Production of ^{11}C-Labeled Radiopharmaceuticals

Decay Characteristics of ^{11}C

Half-life = 20.3 min
Decay modes: 99.8% by positron emission and 0.2% by electron capture
Decay product: ^{11}B
Maximal positron energy = 0.96 MeV
Maximal range in water = 4.1 mm.

Specific Radioactivity Considerations

Carrier is the non-radioactive version of a radiopharmaceutical.
Pseudo-carrier is a term used to describe material closely resembling true carrier in some respect (*e.g.* biological activity, receptor binding affinity).
Specific radioactivity of a radiopharmaceutical is defined as the ratio of radioactivity (Ci) to accompanying carrier (mol), and is expressed in units of Ci/mol or equivalent.

For ^{11}C-labeled radiopharmaceuticals there is substantial dilution with carrier. The carrier usually remains constant, while the radioactivity decays. Hence, specific radioactivity generally decreases according to the half-life of the radioisotope. Specific radioactivities for PET radiopharmaceuticals should be cited with respect to a particular time *e.g.* end of radionuclide production (**EOB**), end of synthesis (**EOS**) or time of injection (**TOI**).

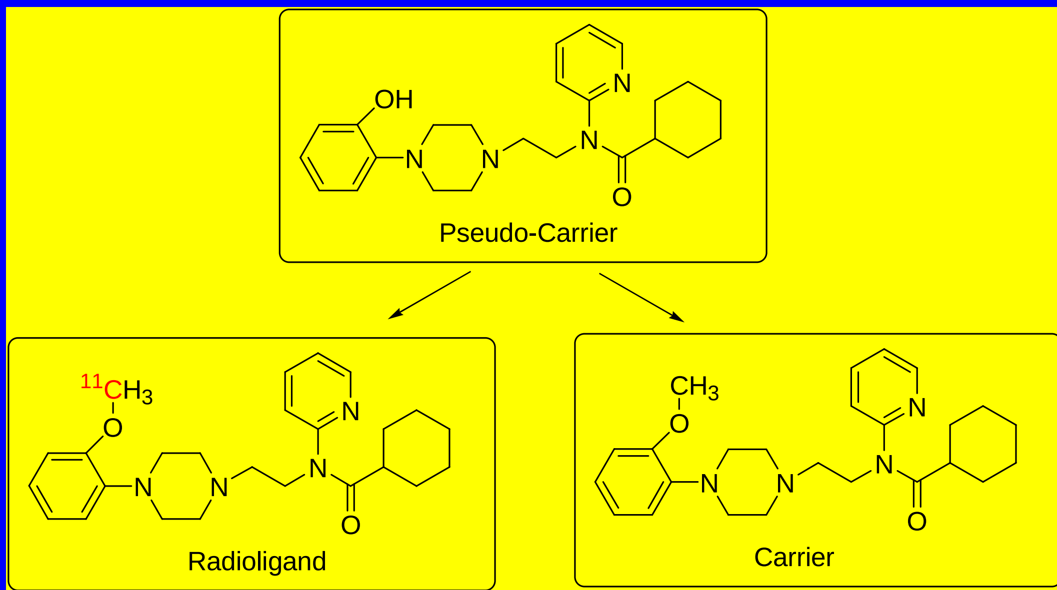
Qualitative Descriptions of Specific Radioactivity

Carrier-free (CF)
A radiopharmaceutical is carrier-free (**CF**) when there is no accompanying carrier.

No-carrier-added (NCA)
A radiopharmaceutical is no-carrier added (**NCA**) when no source of carrier has been added deliberately during its production, and when all reasonable precautions have been taken against the intrusion of sources of carrier.

Carrier-added (CA)
A radiopharmaceutical is carrier-added (**CA**) when a source of carrier has been added deliberately during its production.

Carrier & Pseudo-carrier



^{11}C - Theoretical Maximal *vs* Practical Specific Radioactivity

$-d\mathbf{N}/dt = \lambda \mathbf{N}$

where $\lambda = \ln 2/t_{1/2}$ and **N** is number of radionuclides

1 mole is an Avogadro number of atoms = 6.02×10^{23} atoms.

Therefore radioactivity per mole = $(0.693/20.3 \times 60) \times 6.02 \times 10^{23}$ Bq.

$= 3.425 \times 10^{20}$ Bq/mol

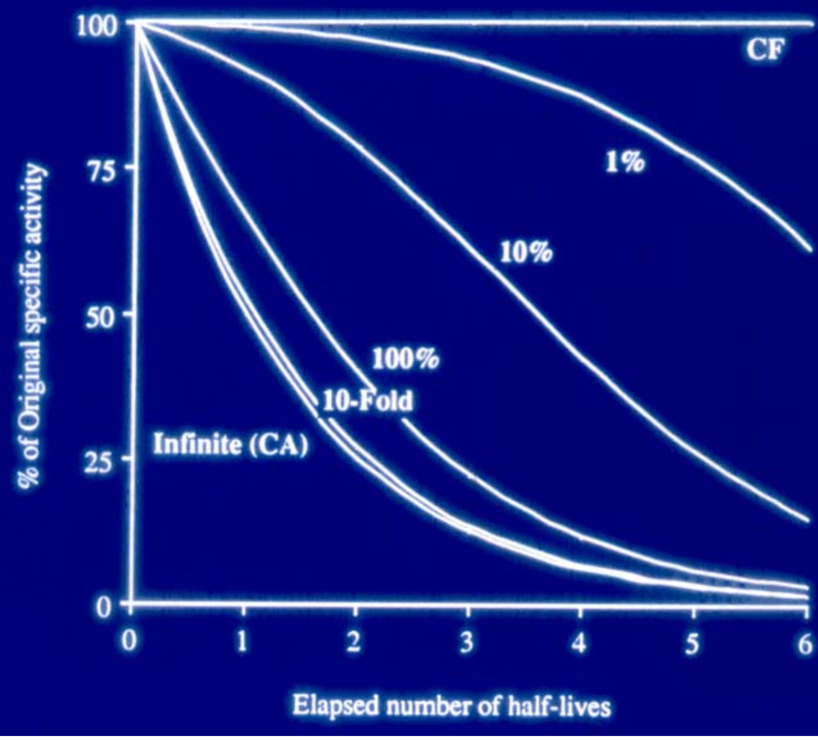
$= 3.425 \times 10^{14}$ Bq/µmol

= **9.25×10^{3} Ci/µmol ~ 10^{4} Ci/µmol**

[1 Ci = 37GBq]

Practical specific radioactivities rarely exceed 100 Ci/µmol and are typically ~10 Ci/µmol. *I.e.* dilution by carrier is typically ~ **1000**.

