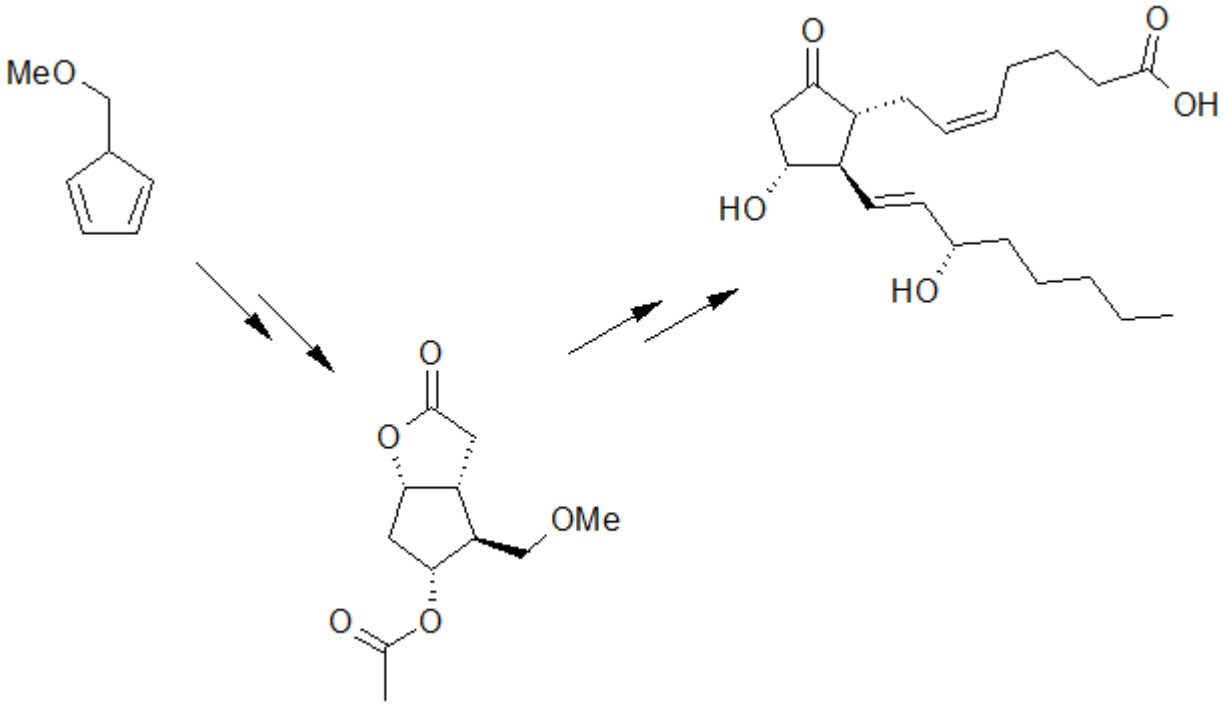
Introdução à Síntese Orgânica



Prostaglandina E2

Corey et al – JACS **1969** 91(20) 5675

Uma Breve História da Síntese Orgânica

Vitalismo – 1780

Compostos Orgânicos: somente obtidos a partir de organismos vivos

Conceito de "força vital"

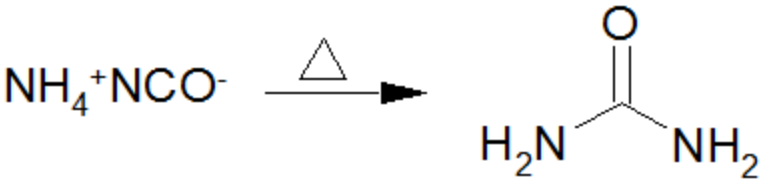
Compostos Inorgânicos: fontes minerais



Uma Breve História da Síntese Orgânica

1828-50

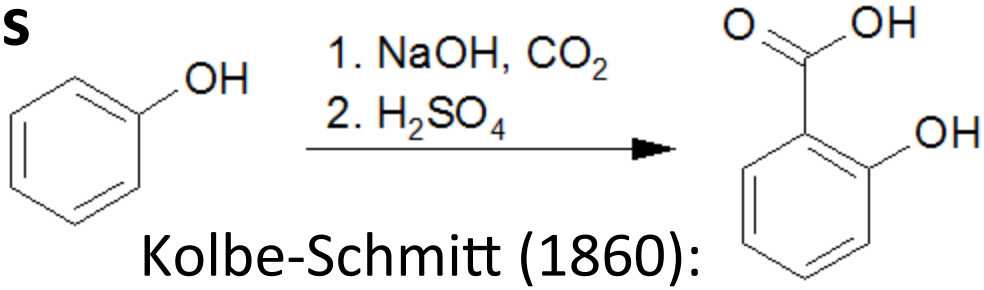
Conversão de compostos inorgânicos a orgânicos



Wöhler (1828)

Outras sínteses importantes

Kolbe (1845): síntese do ácido acético, a partir dos elementos



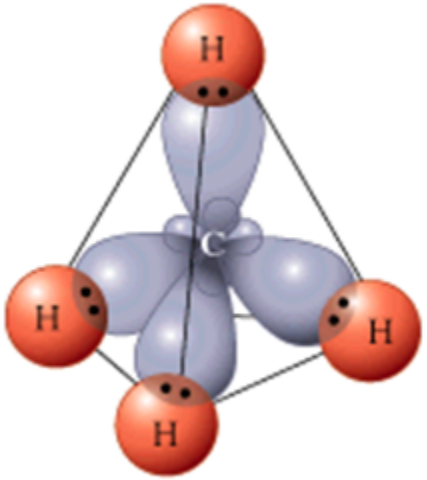
Kolbe-Schmitt (1860): Síntese do Ácido Salicílico

Berthelot (1856): síntese de acetileno a partir de hidrogênio e carbono

Uma Breve História da Síntese Orgânica

1874

Van't Hoff e Le Bel propuseram que os átomos constituintes do metano formam um tetraedro

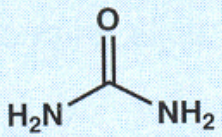


As sínteses do século XIX baseavam-se na disponibilidade de materiais de partida contendo uma grande parte do esqueleto final da molécula

1926

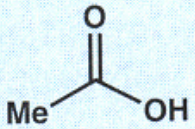
Mecânica Quântica: relação estrutura-reatividade

Sínteses Totais (1828-1929)



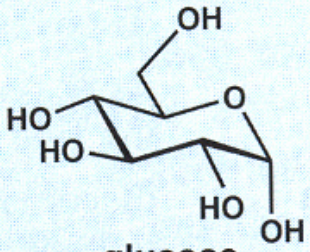
urea

(Wöhler, 1828)



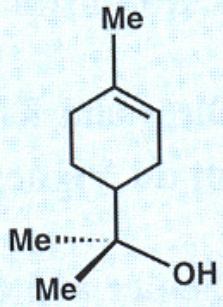
acetic acid

(Kolbe, 1845)



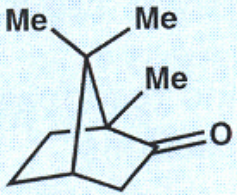
glucose

(Fischer, 1890)



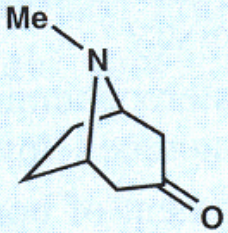
α-terpineol

(Perkin, 1904)



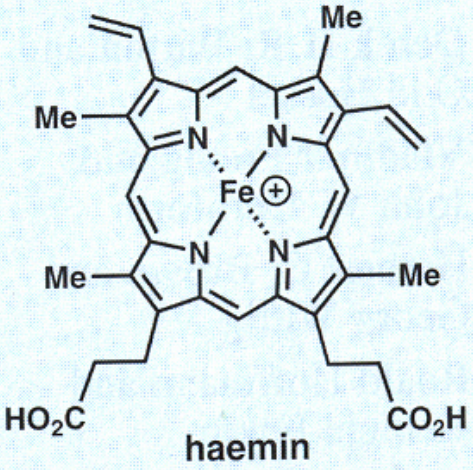
camphor

(Komppa, 1903;
Perkin, 1904)



tropinone

(Robinson, 1917)



haemin

(Fischer, 1929)

Avanços na Síntese Orgânica

Período após a 2ª Guerra Mundial

Woodward (Nobel, 1965)

(1) Formulação dos mecanismos das reações fundamentais da química orgânica de maneira detalhada, incluindo estados de transição

(2) Introdução da análise conformacional para estruturas orgânicas

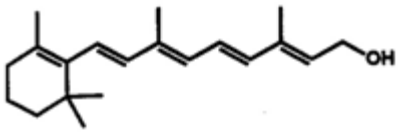
(3) Desenvolvimento da análise espectroscópica

(4) Uso de métodos cromatográficos

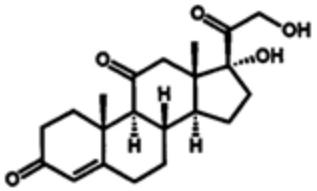
(5) Descoberta de uma série de novos reagentes

Sínteses Totais (1949-1960)

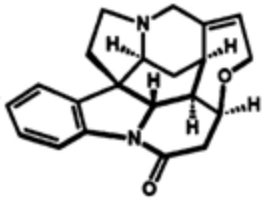
Método intuitivo era utilizado na resolução das sínteses



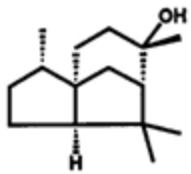
Vitamin A
(Isler, 1949)



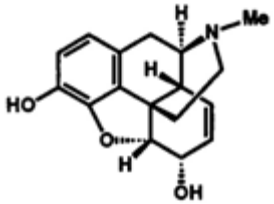
Cortisone
(Woodward, Robinson, 1951)



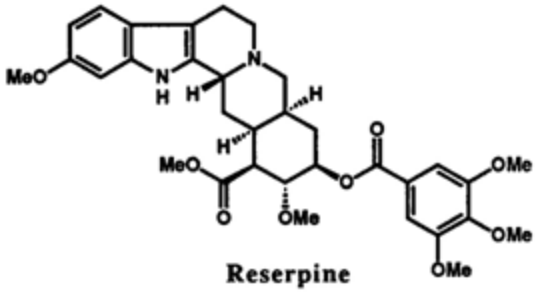
Strychnine
(Woodward, 1954)



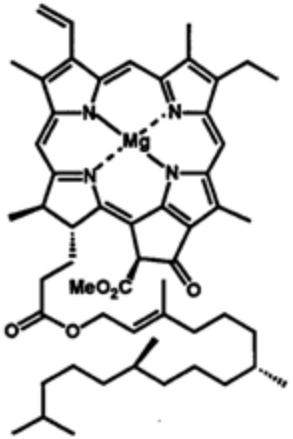
Cedrol
(Stork, 1955)



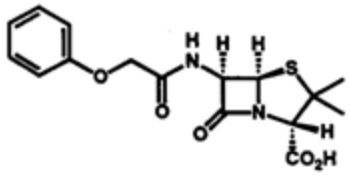
Morphine
(Gates, 1956)



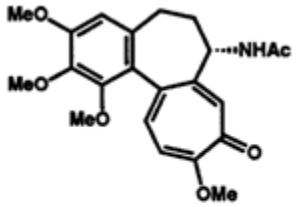
Reserpine
(Woodward, 1956)



Chlorophyll
(Woodward, 1960)



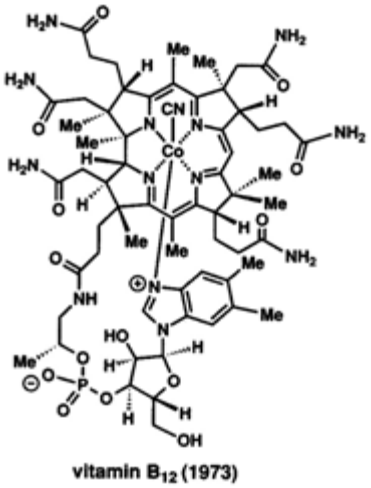
Penicillin V
(Sheehan, 1957)



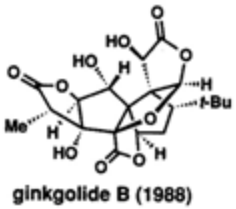
Colchicine
(Eschenmoser, 1959)

Sínteses Totais (1960-1990)

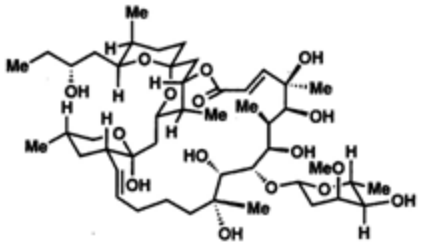
Era Corey (Nobel, 1990): *Análise Retrossintética*



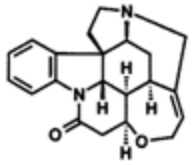
vitamin B_{12} (1973)



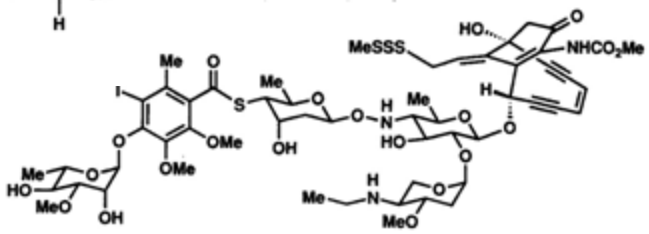
ginkgolide B (1988)



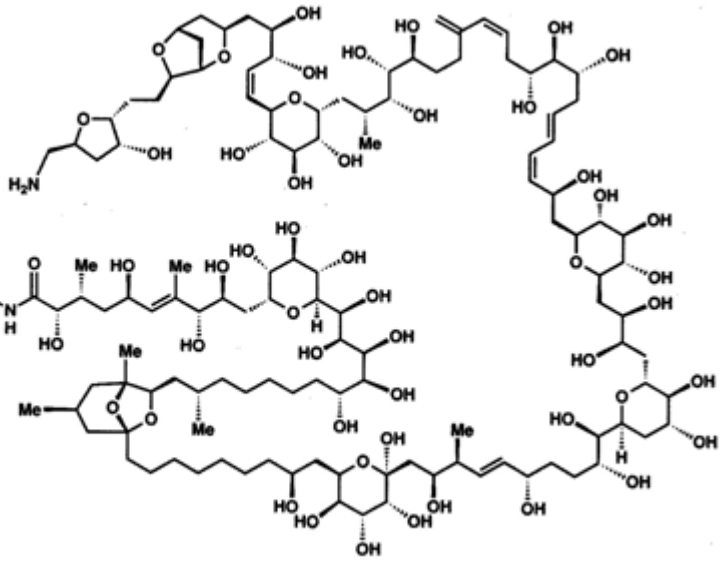
cytovaricin (1990)



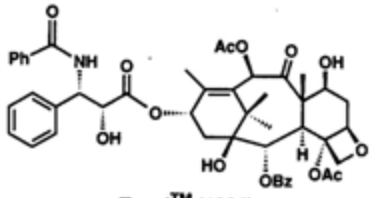
strychnine (1954)



