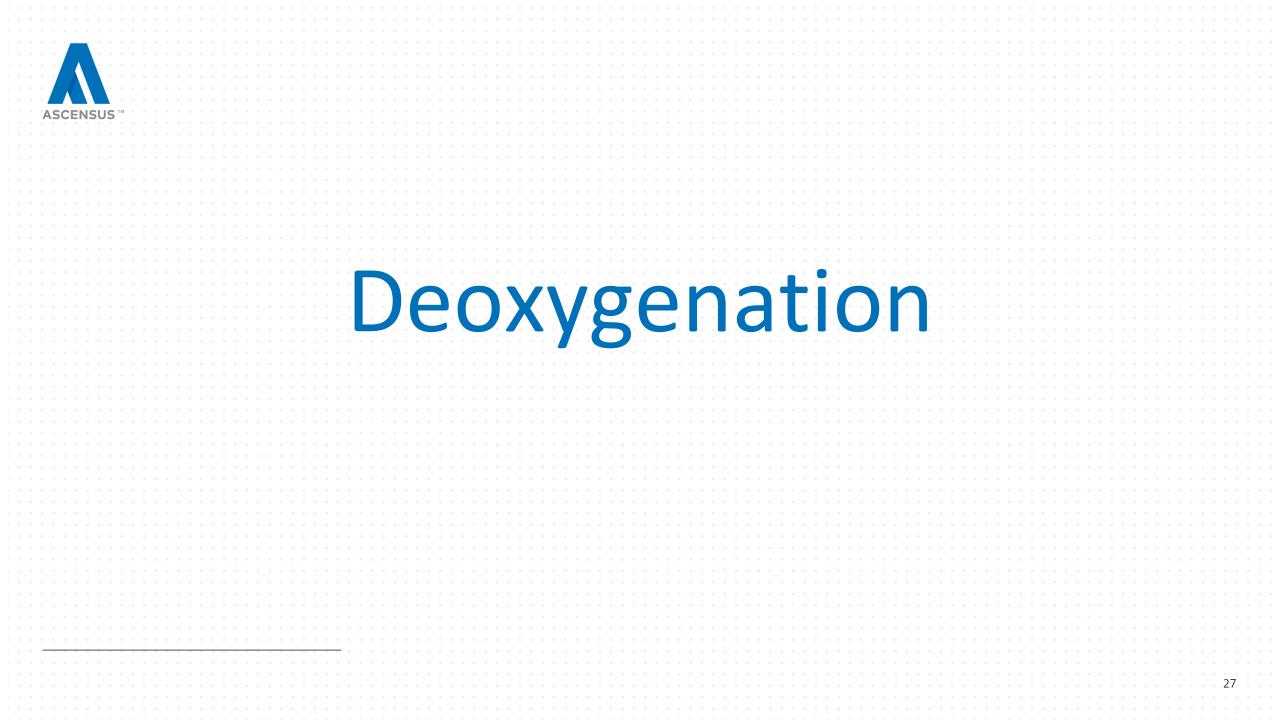
M Barniol-Xicota, et. al.; Syntheses of Cinacalcet: An Enantiopure Active Pharmaceutical Ingredient (API); DOI: 10.1055/s-0035-1561506



### Lurasidone

- An antipsychotic medication used to treat schizophrenia and bipolar disorder
- Approved for medical use in the United States in 2010
- 220th most prescribed medication in the United States, with more than 2 million prescriptions
- Patent examples CN102952001A, WO2005090273 A1
- ▶ Commercial batch size 500 kg



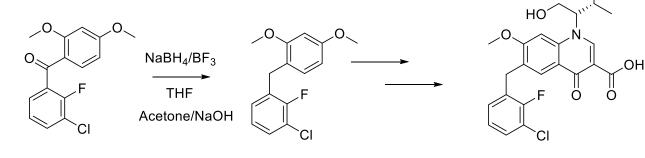




### **ELVITEGRAVIR**

EVG – Stribild, Vitekta (Gilead)