Time-dependence of Specific Radioactivity on Dilution with Carrier



The Importance of Specific Radioactivity

Radiopharmaceuticals

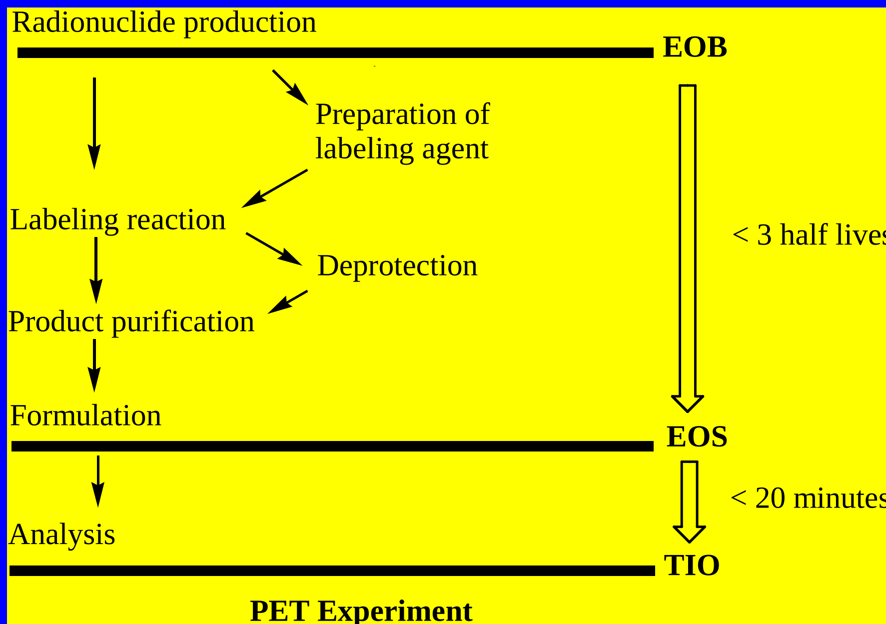
Radiotracers
trace in vivo processes
e.g.
metabolism
blood flow

*Generally, high specific radioactivity **is not** required*

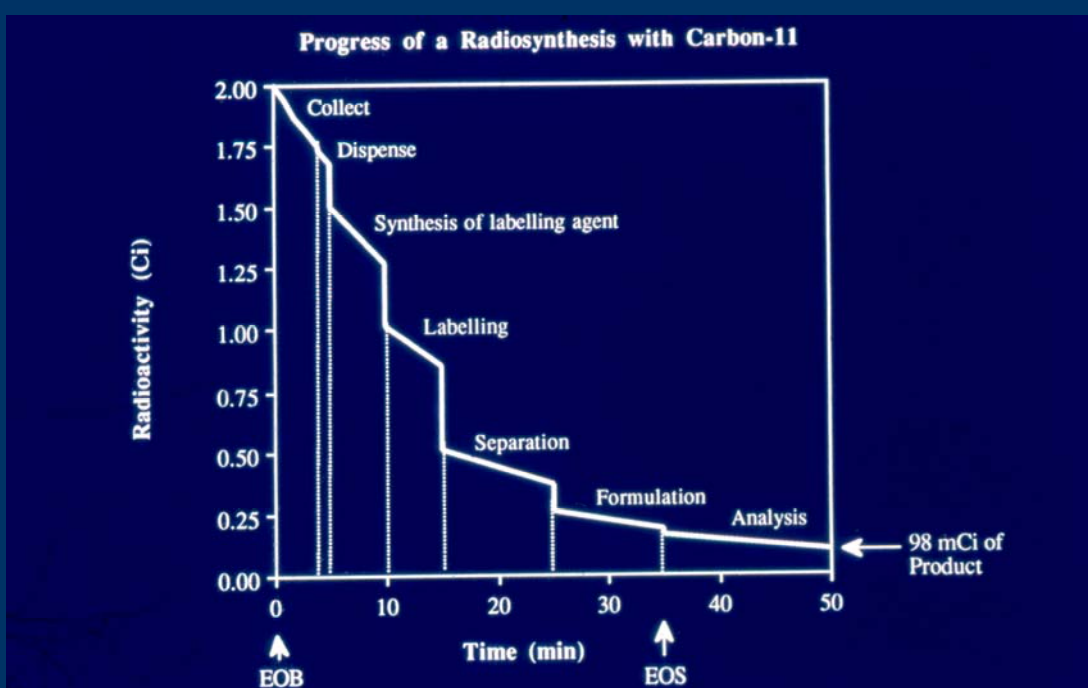
Radioligands
bind to molecular targets
e.g.
neuroreceptors
transporter proteins
enzymes