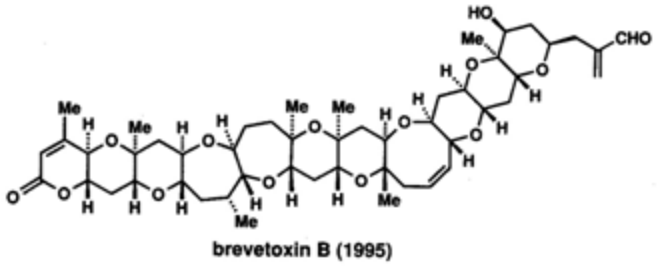
calicheamicin γ_1^I (1992)



palytoxin (1994)



Taxol™ (1994)



brevetoxin B (1995)

Definições e Conceitos Gerais

Síntese Orgânica

Ciência da construção de moléculas a partir de moléculas mais simples, usualmente disponíveis comercialmente

Síntese Total

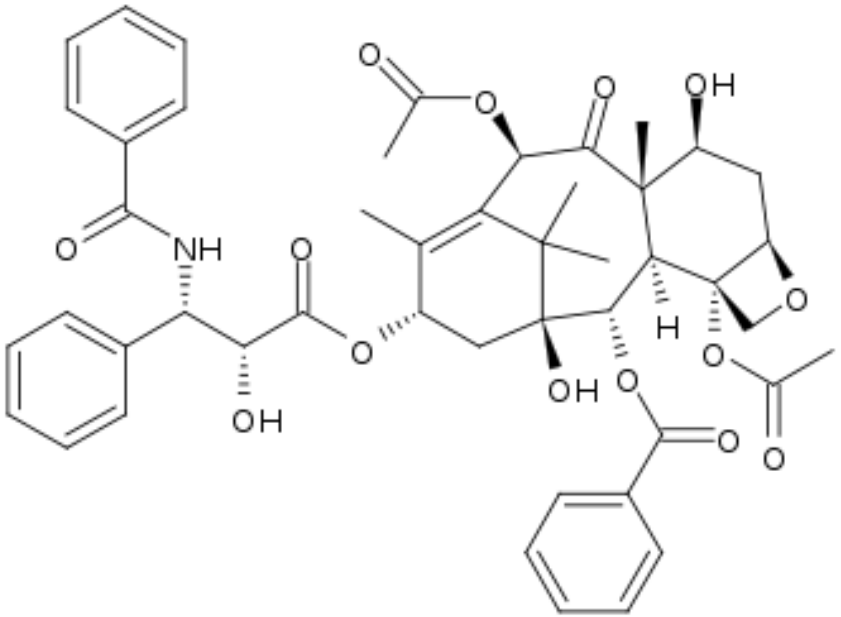
Síntese de uma molécula – natural ou não – a partir de materiais de partida relativamente mais simples

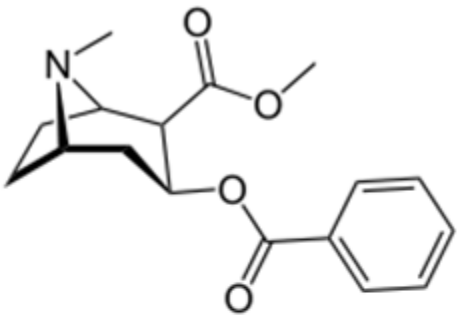
Definições e Conceitos Gerais

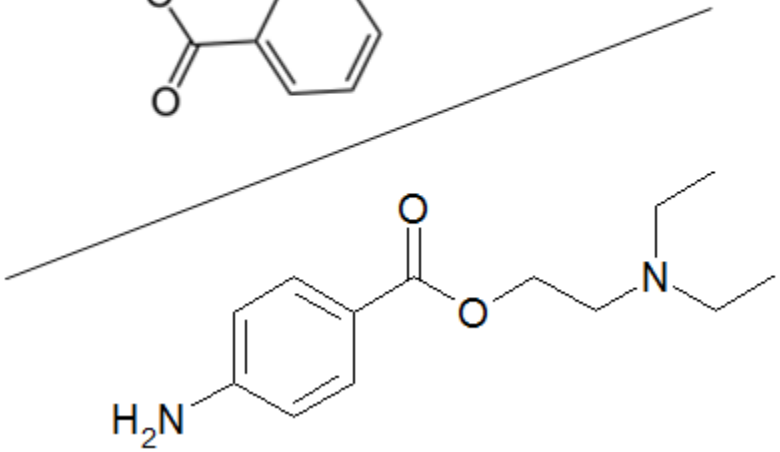
Porque sintetizar substâncias orgânicas?

Não depender de estoques naturais

Exemplo: Taxol™, tratamento de câncer







Eliminar efeitos indesejados

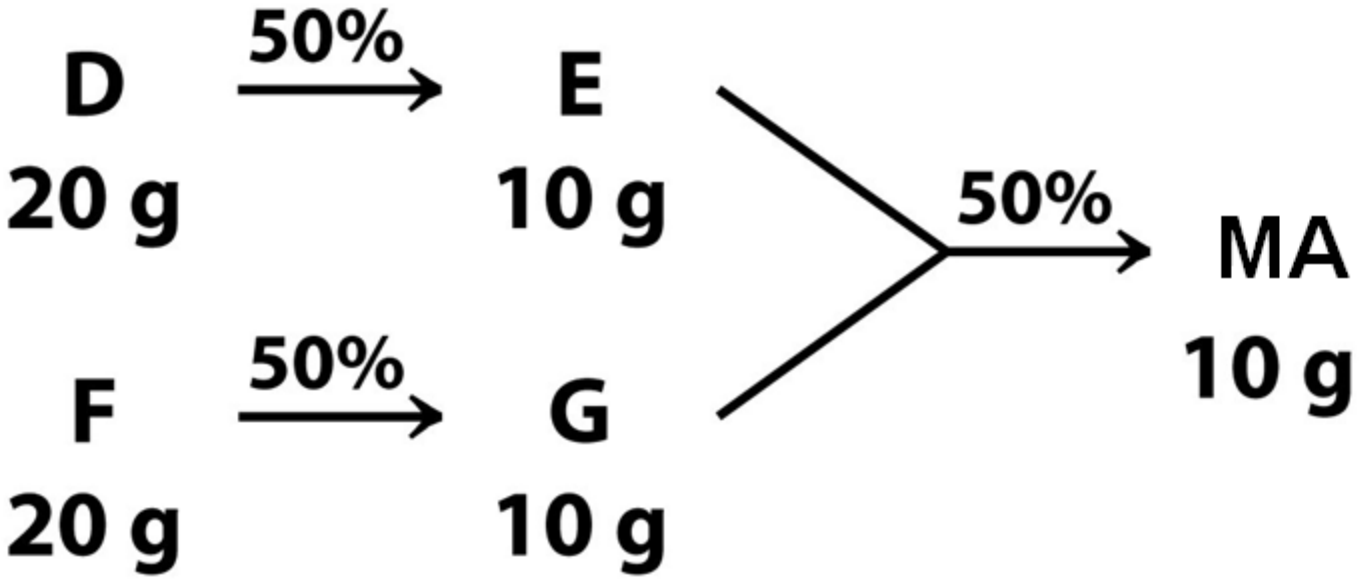
Exemplo: Cocaína e Novocaína

Abordagens em Síntese

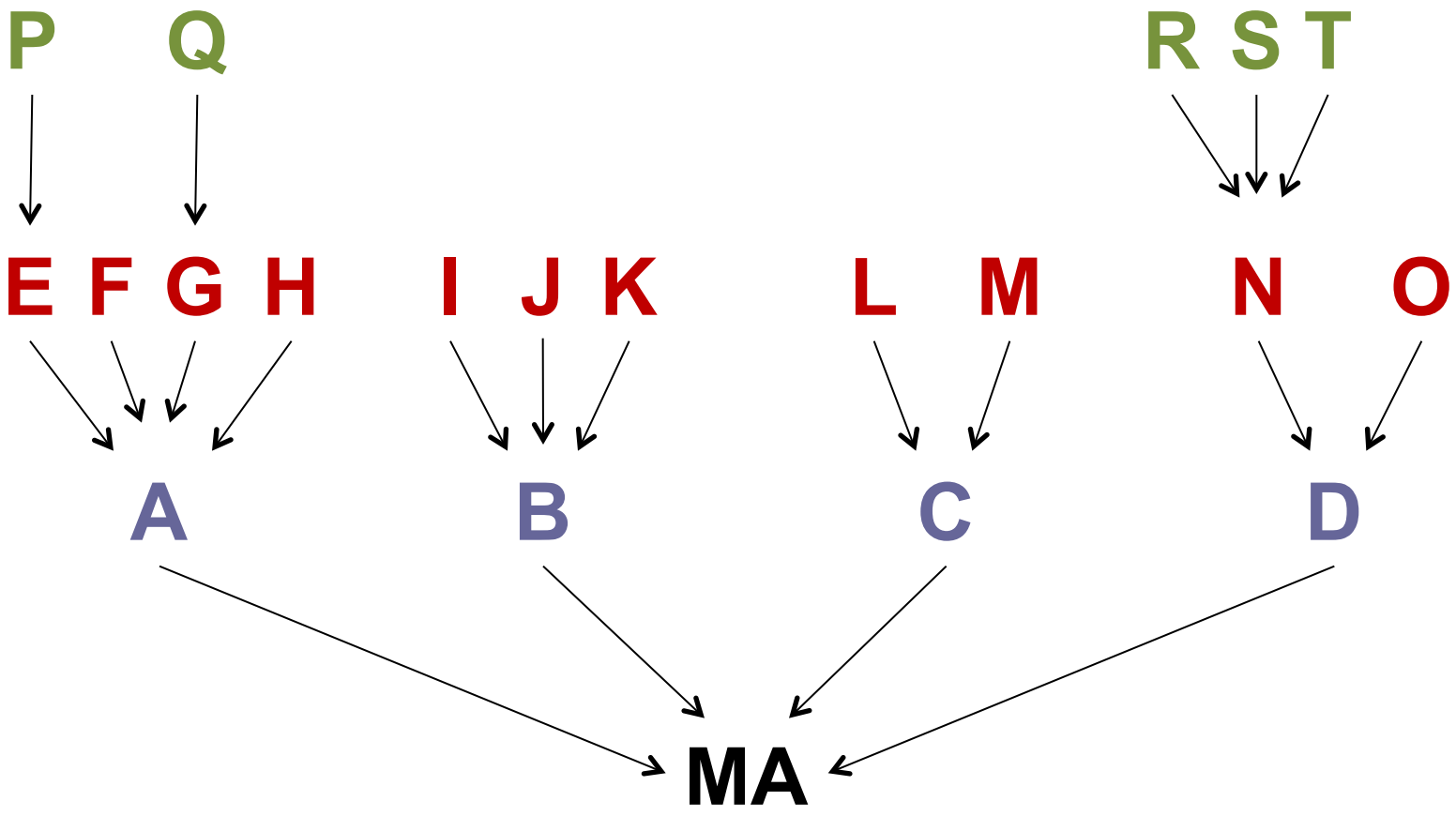
Síntese Linear de uma Molécula-Alvo (MA)



Síntese Convergente de uma Molécula-Alvo (MA)



Árvore Sintética de uma Molécula-Alvo (MA)



Estratégia em Síntese Orgânica?

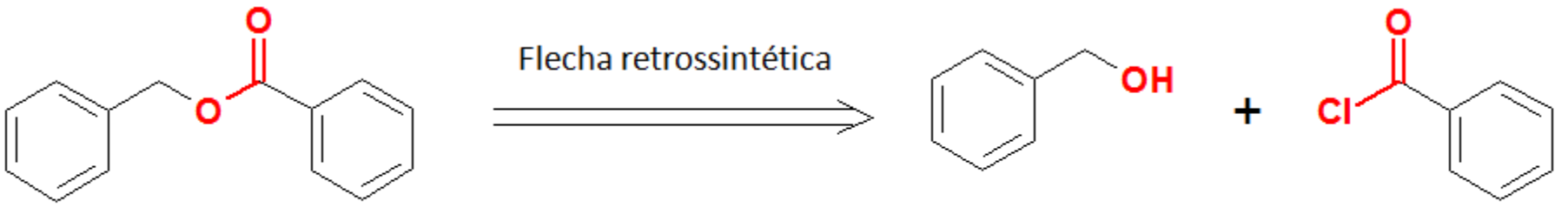




Análise Retrossintética

Estratégia para a elaboração de uma síntese

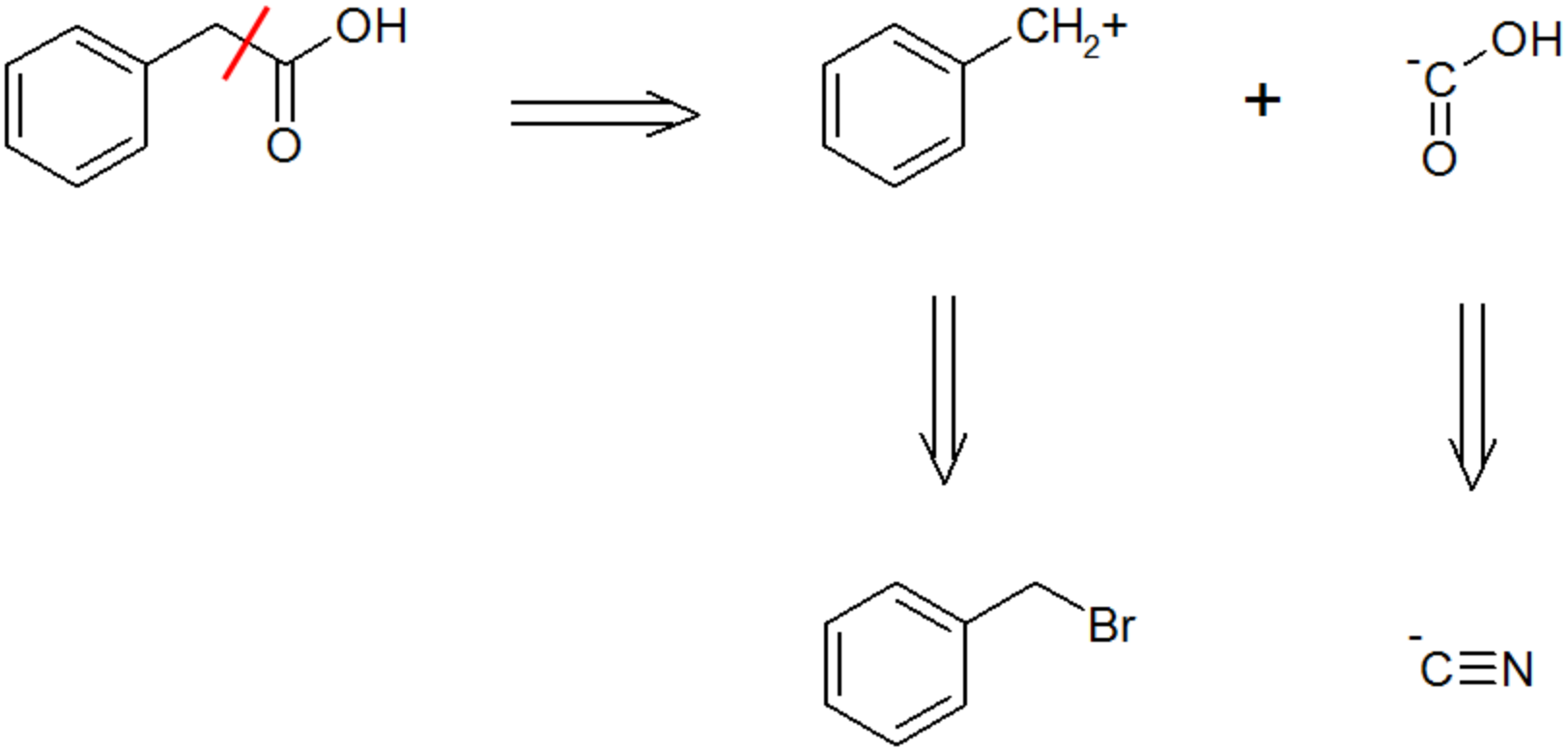
Análise retrossintética é uma técnica de resolução de problemas para transformar a estrutura de um alvo sintético em uma seqüência de materiais de partida progressivamente mais simples