- Integrase inhibitor used to treat
  HIV infection
- Gilead Sciences licensed EVG from Japan Tobacco in 2008
- ▶ 2014 the FDA approved
- ▶ BH3-THF is an alternative reagent
- ▶ Synthesis at 100 kg scale



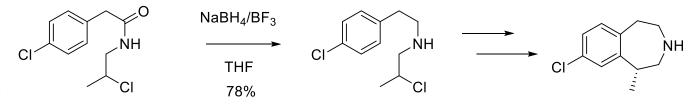
Elvitegravir



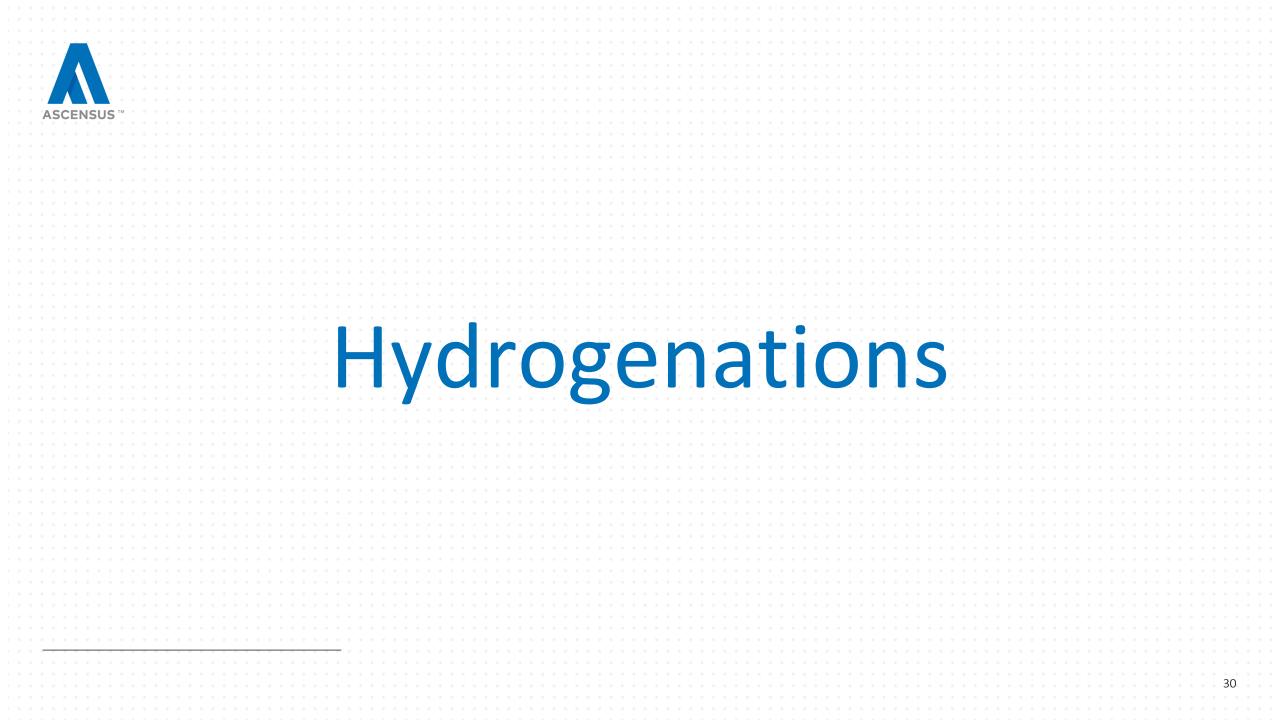
### Lorcaserin

Belviq (Eisai)

- Reduces appetite by activating a type of serotonin receptor
- In 2012, the FDA approved Lorcaserin for use in adults with a body mass index (BMI) of 30
- Removed from the market in the United States in 2020 due to an increased risk of cancer detected in users
- $\blacktriangleright$  BH<sub>3</sub>-THF is an alternative