*Generally, high specific radioactivity **is** required*

Steps in Preparation of a ^{11}C-Labeled Radiotracer for PET

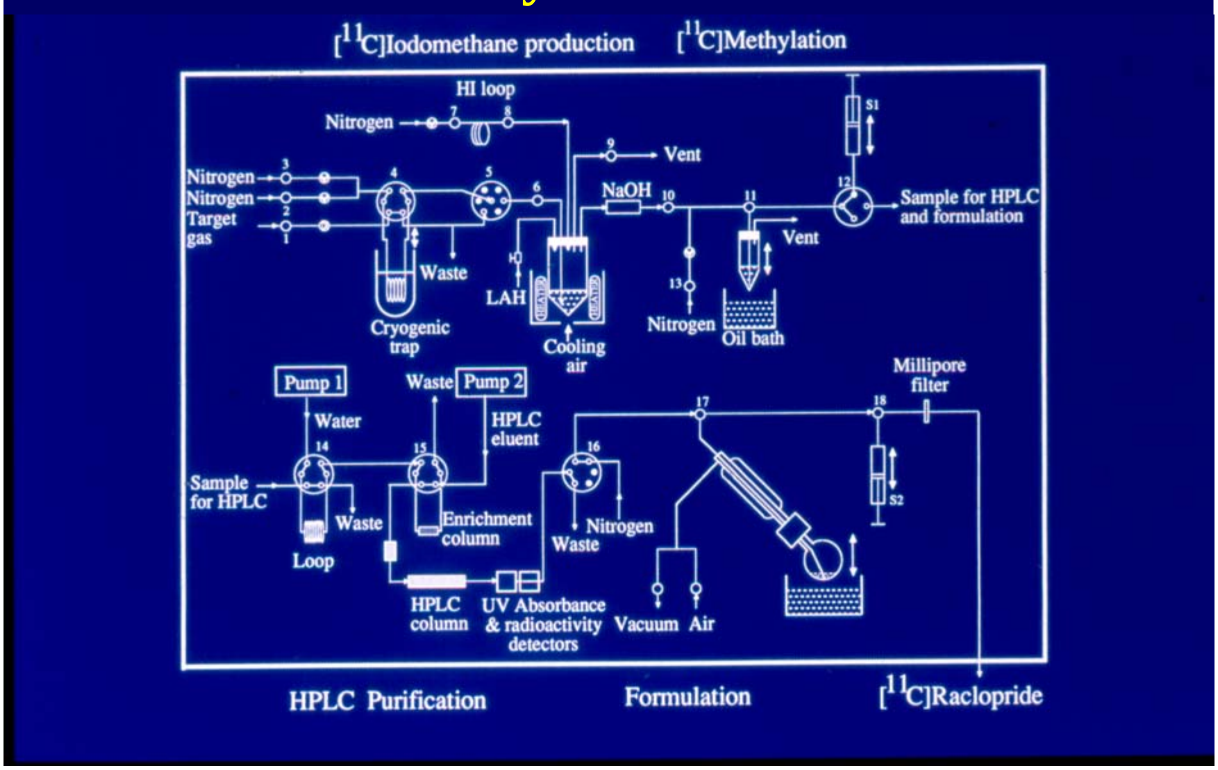


The Importance of Time & Process Efficiency

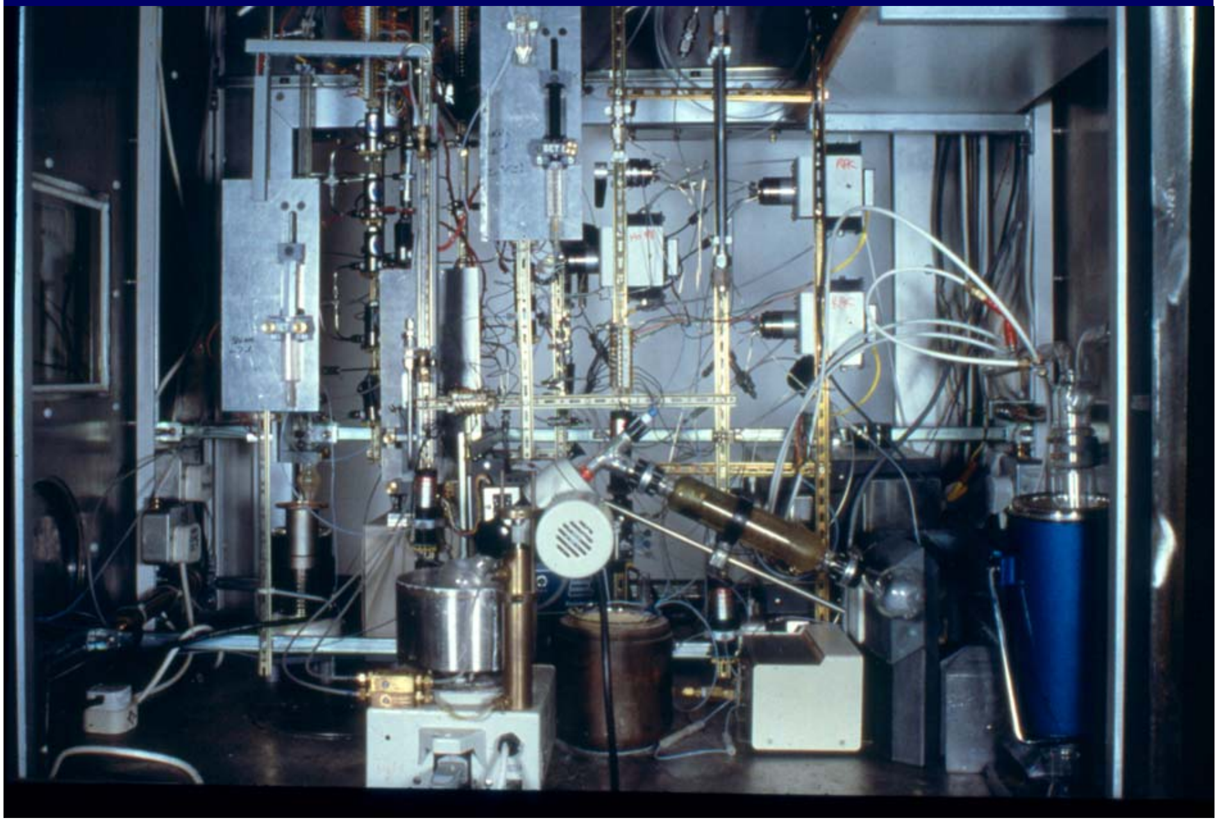


Hot-cells for Radiochemistry

Automated [*O-methyl*-^{11}C]Raclopride Synthesis



Automated [^{11}C]Raclopride Synthesis Apparatus

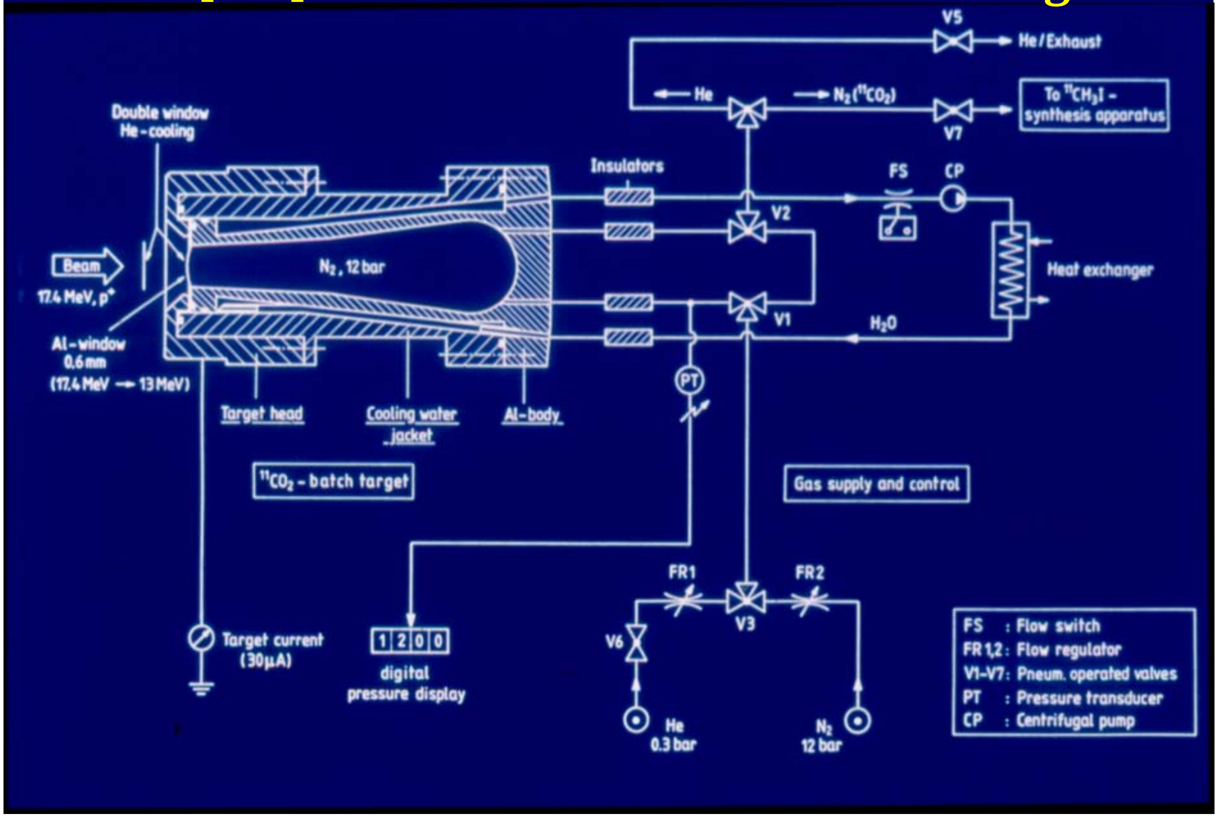


Production Methods for ^{11}C

Reaction	Target isotope abundance (%)	Thresh'd energy (MeV)	Max cross section (mb)	Energy at max cross section (MeV)	Calc'd thick target yield at saturation (GBq/μA)
^{10}B(d,n)^{11}**C**	19.90	0	~ 200	3.0–5.4	0.82 (E_d = 10 MeV)
^{11}B(d,2n)^{11}**C**	80.10	5.9	48	10	
^{11}B(p,n)^{11}**C**	80.10	3.02	180	6.0– 6.5	
			~ 350	8.7–10	4.1 (E_p = 10 MeV)
					7.8 (E_p = 15 MeV)
^{14}N(p,α)^{11}**C**	99.63	3.13	~ 290	~ 7.5	
			146	6.9	2.30 (E_p = 10 MeV)
					7.25 (E_p = 15 MeV)

Currently, the ^{14}N(p,α)^{11}C reaction is nearly always used.

[^{11}C]Carbon Dioxide Production Target



Typical Production Parameters

Production reaction	Irradiation conditions (MeV, µA, min)	Main product(s)	Typical yield (GBq)	Typical specific activity* (GBq/µmol)
p on $^{14}N_2$ (0.1% O_2)	19, 30, 30	$^{11}CO_2$	67	150
p on $^{14}N_2$ (5% H_2)	18, 30, 40	$^{11}CH_4$	67	130

*Varies greatly according to production system (target etc). Values up to 100 Ci/µmol (3.7 TBq/µmol) are possible for [^{11}C]methane.

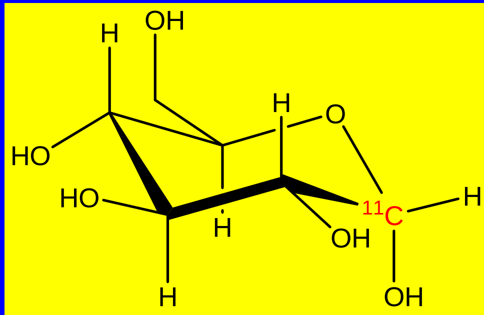
Organic Chemistry with ^{11}C

In principle, ^{11}C is a candidate for the **isotopic** or **non-isotopic** labeling of any organic compound and is thus of major importance to PET.

Isotopic labeling: ^{11}C replaces stable $^{12}C/^{13}C$ in the molecule. The biological fate of the molecule is *virtually* unchanged.

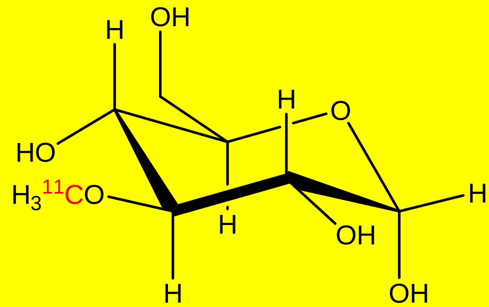
Non-isotopic labeling: a group containing ^{11}C is added to the molecule of interest, producing a new compound with different properties to the original.

Isotopic and Non-isotopic



[1-^{11}C]Glucose

Isotopically labelled glucose



[3-^{11}C]3-*O*-methyl-Glucose