Benzoato de benzila | Álcool benzílico | Cloreto de benzoíla

Análise Retrossintética

Desconexão

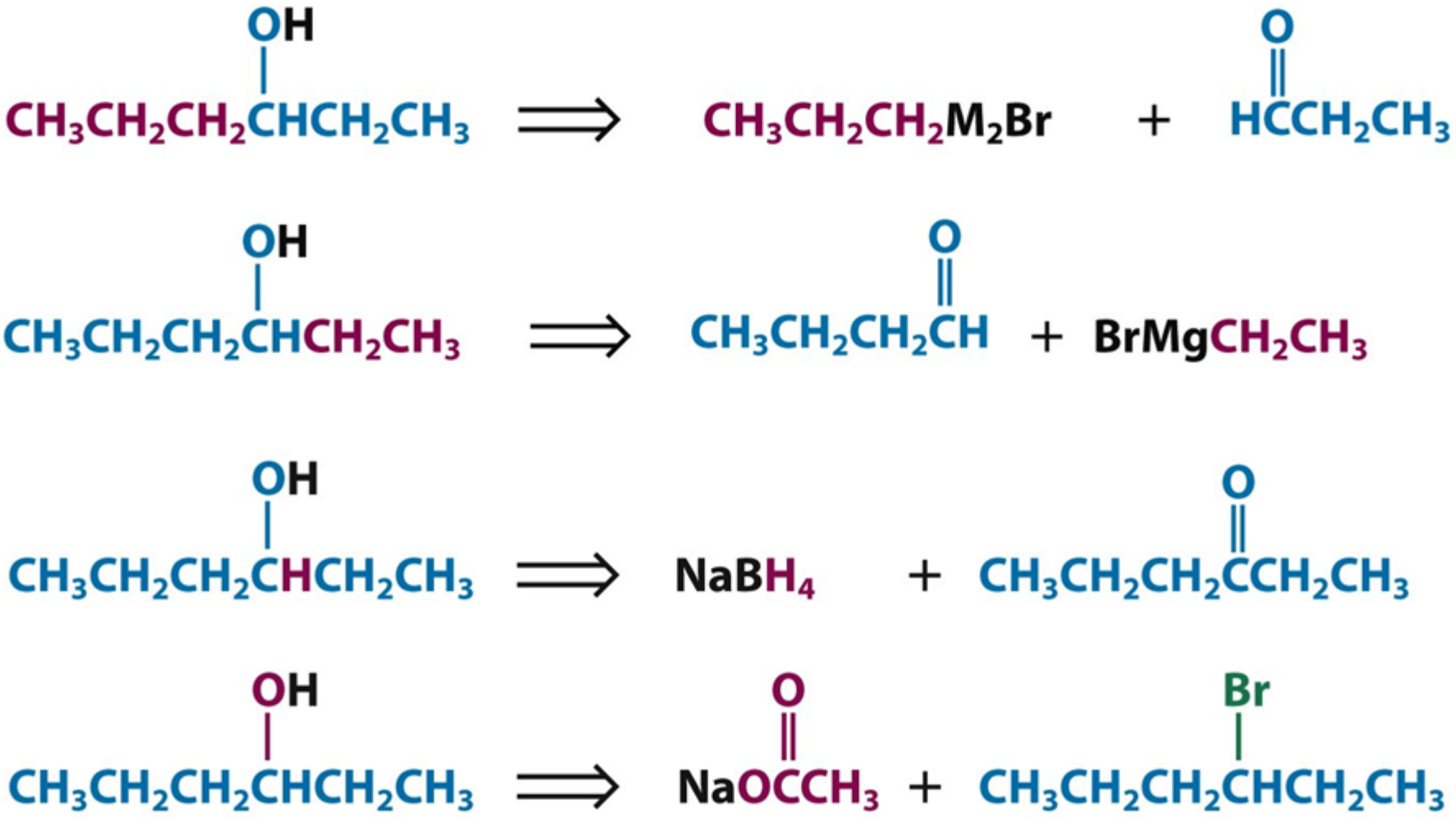


Sintons

Equivalentes sintéticos

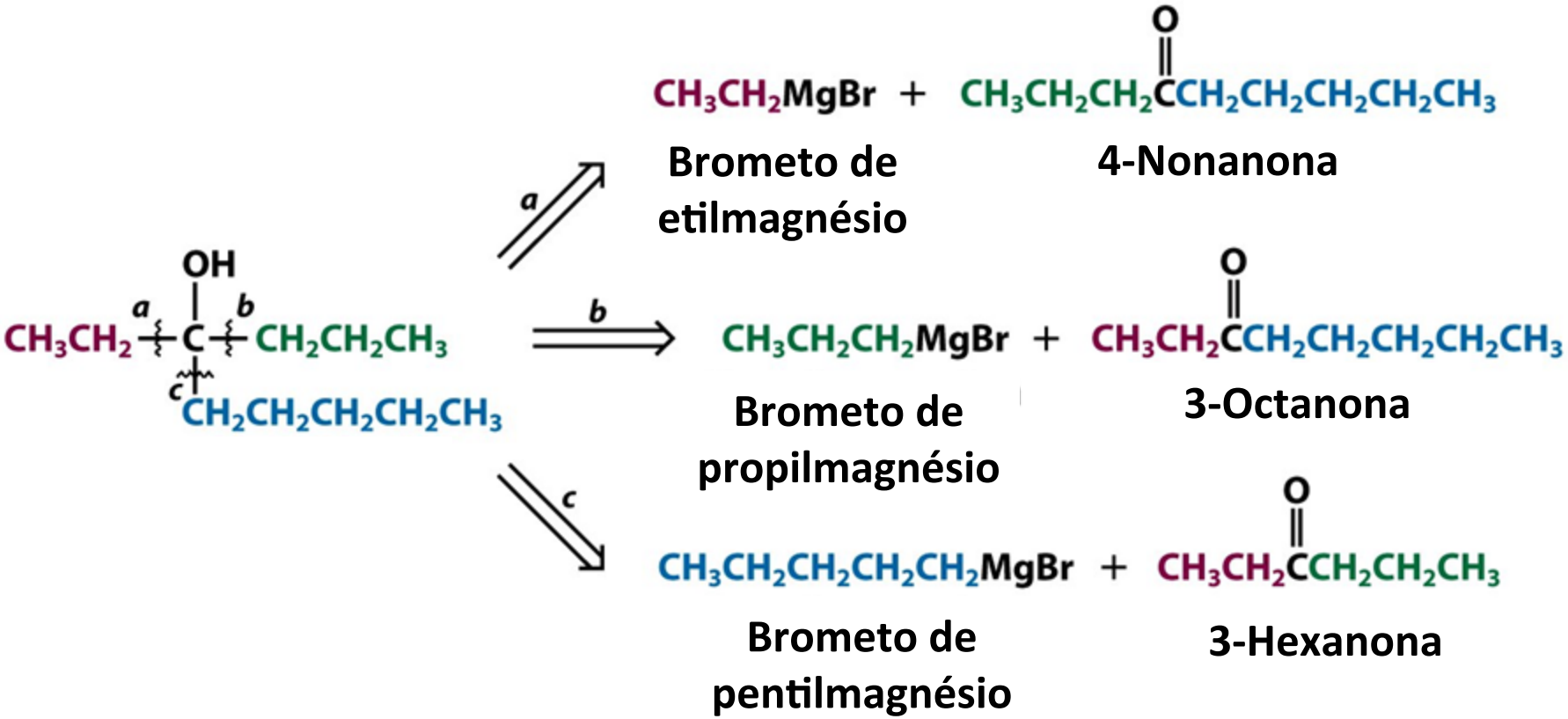
Análise Retrossintética

3-Hexanol



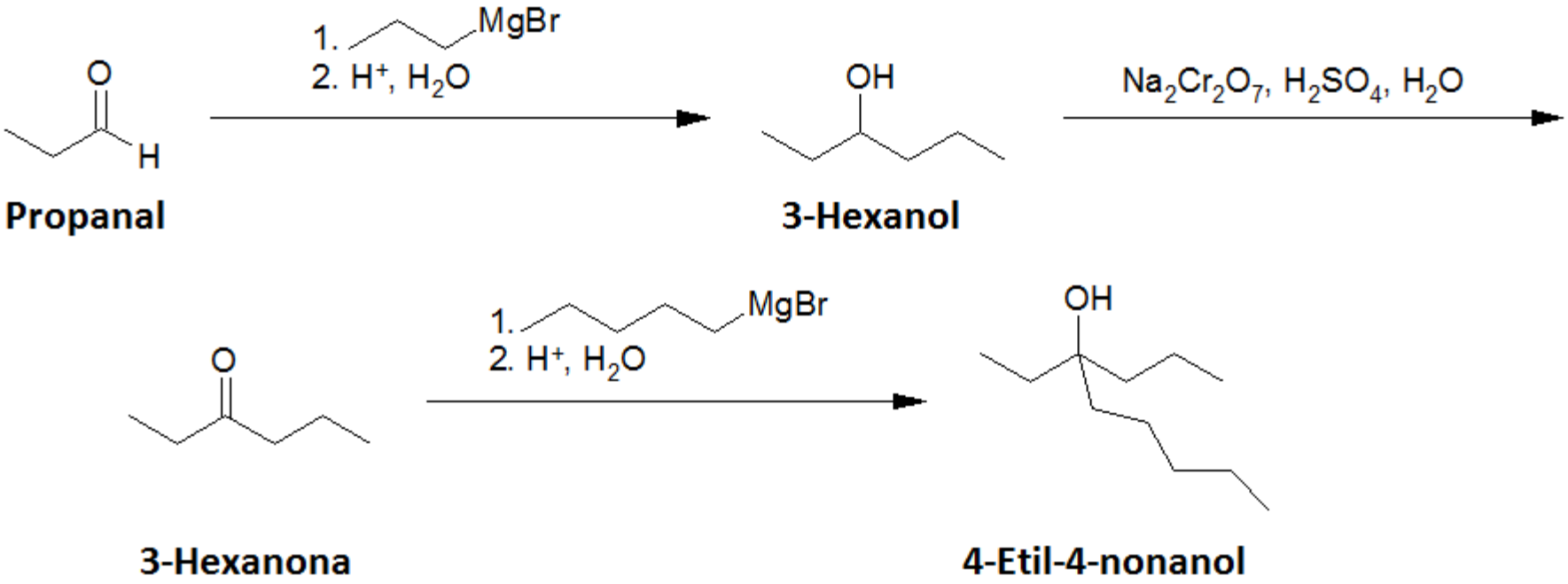
Análise Retrossintética

4-Etil-4-nonanol



Análise Retrossintética

4-Etil-4-nonanol

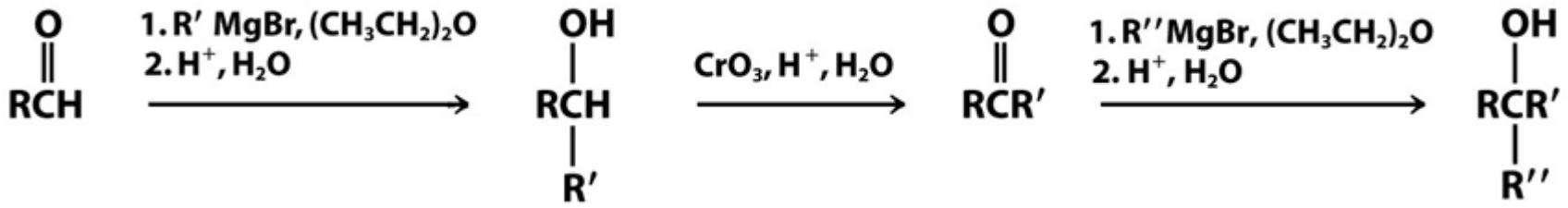


Propanal **3-Hexanol**

3-Hexanona **4-Etil-4-nonanol**

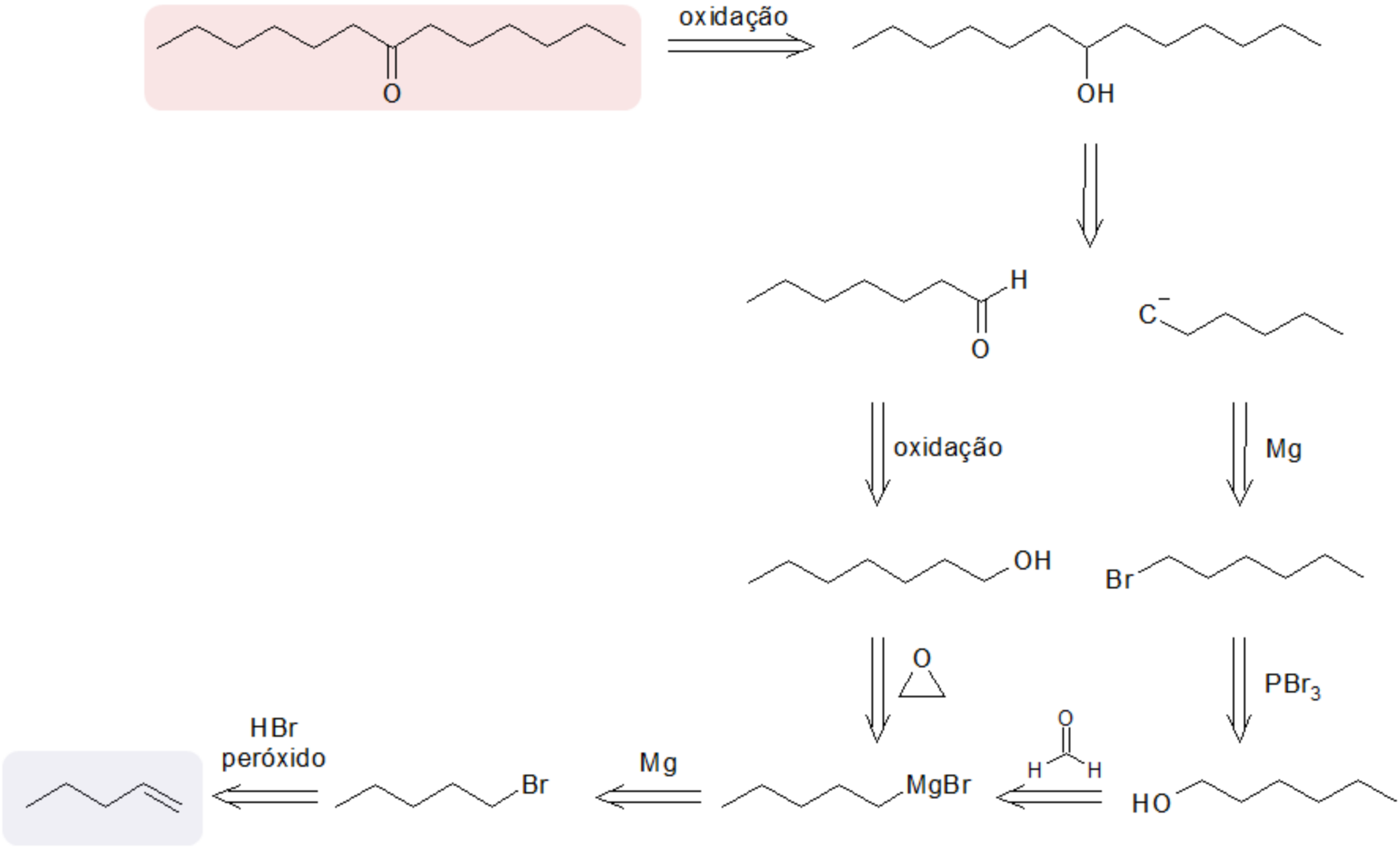
Análise Retrossintética

Oxidação de álcoois em síntese orgânica

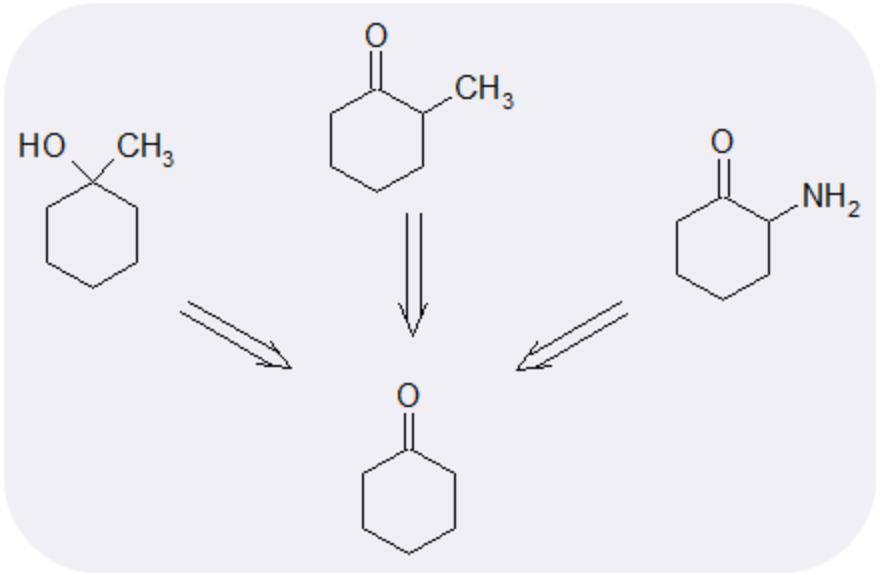


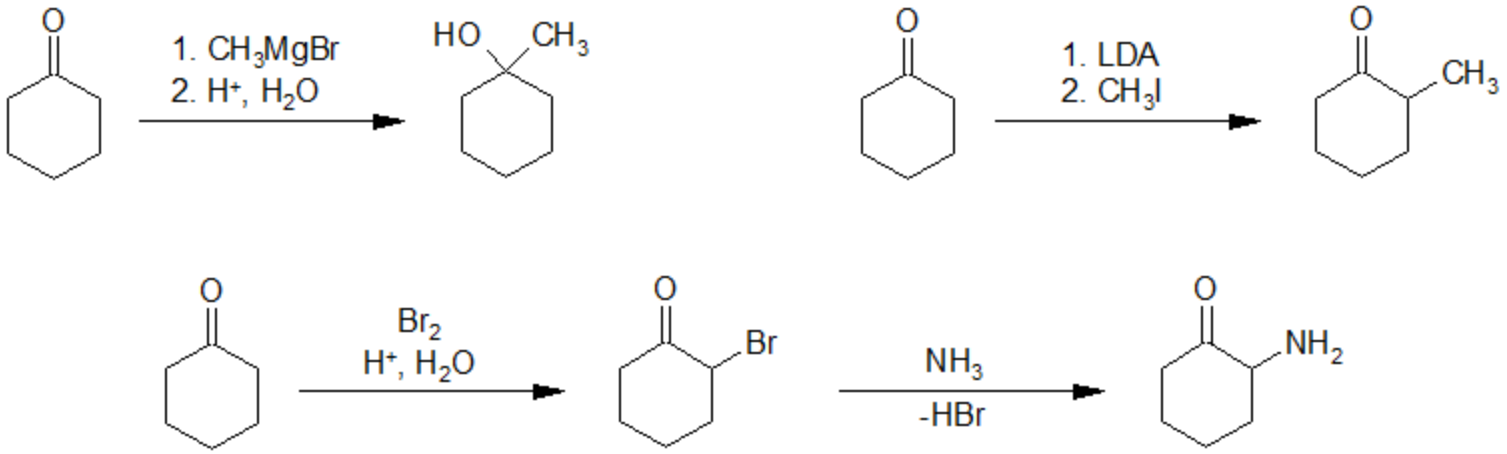
Aldeído — **Álcool secundário** — **Cetona** — **Álcool terciário**