Lorcaserin

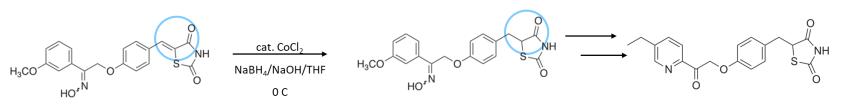




### MSDC-0160

#### Metabolic Solutions Development Company

- Phase II Trails for Alzheimer's -Metabolic Solutions, oral insulin sensitizer that works through a new drug target located in the inner mitochondrial membrane
- Metal-Catalyzed Reductions without hazards of hydrogen gas handling
- ▶ Raney Nickel, Pd/C, Co, Rh, etc...
- ▶ Reaction scale-up simplified
- Safety no high pressure H<sub>2</sub> required
- ► Low Capex no catalyst can be run in standard production equipment
- ▶ No specialized reactors needed

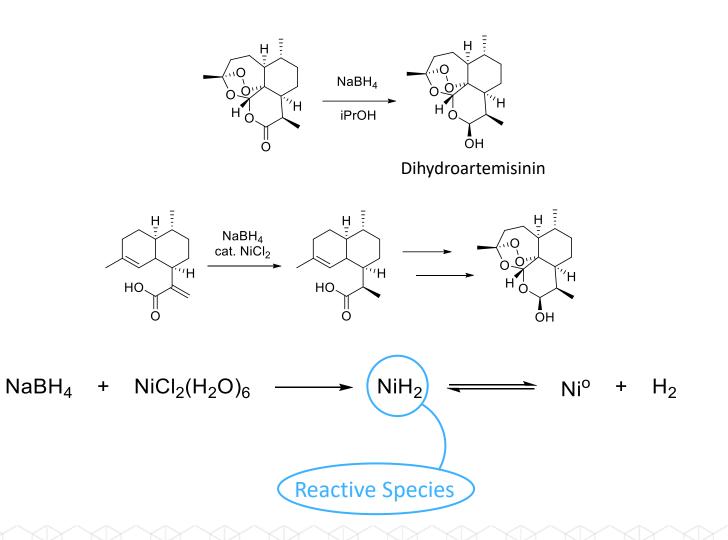


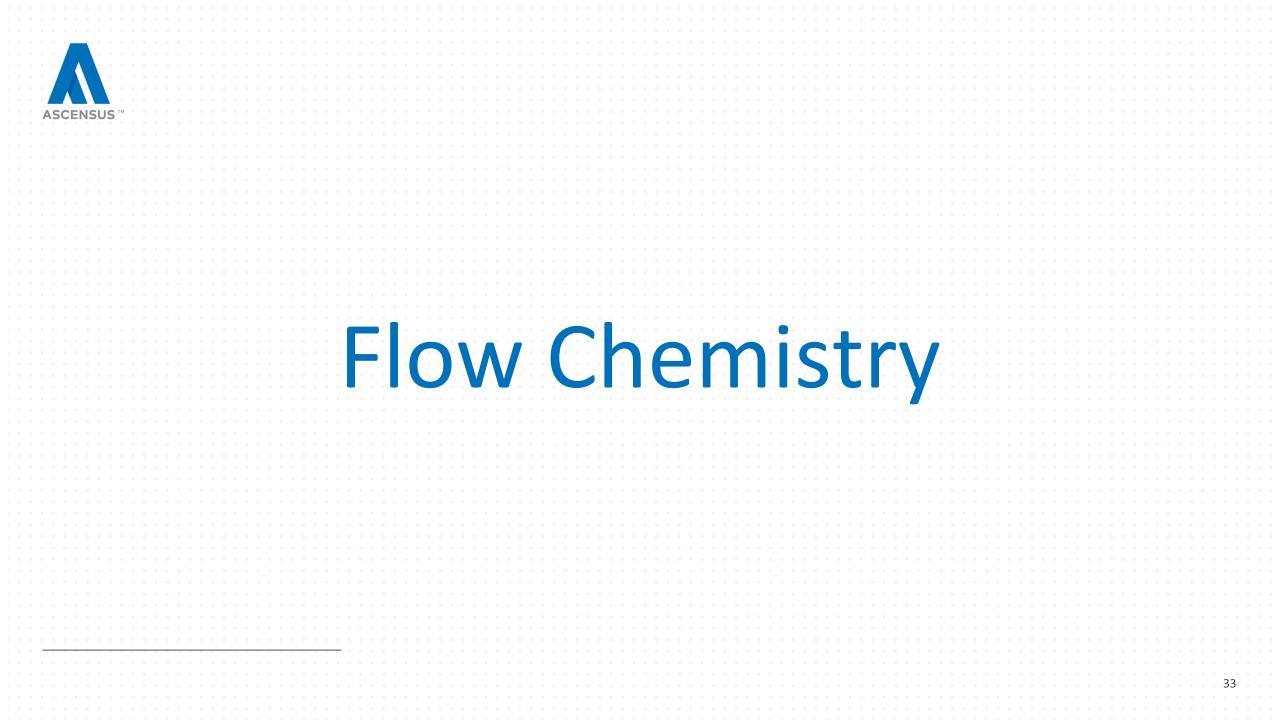
MSDC-0160





- ► Used to treat Malaria
- Original chemistry from Brown in 1963, JACS paper on olefin hydrogenation