Non-isotopically labeled glucose
Isotopically labeled 3-*O*-methyl-glucose

Kinetic Considerations in Radiochemistry with Carbon-

Precursor + [^{11}C]Labeling agent $\longrightarrow$ [^{11}C]Product

The reaction time needs to be as short as possible. Clearly the reactions needs to be driven to give useful yields within one physical half-life.

Generally, fast reactions are promoted by:

- using a large excess of precursor to consume labeling agent
- use of high precursor concentration in small volumes (Law of Mass Action)
- use of sealed vessels for elevated reaction temperature

Other means may be used *e.g.*

- use of microwaves, sonication
- use of solid supports for reagents

Yield Description and Measurement

- The practical **radiochemical yield (**%) of [^{11}C]product from a ^{11}C-labeling agent is defined as:

$$(100 \text{ x } [^{11}\text{C}]\text{P})/[^{11}\text{C}]\text{L}$$

where [^{11}C]L is the initial radioactivity of the labeling agent and [^{11}C]P is the measured radioactivity of the product.

- The conversion of labeling agent into radioactive product is given by the **decay-corrected radiochemical yield (%**):

$$(100 \text{ x } [^{11}\text{C}]\text{P.e}^{\lambda t})/[^{11}\text{C}]\text{L}$$

where t is the time taken for the radiosynthesis and λ is the decay constant for carbon-11.

The Direct Utility of [^{11}C]Carbon Dioxide for Radiolabeling

1. Reactions with organometallic reagents

e.g. Grignard reagents (RMgX), alkyllithiums (MeLi)

2. Photosynthesis

e.g. with leaves, algae

[^{11}C]Carbon dioxide is reactive!

a. Reactions with Grignard Reagents

$$^{11}CO_2/N_2 \xrightarrow{RMgX} [R^{11}COOMgX] \xrightarrow{H^+} R^{11}COOH$$

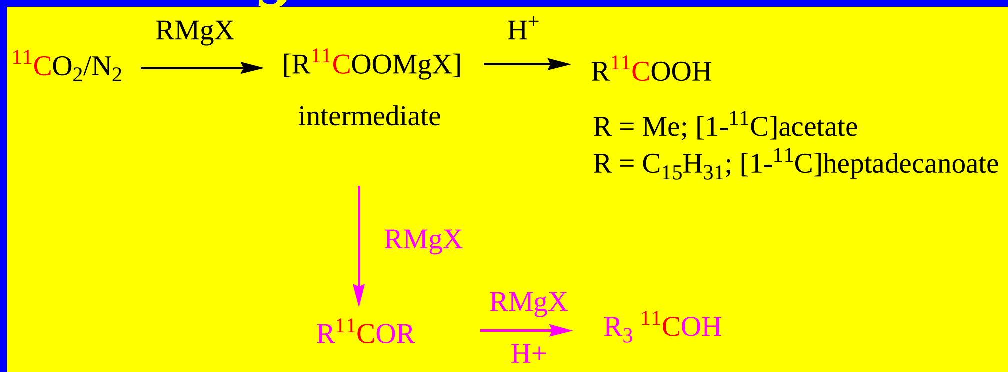
intermediate

R = Me; [1-^{11}C]acetate

R = $C_{15}H_{31}$; [1-^{11}C]heptadecanoate

- These reactions generally proceed rapidly in very high radiochemical yield.
- R can vary greatly and can also be aromatic (Ar).
- High specific radioactivity can be achieved if precautions are taken.
- The reactions must be carried out under controlled conditions, to avoid possible side reactions.