Análise Retrossintética



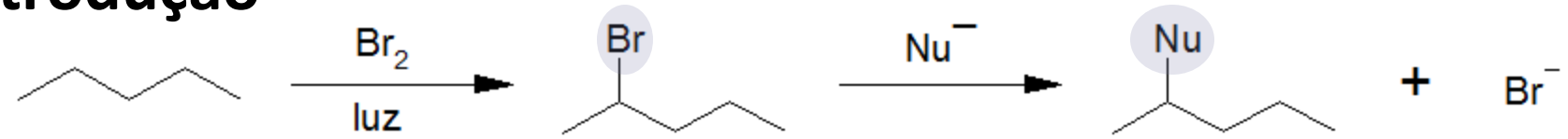
Análise Retrossintética



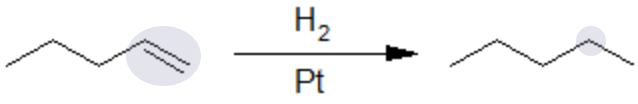


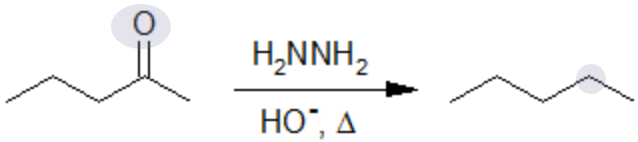
Grupos Funcionais

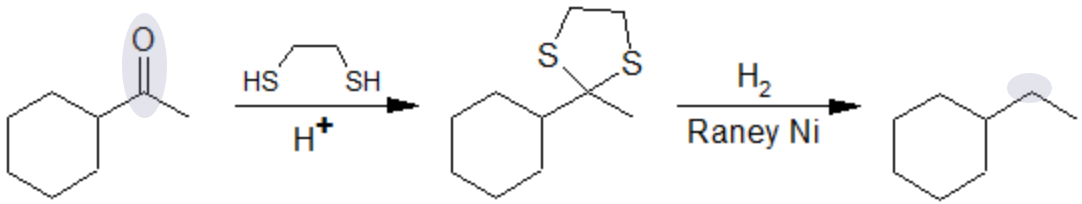
Introdução

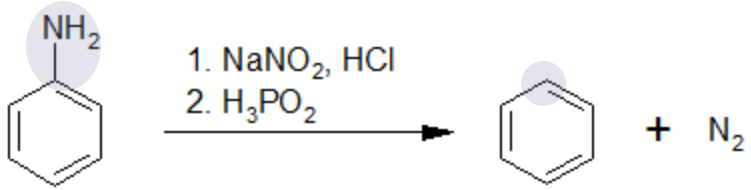


Remoção



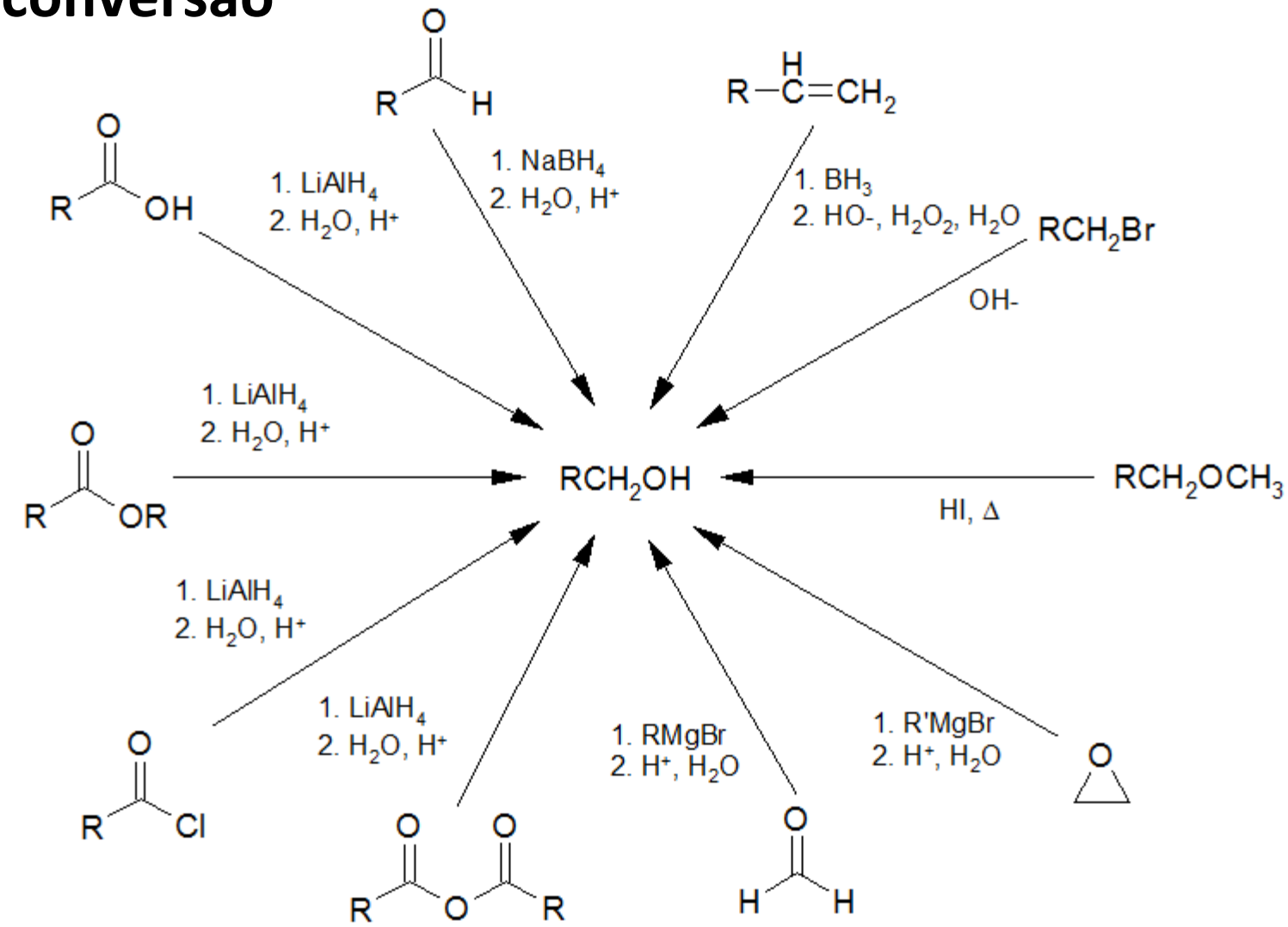






Grupos Funcionais

Interconversão



Adição de Uma Unidade de Carbono



Grupo Alquila

+



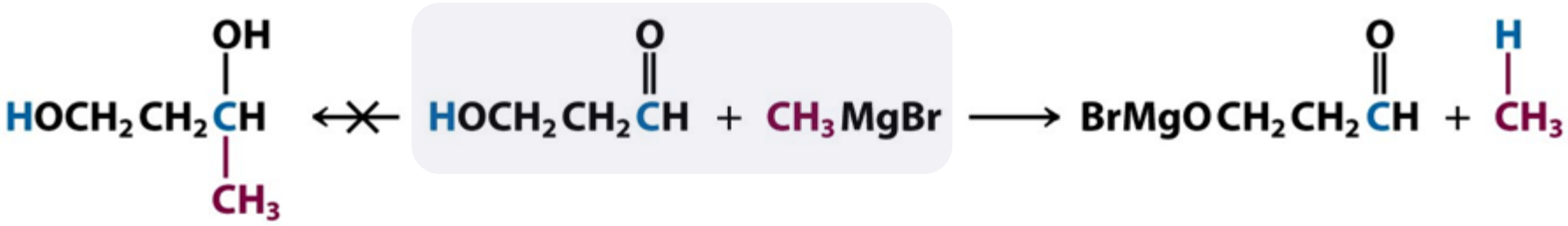
Uma Unidade de Carbono

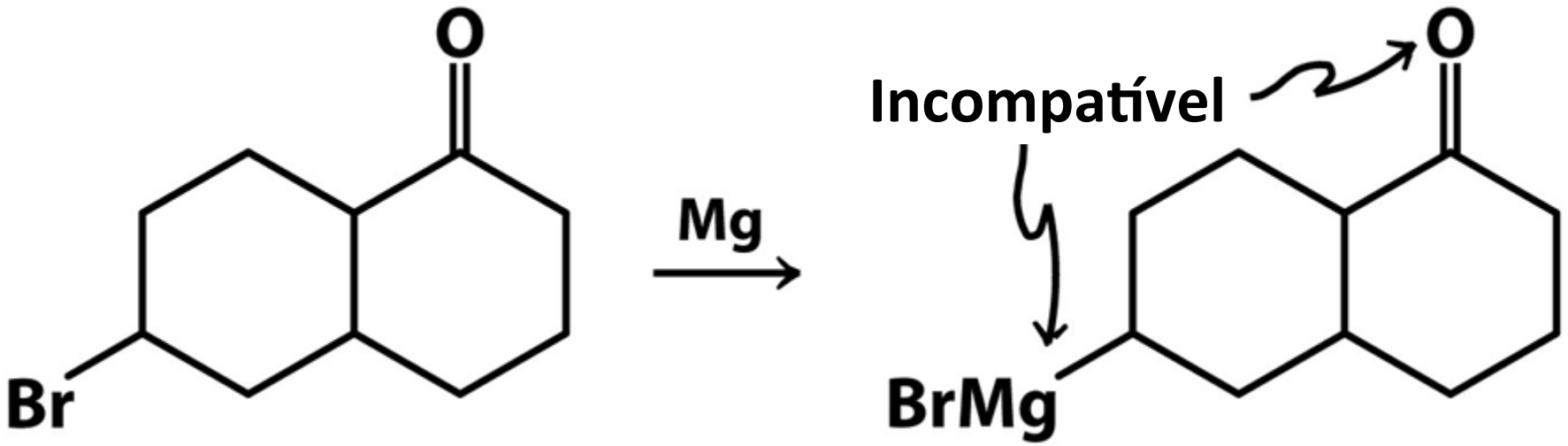
↓



Limitações

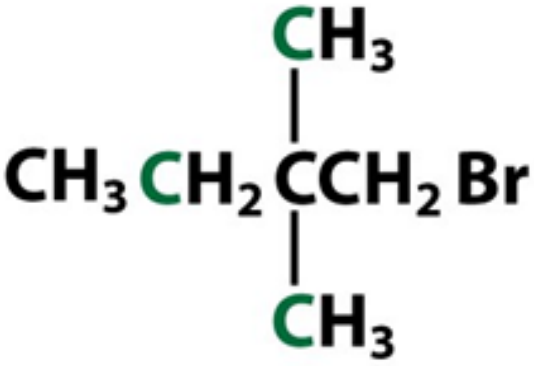
Incompatibilidade

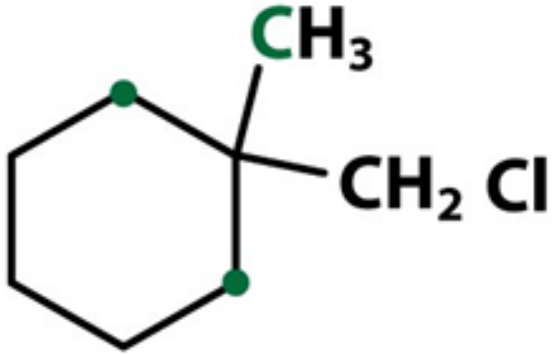


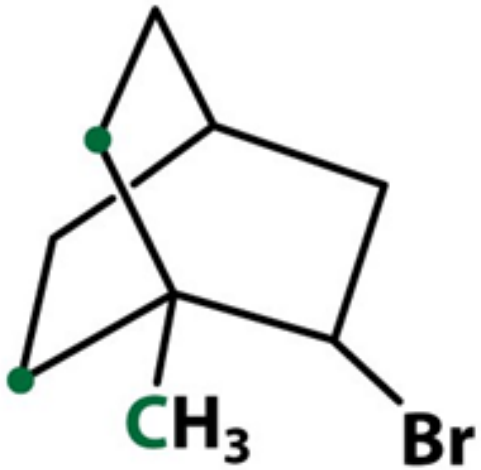


Limitações

Haloalcanos 2,2-disubstituídos impedidos







Estratégias de Síntese de Benzenos Trisubstituídos

Síntese de Benzenos Trisubstituídos (1)

Estratégia

(1)Desenhar a molécula-alvo

(2)Identificar os substituintes: -Br; -CH_3; -NO_2

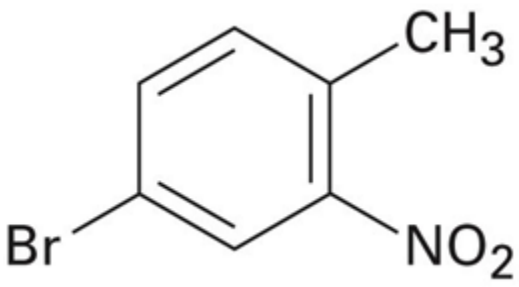
(3) Verificar como cada grupo pode ser inserido separadamente:

-Br: bromação com $Br_2/FeBr_3$

-CH_3: alquilação de Friedel-Crafts com $CH_3Cl/AlCl_3$

-NO_2: nitração com HNO_3/H_2SO_4

(4)Desenhar a reação retrossinteticamente

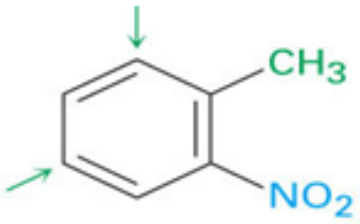


4-Bromo-2-nitrotolueno

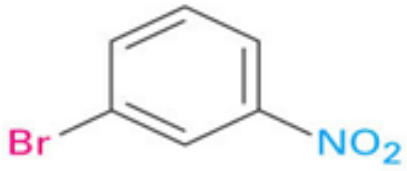
Síntese de Benzenos Trisubstituídos (1)

Solução

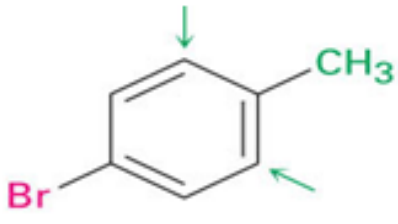
Conversão de um benzeno disubstituído para um trisubstituído



***o*-Nitrotolueno**
Fornece dois isômeros de bromação



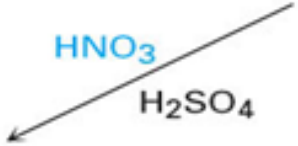
***m*-Bromonitrobenzeno**
Anel desativado frente uma Friedel-Crafts

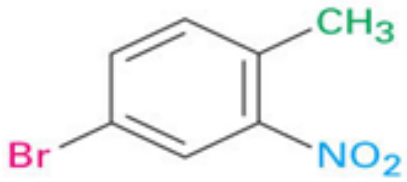


***p*-Bromotolueno**
Fornece somente um isômero de nitração







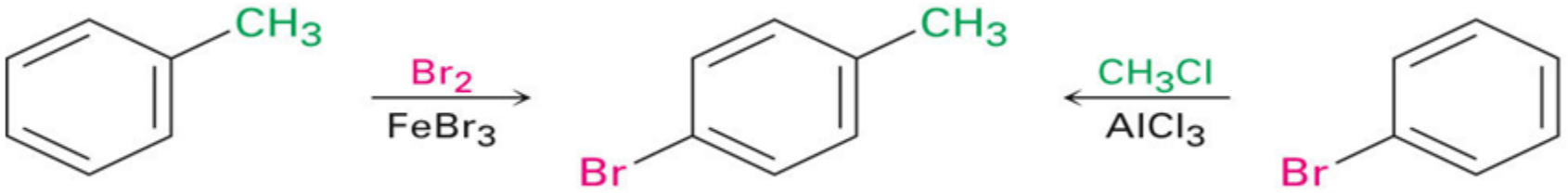


4-Bromo-2-nitrotolueno

Síntese de Benzenos Trisubstituídos (1)

Solução

Precursores do *p*-Bromotolueno: Tolueno & Bromobenzeno