- ► This example from patent CN103193790B
- Borohydride is a replacement for hydrogen in this case

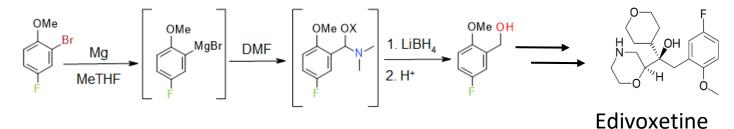




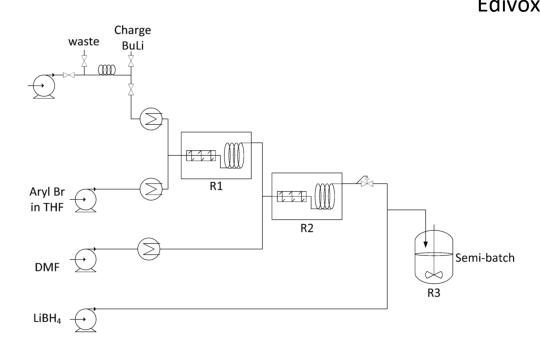


### Edivoxetine

#### LY-2216684 (Eli Lilly)



- Developed in 2012 for ADD, but failed
- Produces high yield of desired benzyl alcohol
- Soluble in a greater range of aprotic solvents enables use of greener solvents (MeTHF)
- LBH use in flow (continuous) strategy reduces hazards by operation in small volumes and metal activation only once

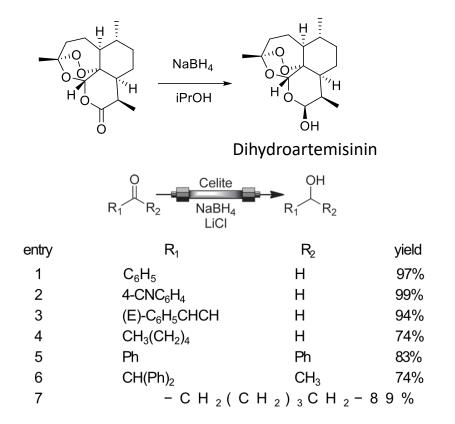


Org. Proc. Res. Dev. 2016, 20, 1581





- Artemisinin Flow Synthesis Using NaBH<sub>4</sub> Packed Beds
- ▶ High Yields
- Goal to reduce cost of production