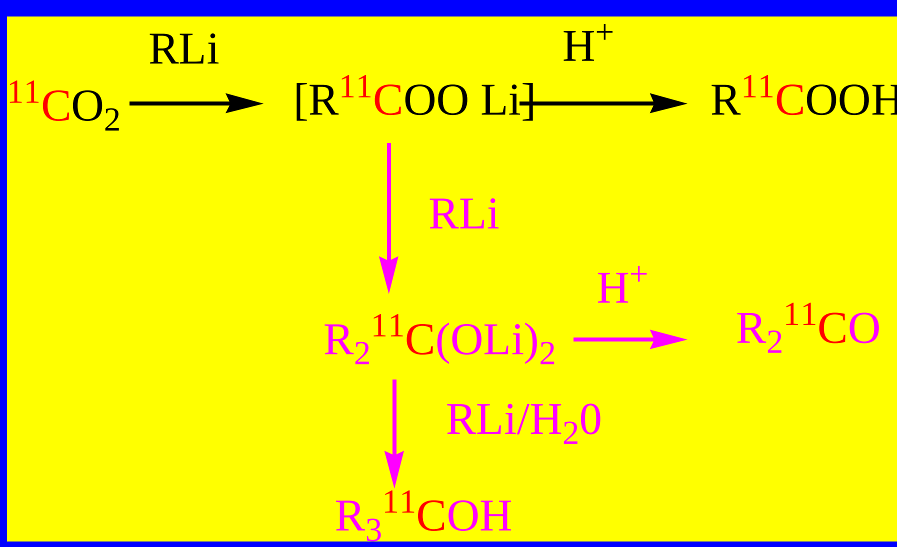
a. (Cont'd) Reactions with Grignard Reagents - Possible Side Reactions



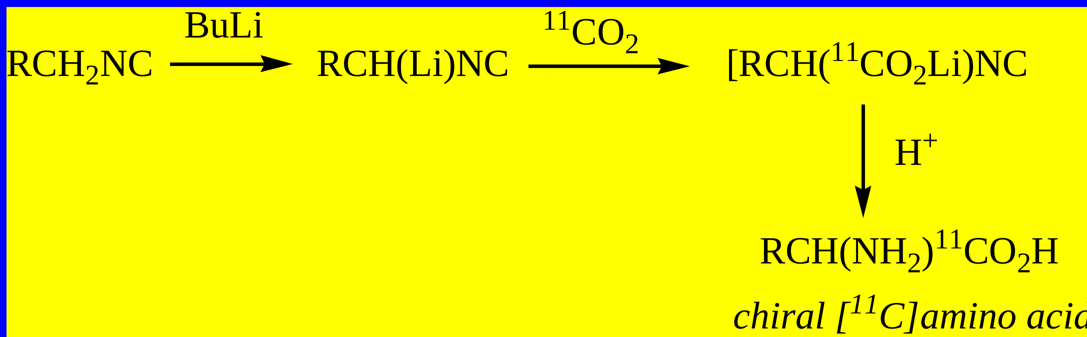
Must control:

- the halogen, X
- rate of delivery of $^{11}CO_2$
- RMgX concentration
- temperature
- reaction time

b. Reactions with Alkyllithiums

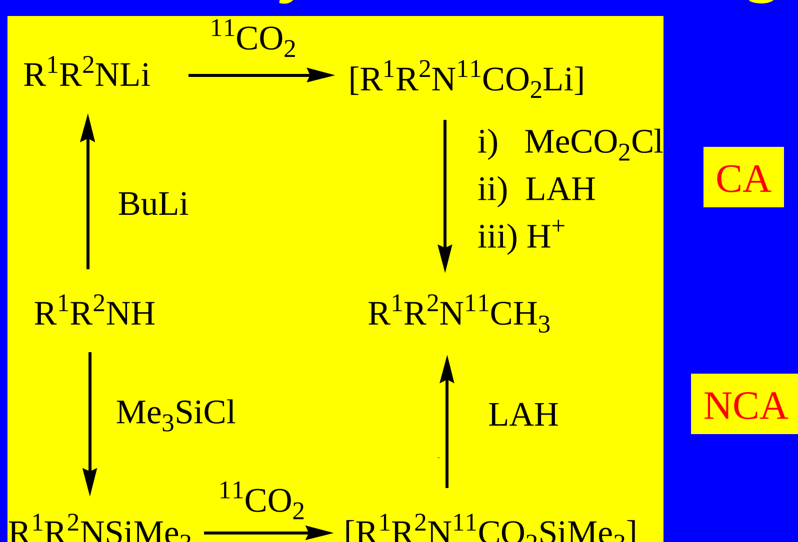


c. Reactions with α-Lithioisocyanides



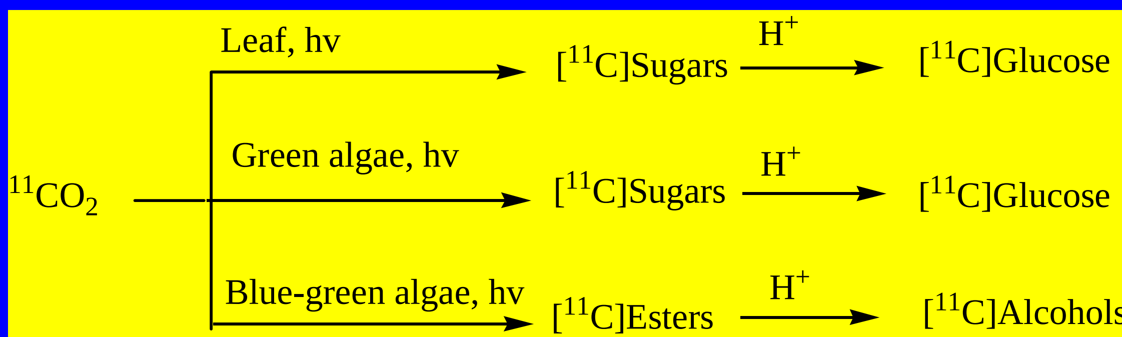
- A variety of ^{11}C-labeled amino acids have been prepared by this route *e.g.* Gly, Ala, Phe, Met, Tyr and DOPA
- Radiochemical yields are moderate.
- Note: racemic amino acids are produced.

d. [^{11}C]Carboxylation at Nitrogen



- These are alternative methods for introducing an [^{11}C]*N*-methyl group.
- R^1, R^2 are alkyl.