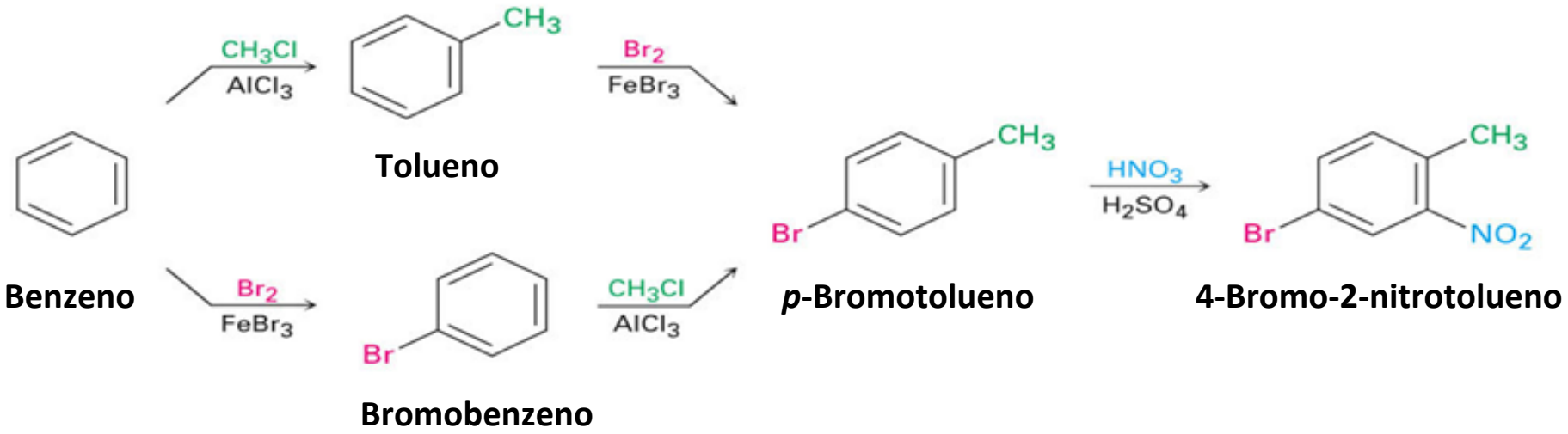
Tolueno | ***p*-Bromotolueno** | **Bromobenzeno**

(Isômero orto como produto secundário)

Síntese de Benzenos Trisubstituídos (1)

Solução

Precursores do Tolueno & Bromobenzeno: Benzeno



Síntese de Benzenos Trisubstituídos (2)

Estratégia

(1)Desenhar a molécula-alvo

(2)Identificar os substituintes: -Cl; -$CH_2CH_2CH_3$; -SO_3H

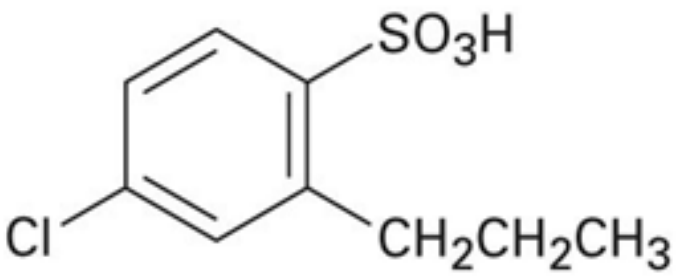
(3) Verificar como cada grupo pode ser inserido separadamente:

-Cl: bromação com $Cl_2/FeCl_3$

-$CH_2CH_2CH_3$: acilação de Friedel-Crafts com $CH_3CH_2COCl/AlCl_3$, seguida de uma redução com H_2/Pd

-SO_3H: sulfonação com SO_3/H_2SO_4

(4)Desenhar a reação retrossinteticamente

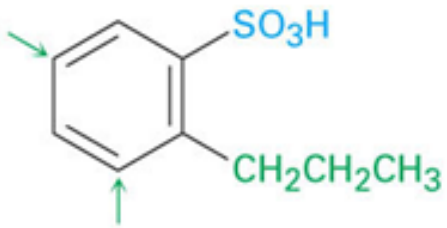


Ácido 4-cloro-2-propilbenzenosulfônico

Síntese de Benzenos Trisubstituídos (2)

Solução

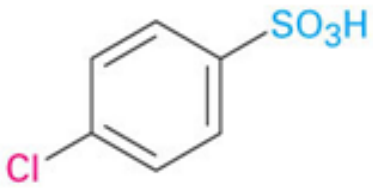
Conversão de um benzeno disubstituído para um trisubstituído



***Ácido-o*-propilbenzeno-sulfônico**

Não fornece o isômero desejado na cloração

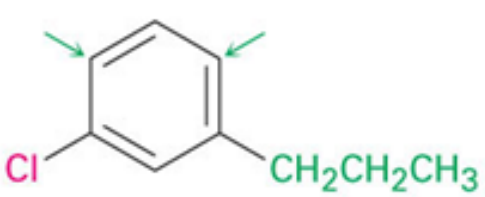




***Ácido-p*-clorobenzeno-sulfônico**

Anel desativado frente uma Friedel-Crafts

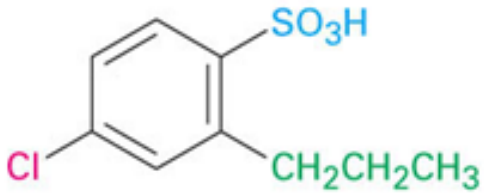




***m*-cloropropilbenzeno**

Fornece o produto desejado de sulfonação





Ácido 4-cloro-2-propilbenzenosulfônico

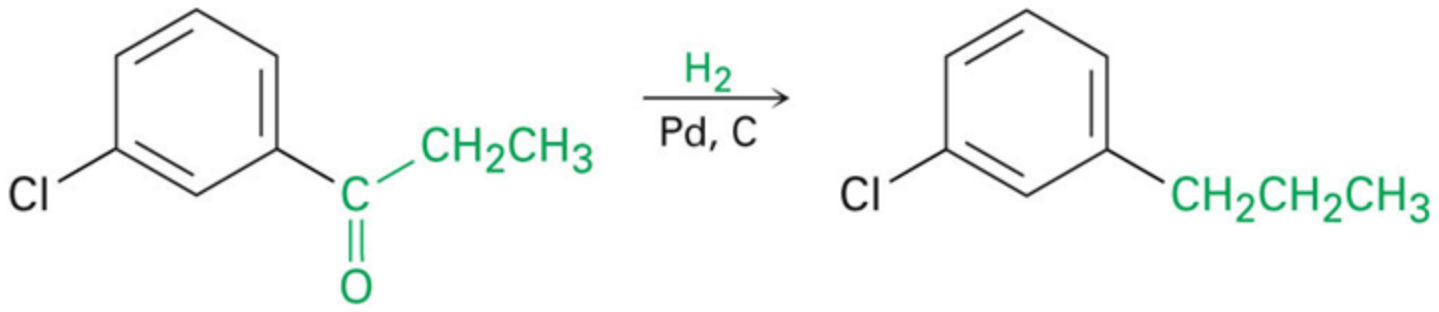
Síntese de Benzenos Trisubstituídos (2)

Solução

Precursor do *m*-cloropropilbenzeno:

(1)Substituintes com uma relação meta – o primeiro substituinte deve ser um *m*-dirigente, para o segundo entrar na posição desejada

(2)Como grupos alquílicos primários não podem ser introduzidos diretamente com uma alquilação de Friedel-Crafts, o precursor do *m*-cloropropilbenzeno é, provavelmente, a *m*-cloropropilfenona

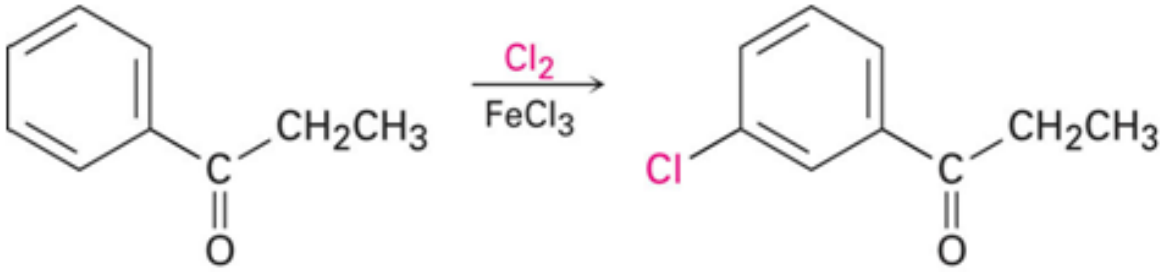


***m*-Cloropropilfenona** ***m*-Cloropropilbenzeno**

Síntese de Benzenos Trisubstituídos (2)