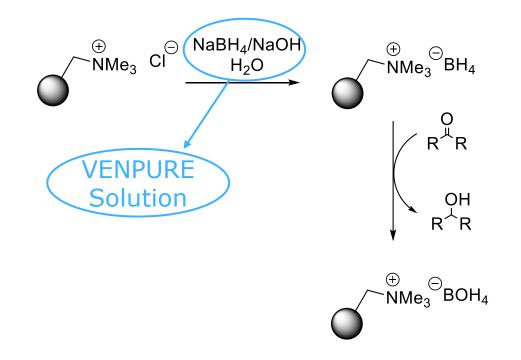
<sup>a</sup>The column was prepared using (1:1:0.76 w/w) Celite/NaBH<sub>4</sub>/LiCl The concentration of aldehyde/ketone was 0.66 M (THF) with 9.5 equiv of MeOH added, run at 0.5 mL/ min ( $T_{res} = 5.6 \text{ min}$ ).<sup>20</sup>



### Borohydride on Resin

BER

- ► Amberlite IRA-900Cl or A-26OH Resin
- ► Anion exchange resin, simply regenerate with sodium borohydride solution, and rinse.
- BER alone will easily reduce aldehydes, ketones, allylic aldehydes, nitro, dehalogenation, aryl azide and aryl sulfonyl azides
- CuSO<sub>4</sub> will allow the reduction of N-oxides, olefins, dehalogenation, azide, and nitro compounds
- ► Nickel or cobalt chloride will allow the reduction of halides, olefins, azides and nitro functionalities



Review: Steven V. Ley, R. Ian Storer; Borohydride Exchange Resin doi/10.1002/047084289X.rn00027



# Q&A



### **Thank You**



### Nathan T. Allen, PhD Principal Scientist

nallen@ascensusspecialties.com

### **Ascensus Offerings**





Broad Technical Knowledge Efficiently tackle challenging synthesis goals



**Custom Synthesis** Capabilities, expertise & equipment to rapidly scale up custom products, boranes and specialty alkoxides



Research & Development Enhanced R&D and application development capabilities



High Pressure Specialized production equipment (1L to 25-gallon autoclaves) allows for enhanced product offerings



**Process Safety** Regulatory and handling expertise to keep your operations and people safe



Analytical Extensive capabilities assures consistent and reliable testing



Scale Up Pilot plant capabilities to demonstrate process in larger scale

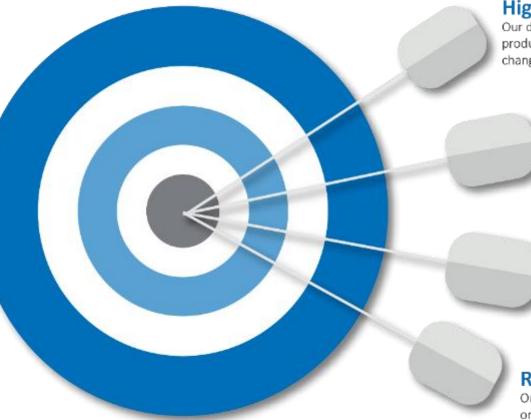


**CGMP** Expertise in manufacturing APIs and intermediates in the USA since 1988



### **Deliverables that Matter**

#### The Ascensus Difference



#### **High Quality Product Options**

Our diversified product portfolio with consistent, high quality products guarantees you can make the best possible products to change people's lives for the better

#### **Customer-Focused Service**

Our experience, response time, and willingness to address concerns and challenges allow us to adhere to ever changing market requirements

#### Safe Handling of Materials

By meeting the modern needs of highly regulated markets and corporate social responsibility programs, we safely handle reactive reagents and provide on-site customer training

#### **Reliable Supply**

Our US and EU facilities ensure safe, secure, and timely delivery of orders as well as a clear pathway to a dependable global supply.