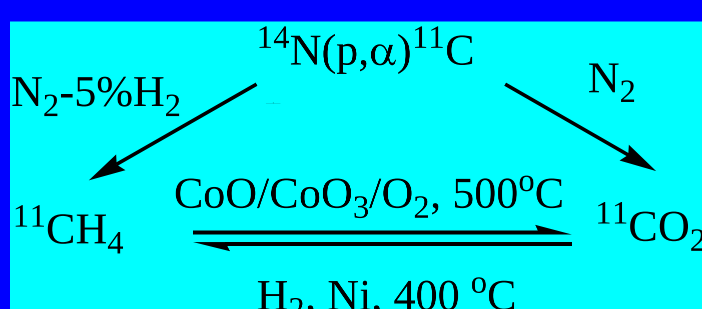
e. Photosynthesis with [^{11}C]Carbon Dioxide



- Processes are difficult to operate.
- Sugars become labeled in all positions

NCA Labeling Agents Derived from Irradiation Products

1. **Use of Cyclotron-produced [^{11}C]Carbon Dioxide to Prepare Labeling Agents**
2. **Use of Cyclotron-produced [^{11}C]Methane to Prepare Labeling Agents**



a. [^{11}C]Methanol

$$^{11}CO_2 \xrightarrow{\text{LAH/THF}} [LiAl(C^{11}CH_3)OMe_3] \xrightarrow{H_2O} {}^{11}CH_3OH$$

Preparation time: ~ 5 min.
Production efficiency: ~ 90%
Applications: preparation of [^{11}C]ethers.

b. [^{11}C]Formaldehyde

$$^{11}CO_2 \xrightarrow[\text{ii) } H_2O]{\text{i) LAH}} {}^{11}CH_3OH \xrightarrow{\text{Ag, 350 } ^{O}C} H^{11}CHO$$

Preparation time: ~ 8 min
Production efficiency: ~ 55%
Applications: ^{11}C-hydroxymethylation; reductive ^{11}C-*N*-methylation.

c. Aryl [^{11}C]Aldehydes

(Ar = Ph, 4-*t*-BuO-C_6H_4- 3,4-di-MeO-C_6H_3-, 4-MeO-C_6H_4- and 3,4-methylenedioxy-C_6H_3-)

$$^{11}CO_2 \xrightarrow{ArMgX} [Ar^{11}CO_2MgX] \xrightarrow[\text{ii) } H_2O]{\text{i) LAH}} Ar^{11}CH_2OH \xrightarrow{TBA^{+}HCrO_4^{-}} Ar^{11}CHO$$

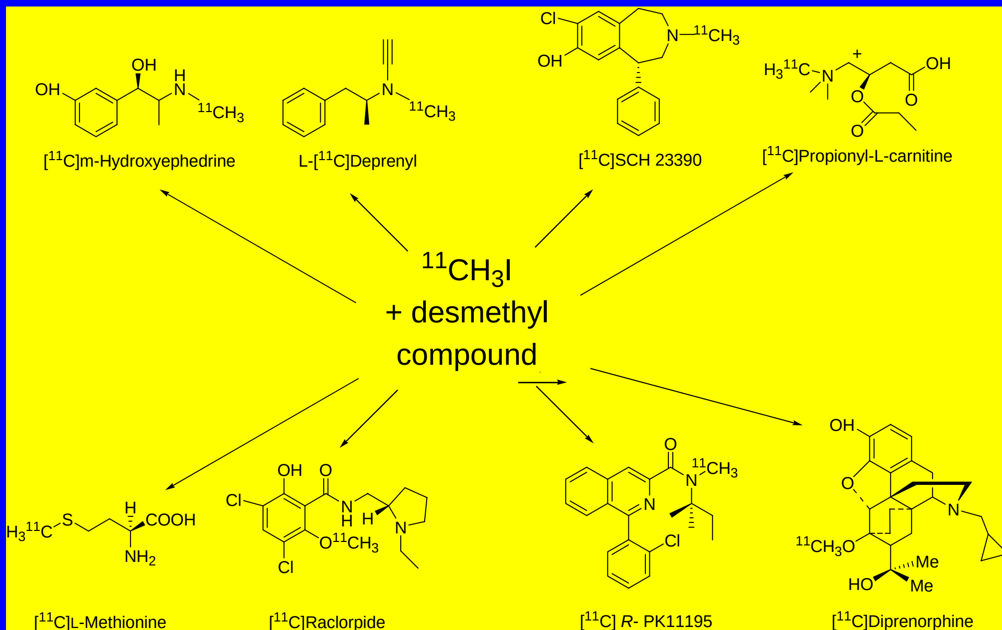
Preparation time: ~ 5 min
Production efficiency: ~ 48–86%
Applications: preparation of [^{11}C]amino acids.

d. [^{11}C]Iodomethane

$$^{11}CO_2 \xrightarrow[\text{ii) } H_2O]{\text{i) LAH}} {}^{11}CH_3OH \xrightarrow{HI} {}^{11}CH_3I$$

Preparation time: ~ 5 min
Production efficiency: ~ 80%
Applications: ^{11}C-methylation of N, O, S, Se, P; preparation of other labeling agents.

d. (Cont'd) Applications of [^{11}C]Methyl Iodide



e. Higher [^{11}C]Iodoalkanes

$$^{11}CO_2 \xrightarrow{\text{RMgX}} [RMg^{11}CO_2X] \xrightarrow[\text{ii) } H_2O]{\text{i) LAH}} R^{11}CH_2OH \xrightarrow{\text{HI}} R^{11}CH_2I$$

(R = Me, Et, Pr, 2-Pr)

[α-^{11}C]Benzyl iodides (Ar^{11}CH$_2$I; Ar = Ph, 4-anisyl, 4-Cl-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-C$_6$H$_4$-C$_6$H$_4$, veratryl, or 3,4-methylenedioxy-C$_6$H$_4$) can be prepared analogously.

$$^{11}CO_2 \xrightarrow{\text{2MeLi}} [Me_2{}^{11}C(OLi)_2] \xrightarrow[\text{ii) HI}]{\text{i) LAH}} Me_2{}^{11}CHI$$