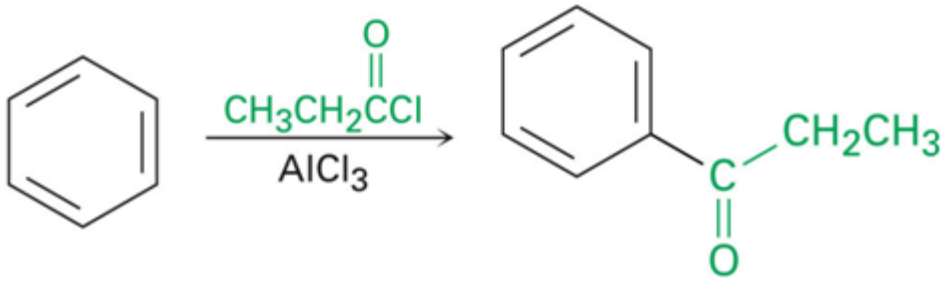
Solução

Precursor da *m*-cloropropilfenona



Propilfenona **m-Cloropropilfenona**

Precursor da *m*-cloropropilfenona

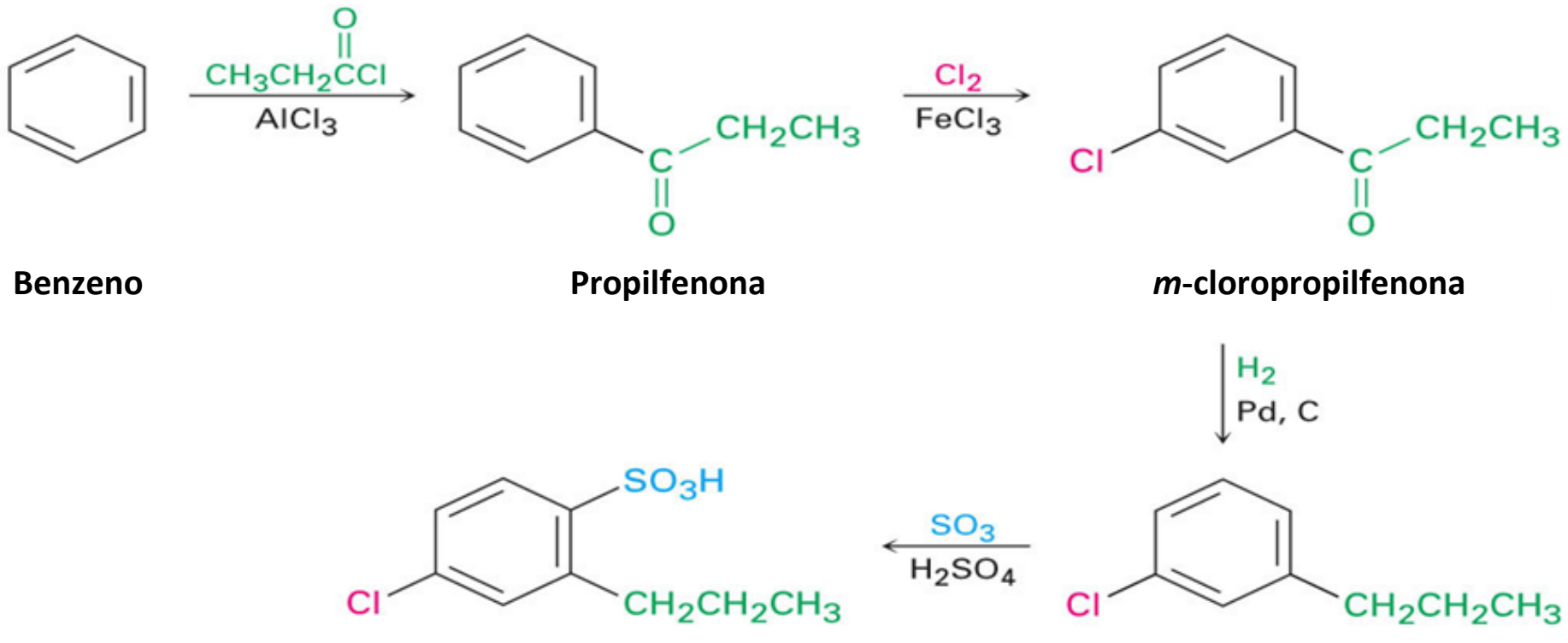


Benzeno **Propilfenona**

Síntese de Benzenos Trisubstituídos (2)

Solução

A síntese final é uma reação com quatro etapas, partindo de benzeno



Benzeno

Propilfenona

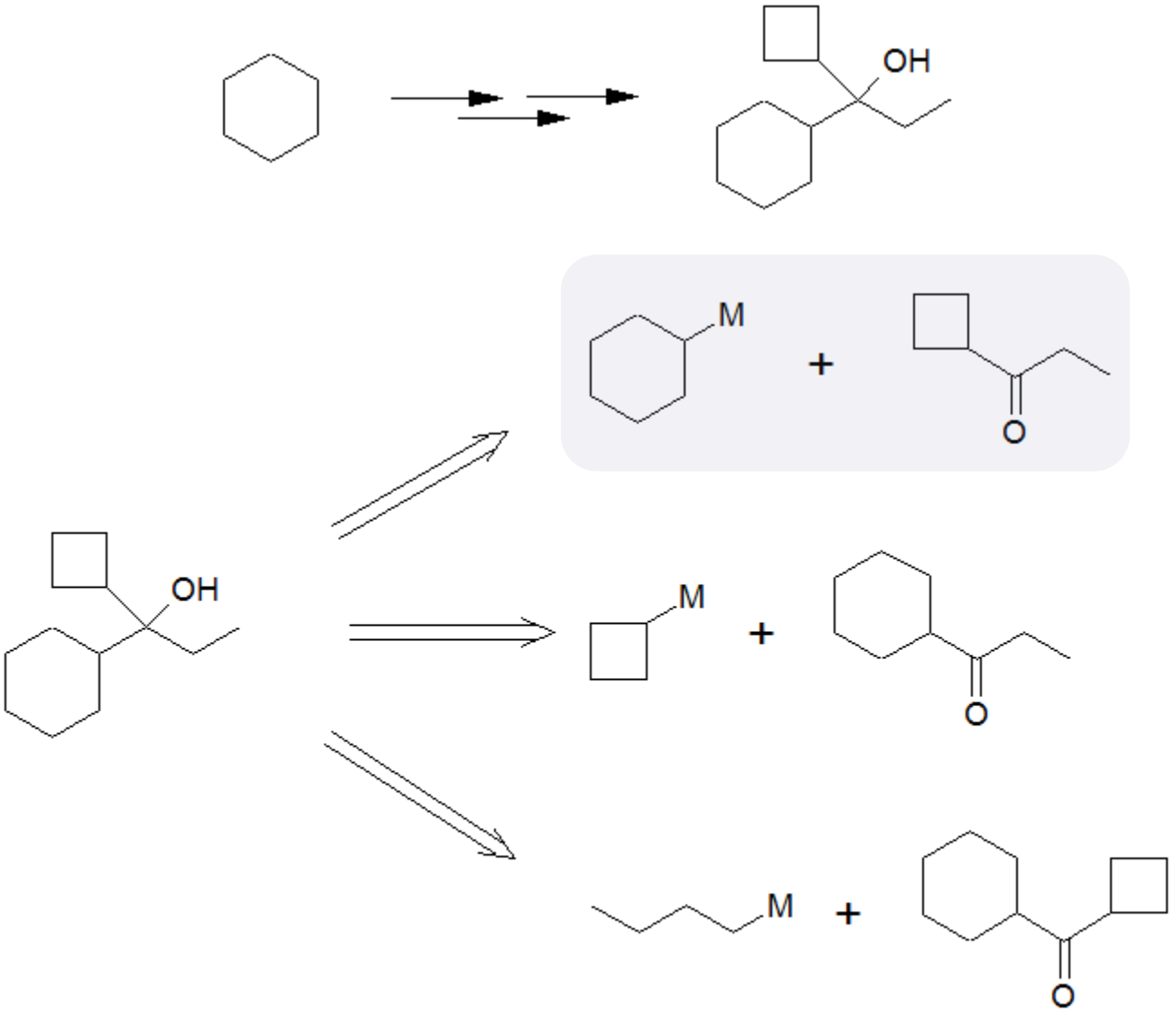
***m*-cloropropilfenona**

***m*-cloropropilbenzeno**

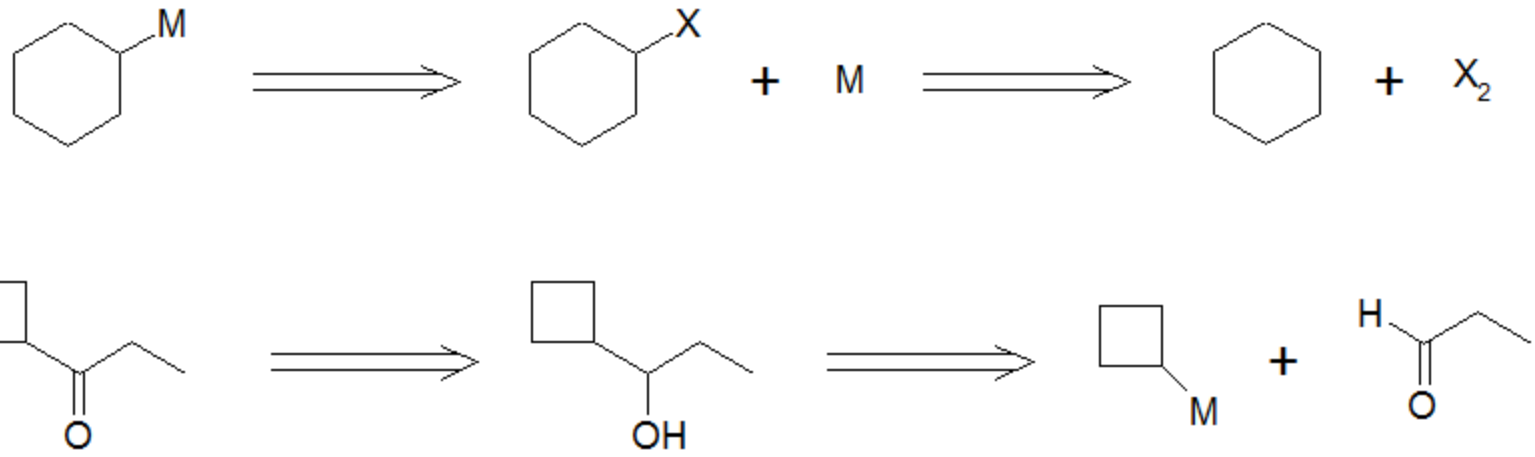
Ácido 4-cloro-2-propilbenzenosulfônico

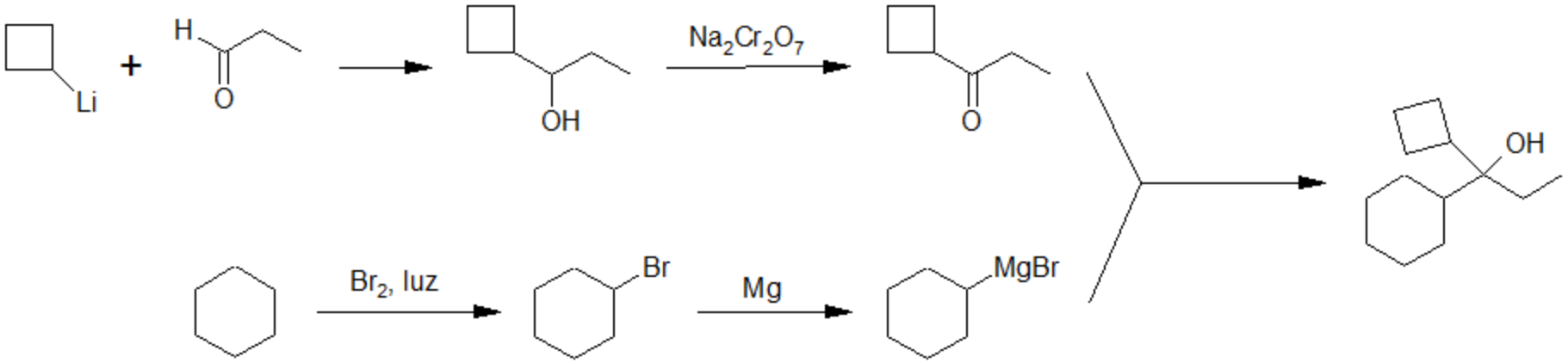
Estratégias de Síntese de Álcoois Terciários

Síntese de Álcoois Terciários



Síntese de Álcoois Terciários

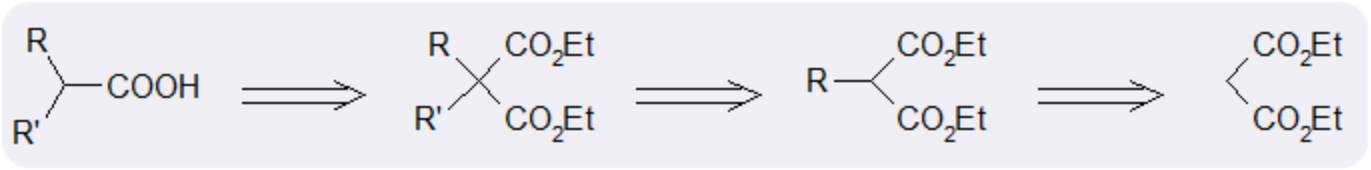


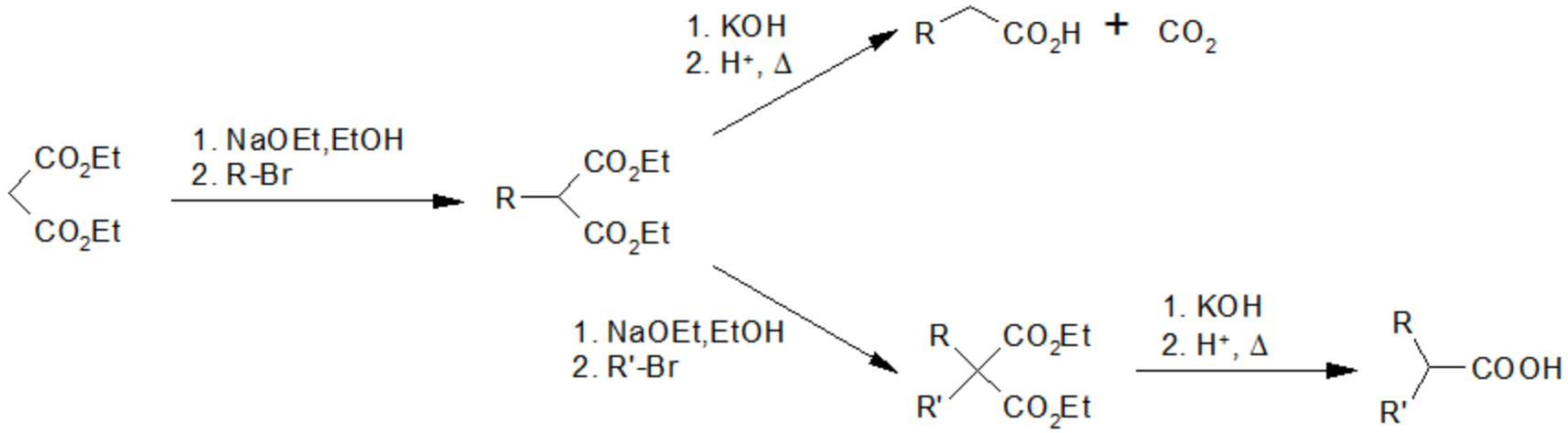


Estratégias de Síntese com Éster Malônico

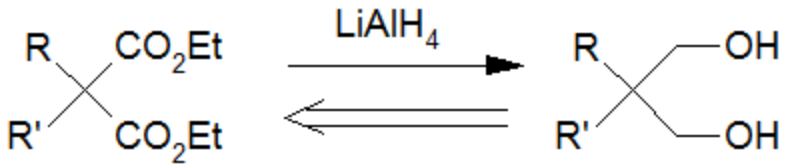
Estratégias de Síntese com Éster Malônico (1)

