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Chiral GC Using Cyclodextrin-Based Capillary Columns

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Gas Separations R&D

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T499136

Outline

- Introduction
  - Chirality and Its Implications
  - Chiral Separation Methods
- Chiral Gas Chromatography
  - Stationary Phases
  - DEX™ Column Selection and Method Development
  - Applications

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Definitions

- **Chirality**
  - **The property of nonsuperimposability of an object on its mirror image.**
- **Chiral Molecule**
  - **Not superimposable on its mirror image.**
- **Achiral Molecule**
  - **Superimposible on its mirror image.**

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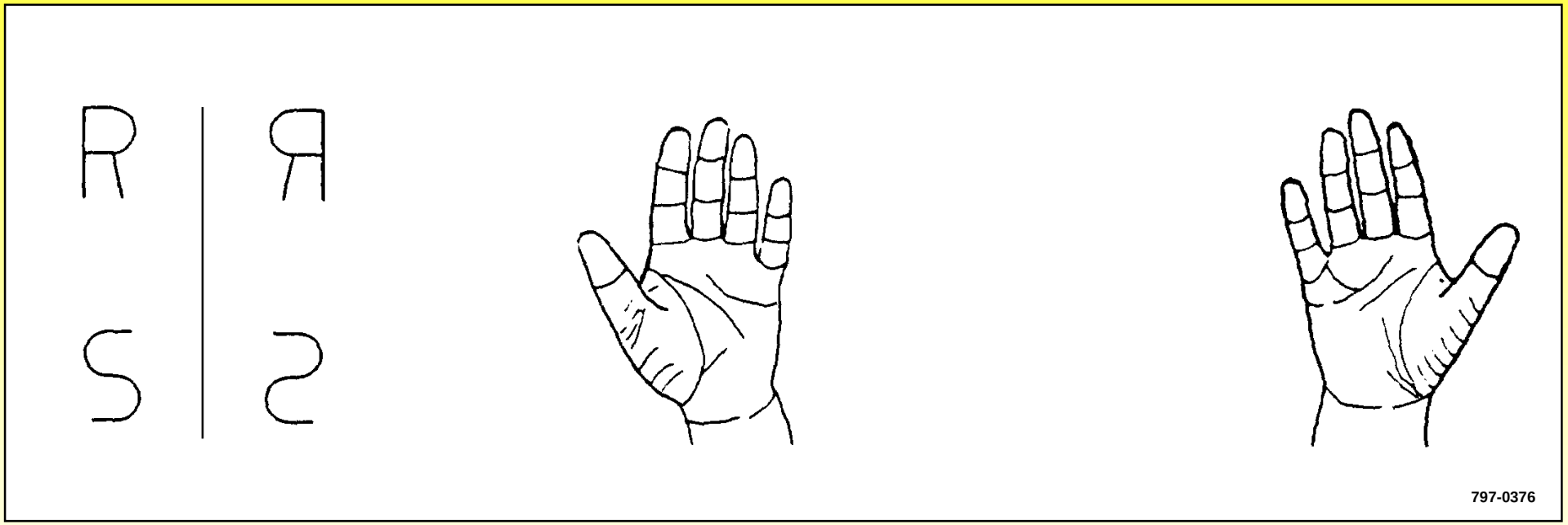
Mirror Image Relationships



Adapted from *Chirotechnology: Industrial Synthesis of Optically Active Compounds* R.A. Sheldon, Marcel Dekker, Inc., New York, 1993. Used with permission.