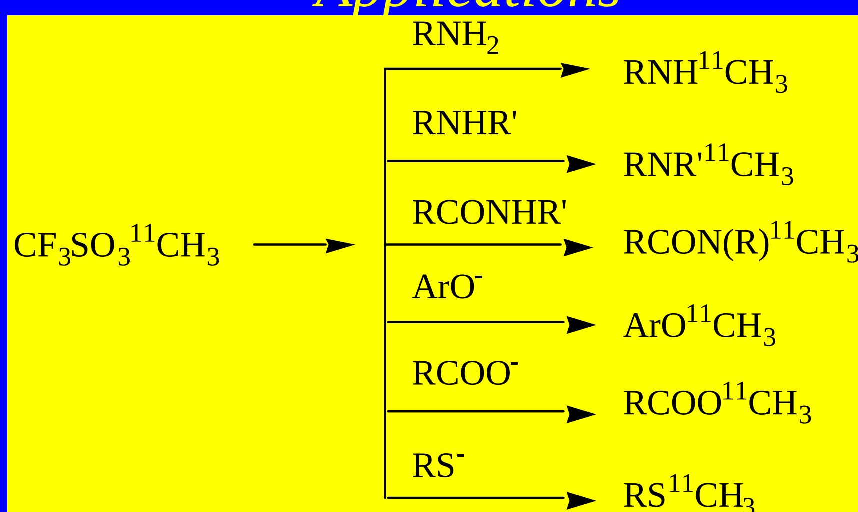
Preparation time: ~ 10–20 min
Production efficiency: ~ 10–50%
Applications: ^{11}C-alkylation of N; preparation of other labeling agents (alkyl iodides) *e.g.* [^{11}C]ethylene.

f. [^{11}C]Methyl Triflate

$$^{11}CH_3I \xrightarrow[280^oC]{CF_3SO_3Ag} {}^{11}CH_3OSO_2CF_3$$

Preparation time: ~ 10–15 min
Production efficiency: ~70%
Applications: rapid ^{11}C-methylation of N, O, S.

f. (Cont'd) [^{11}C]Methyl Triflate
- Applications



- [^{11}C]Methyl triflate is generally more reactive than [^{11}C]methyl iodide.
- Labeling reactions can be carried out with smaller amounts of precursor, at lower temperatures and over shorter times.

g. [^{11}C]Nitroalkanes

$$R^{11}CH_2I \xrightarrow{AgNO_2 \text{ or } NaNO_2} R^{11}CH_2NO_2$$

(R = H, Me, Et)

Preparation time: ~ 8–15 min
Production efficiency: ~ 30–50%
Applications: preparation of ^{11}C-labeled glucose; reaction with aromatic aldehydes.

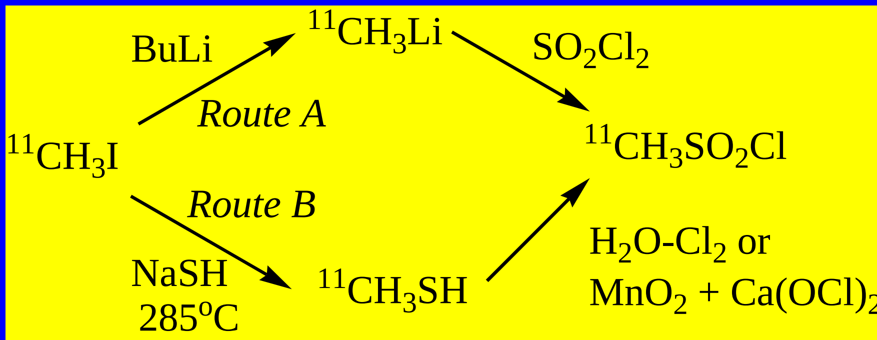
h. [^{11}C]Methyllithium

$$^{11}CH_3I \xrightarrow{BuLi} {}^{11}CH_3Li$$

- A relatively large quantity of the butylated analogue of any ^{11}C-methylated compound is co-produced when using this labeling agent, complicating product separation.
- [^{11}C]Methyllithium must be used without isolation.

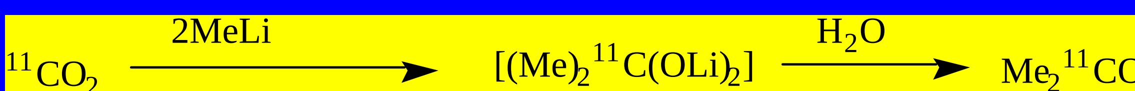
Preparation time: 15 min
Production efficiency: ~ 90%
Applications: ^{11}C-methylation of C; preparation of other labeling agents *e.g.* [^{11}C]methanesulfonyl chloride.

i. [^{11}C]Methanesulfonyl chloride



Preparation time: 15 min (Routes A, B)
Production efficiency: ~ 80% (Route A); 30% (Route B)
Applications: Preparation of [^{11}C]methanesulfonamides

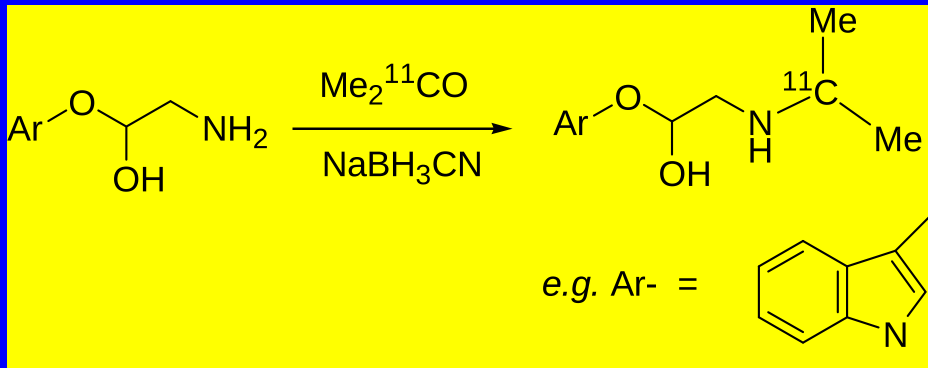
j. [2-^{11}C]Acetone



Preparation time: ~ 5 min.
Production efficiency: ~ 57%
Applications: introduction of [^{11}C]*N*-isopropyl group by reductive methylation.

j. (Cont'd) [2-^{11}C]Acetone

- Preparation of β-Receptor Radioligands



[^{11}C]Pindolol

This reductive alkylation route is an alternative to direct ^{11}C-alkylation with [^{11}C]isopropyl iodide.

k. [1-^{11}C]Acid Chlorides

Volatile acid chlorides (R = Me, Et, Pr, *cyclo*-Pr, and *cyclo*-Bu)