Ácidos Carboxílicos



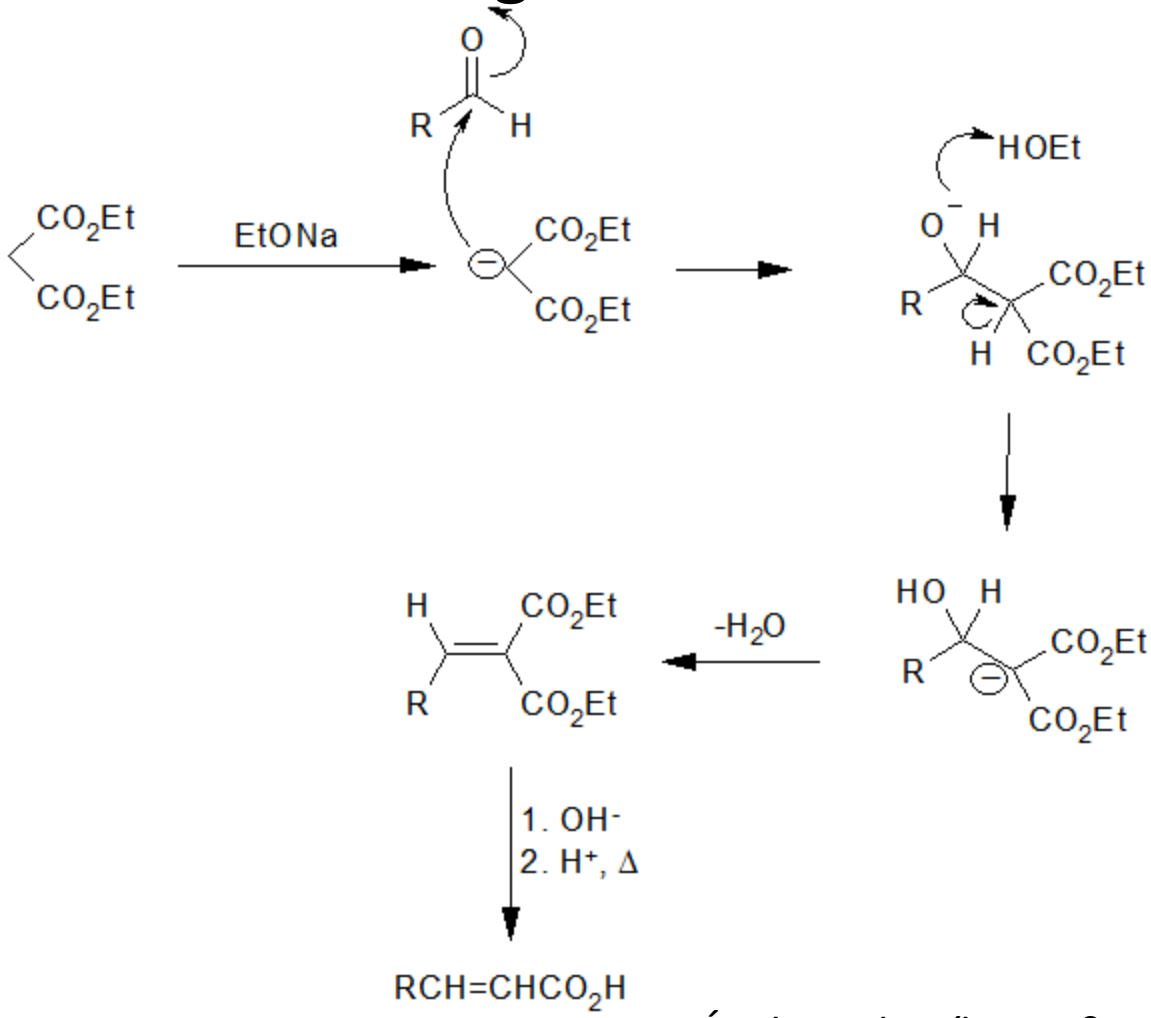


1,3-Dióis



Estratégias de Síntese com Éster Malônico (2)

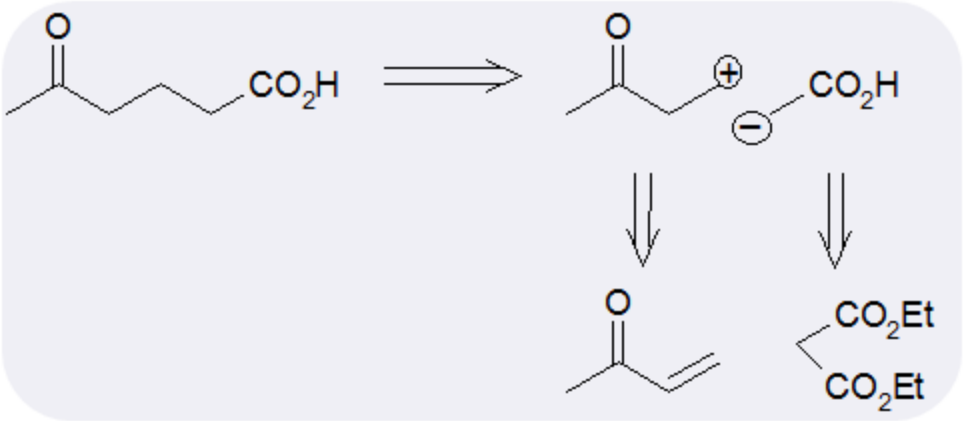
Condensação de Knoevenagel

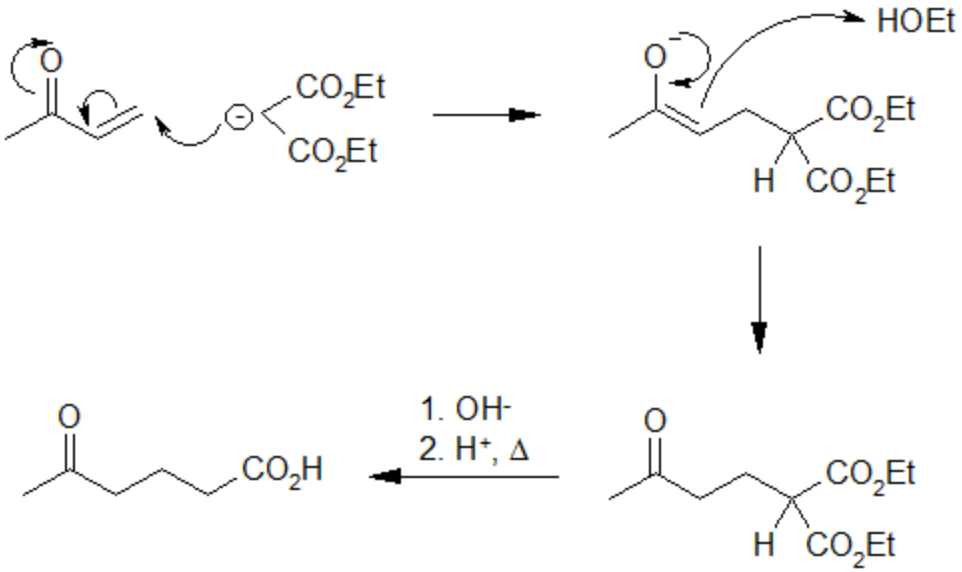


Ácido carboxílico α,β-insaturado

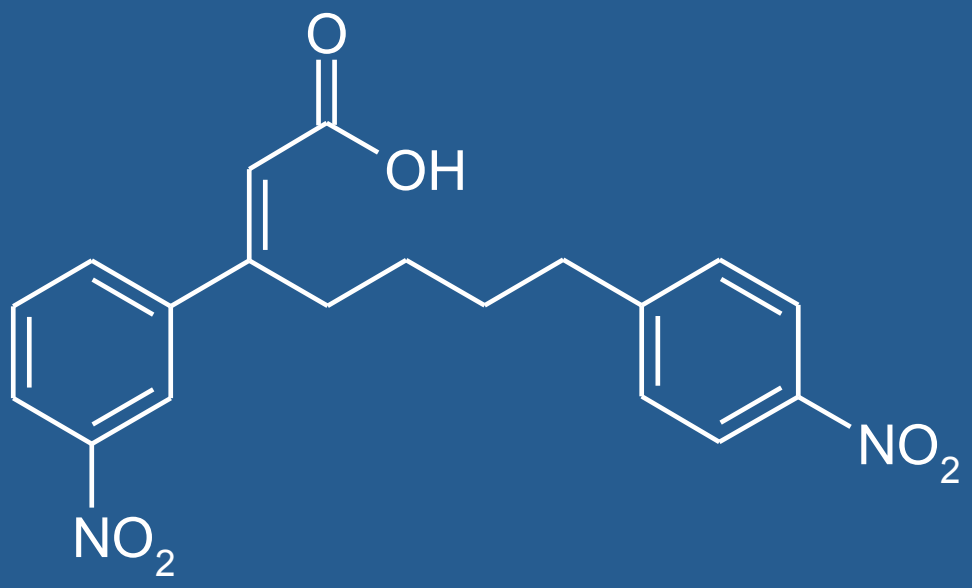
Estratégias de Síntese com Éster Malônico (3)