$^{11}CO_2$ —RMgBr→ [$R^{11}CO_2MgBr$] —PDC-DTBP→ $R^{11}COCl$

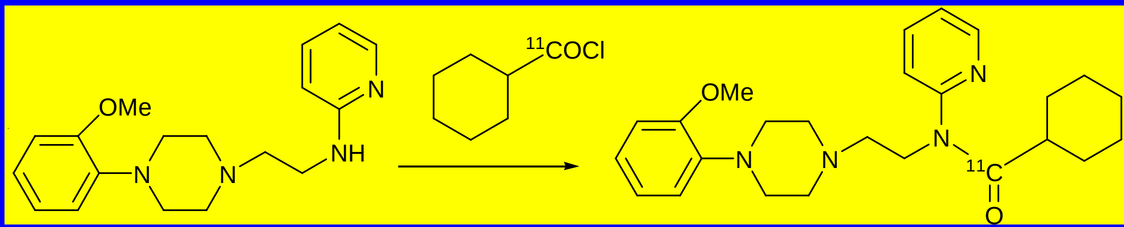
Involatile acid chlorides (R = *cyclo*-Hex, Ph)

$^{11}CO_2$ —Immobilised RMgX→ [$R^{11}COOMgX$] —$SOCl_2$→ $R^{11}COCl$

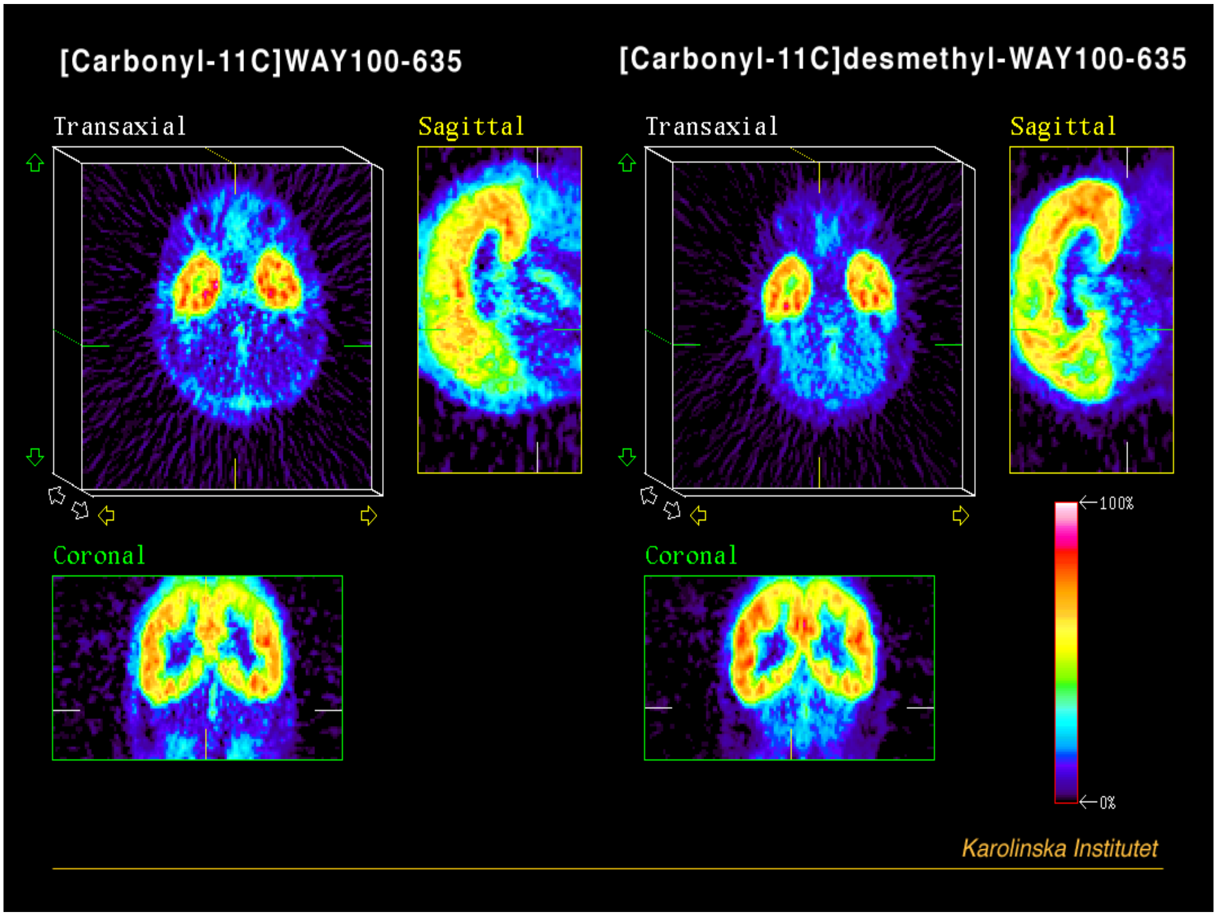
Preparation time: 15 min
Production efficiency: ~ 35–80%
Applications: ^{11}C-acylation of N, O, S.

k. (Cont'd) [1-^{11}C]Acid Chlorides

-Preparation of [carbonyl-^{11}C]WAY-100635



- [*carbonyl*-^{11}C]WAY-100635 is a 5-HT$_{1A}$ receptor radioligand
- The carbonyl position is the preferred position for labeling.

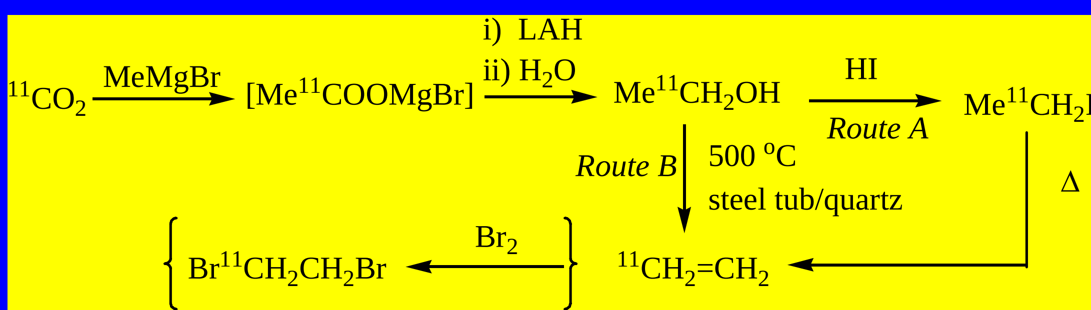


l. [^{11}C]Methyl Isocyanate

$$^{11}CH_3I \xrightarrow[180^oC]{AgCNO} {}^{11}CH_3NCO$$

Preparation time: 10 min
Production efficiency: ~ 70%
Applications: ring closure reactions.

m. [^{11}C]Ethylene



Applications: wide potential; preparation of other bifunctional labeling agents *e.g.* [^{11}C]dibromoethane.
Preparation time: 20 min
Production efficiency: 30%

n. [^{11}C]Carbon Monoxide

$$^{11}CO_2 \xrightarrow[390^{o}C]{Zn} {}^{11}CO$$

Preparation time: 5 min
Production efficiency: ~ 90%
Applications: ^{11}CO insertion ; preparation of other labeling agents
e.g. [^{11}C]phosgene.