Reação de Michael

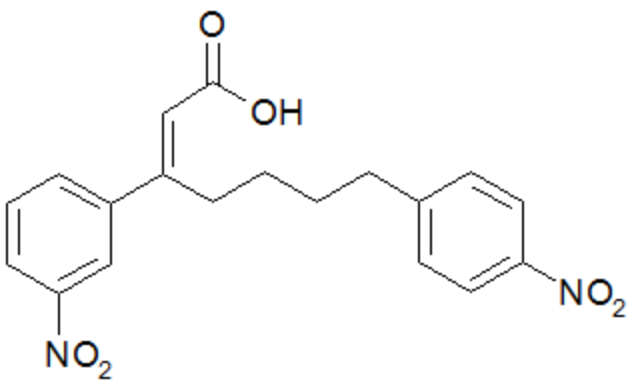


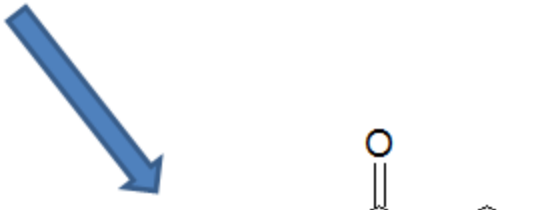


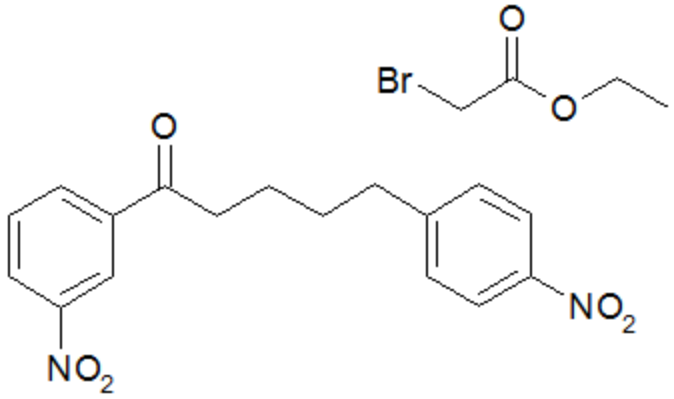
Exercício

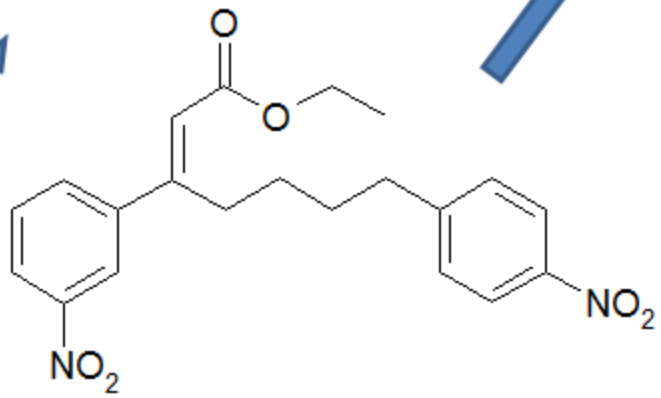


Exercício

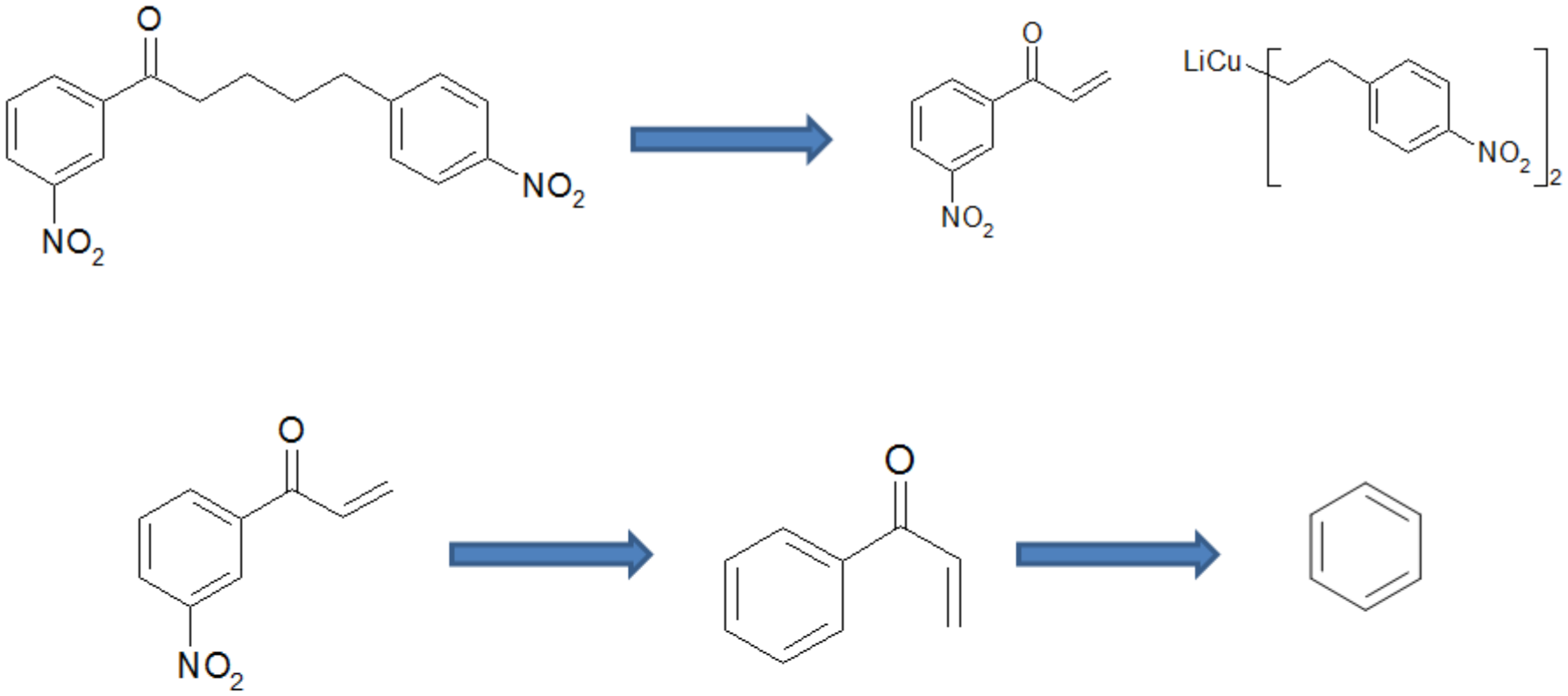




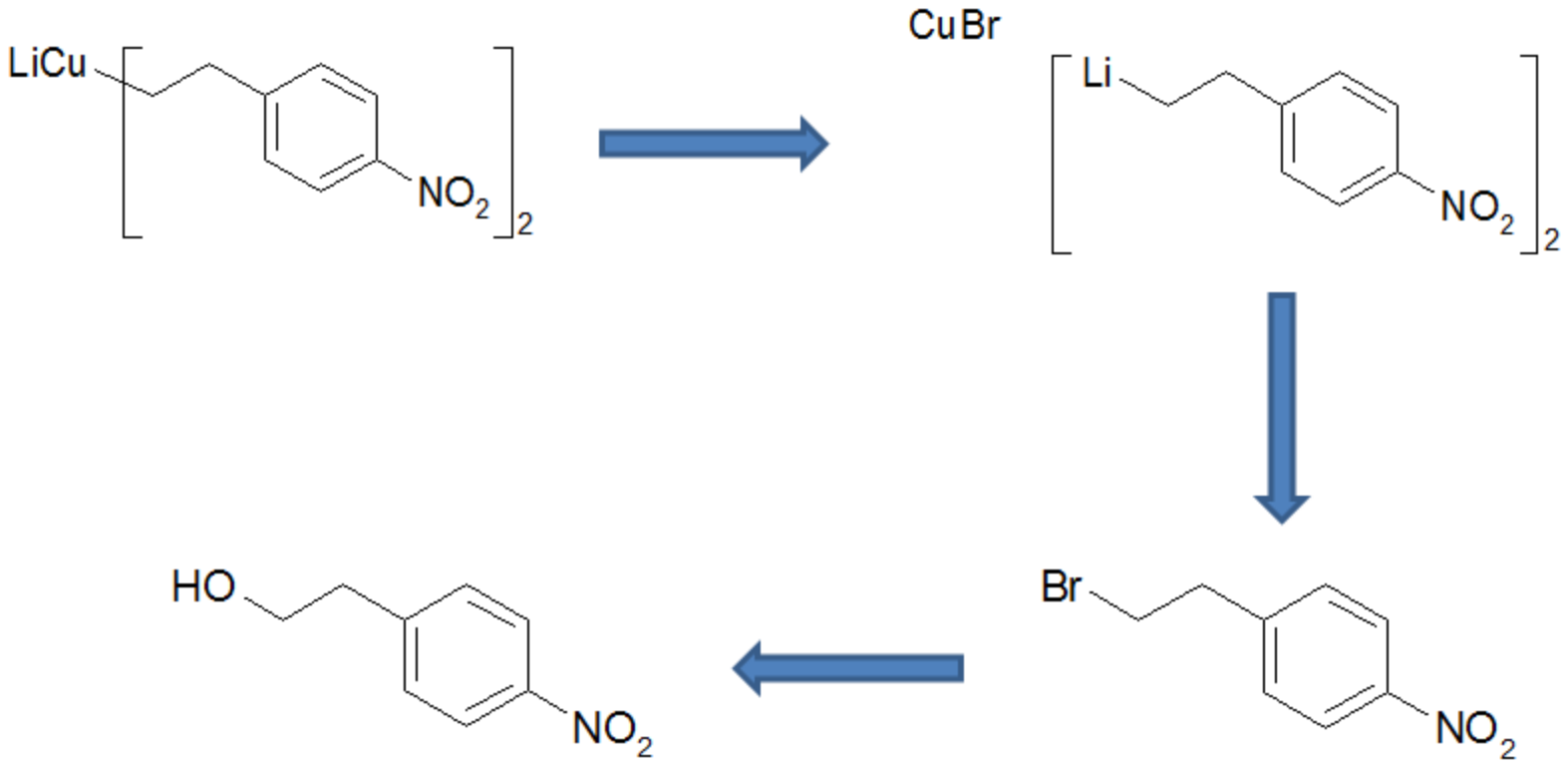




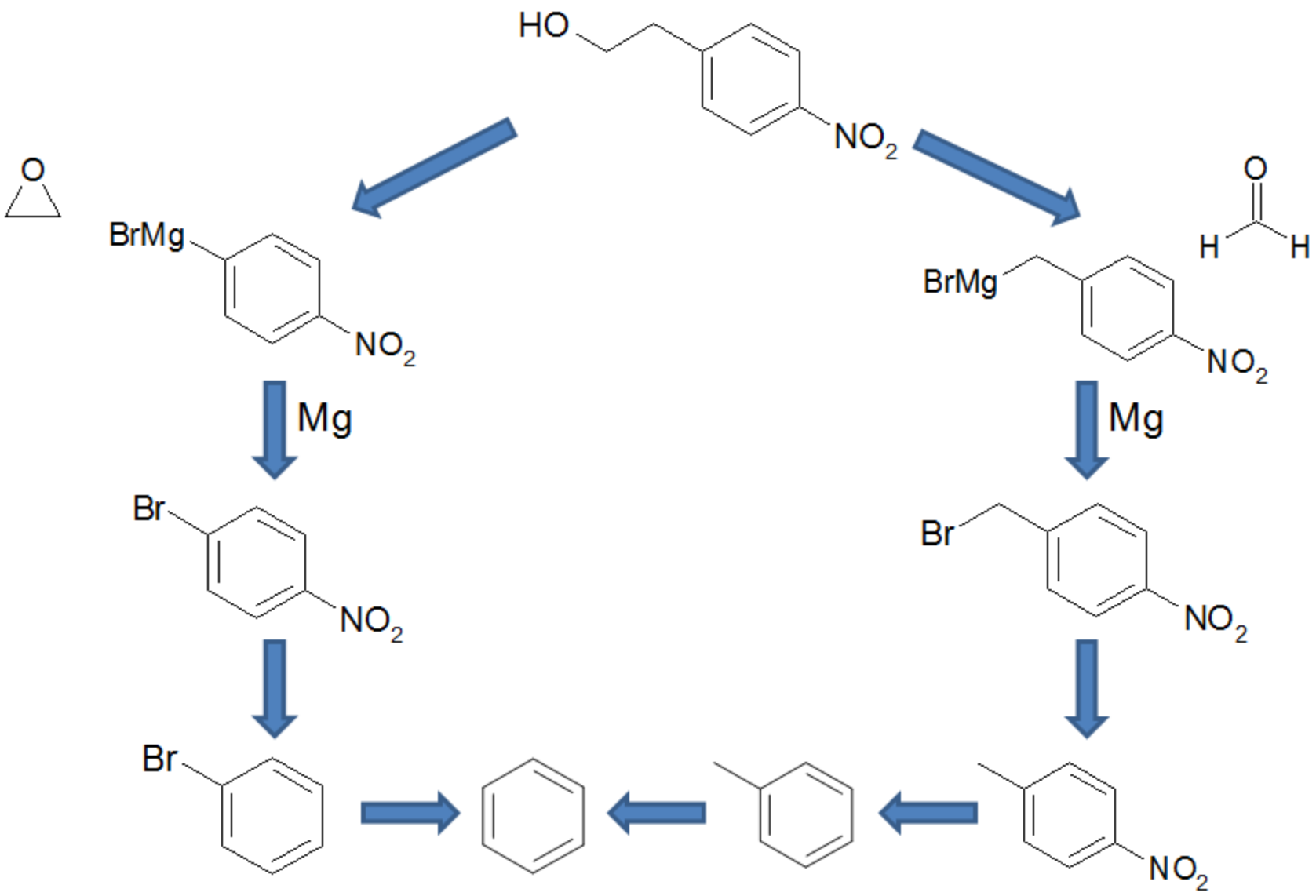
Exercício



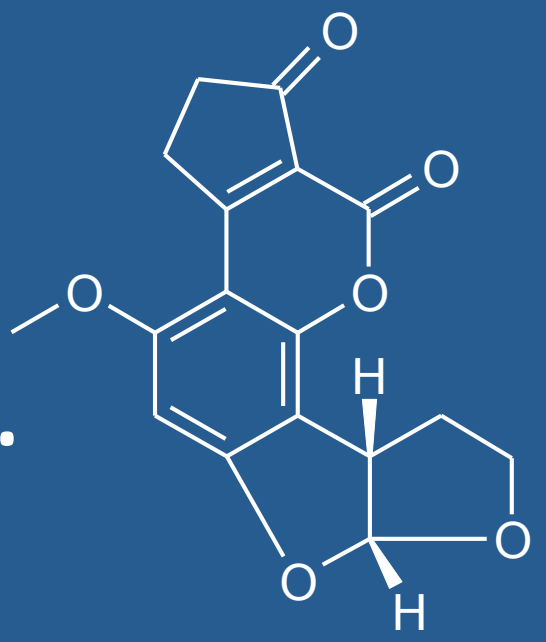
Exercício



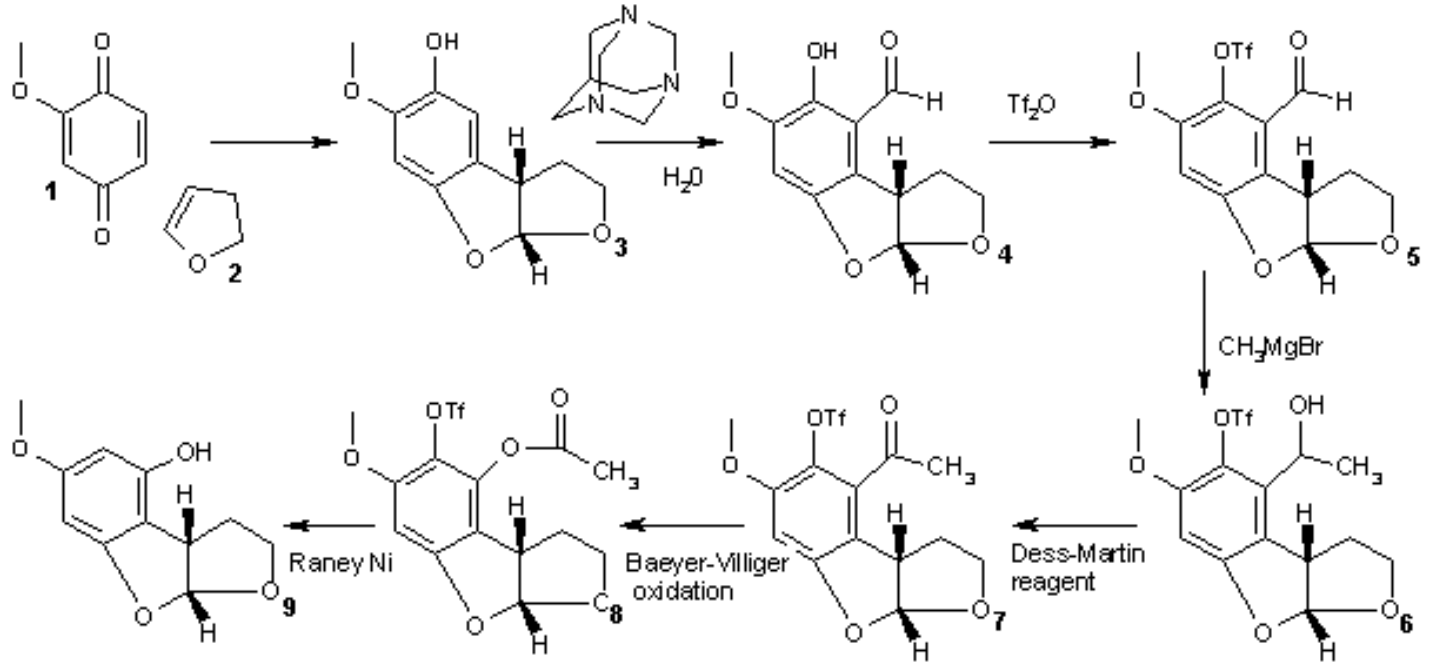
Exercício

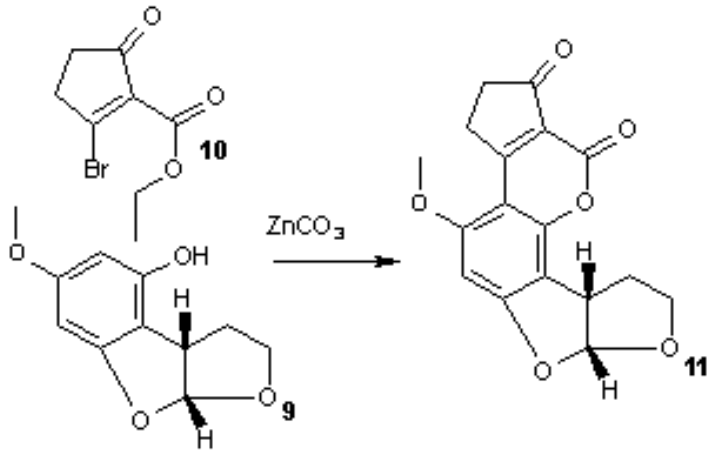


Um pouco mais complicado...



Aflotoxina B2





Foram necessárias sete etapas somente para mudar um grupo –OH de lugar!!!!

Zhou & Corey – JACS **2005** 127 11958