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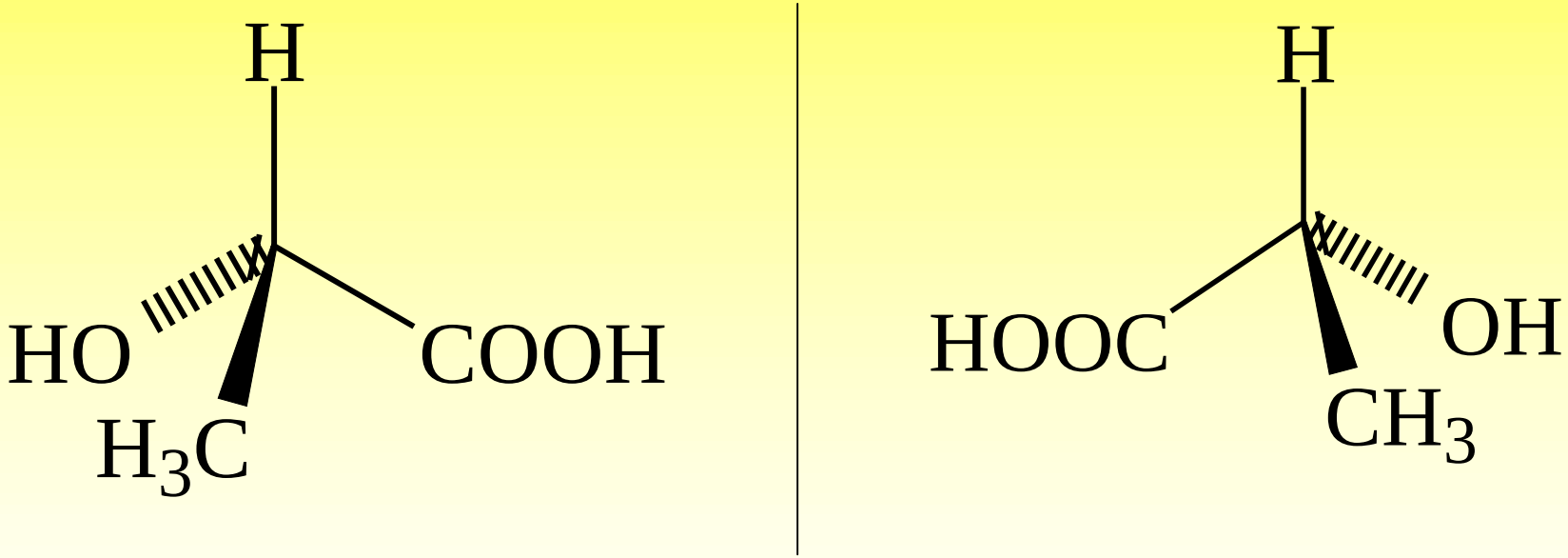
Lactic Acid Enantiomers



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Enantiomers

- **Differ in Structure Only in the Left- and Right-Handedness of their Spatial Orientations.**
- **Rotate the Plane of Polarized Light in the Opposite Directions in Equal Amounts.**
- **React at Different Rates with Other Chiral Compounds.**

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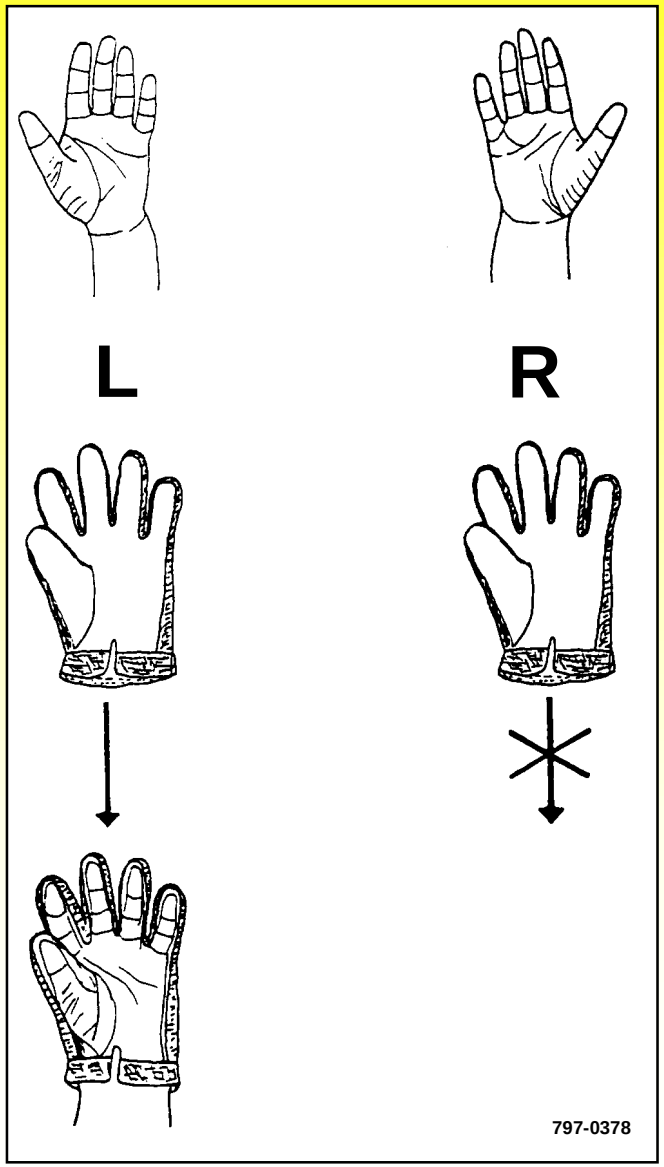
Enantioselectivity



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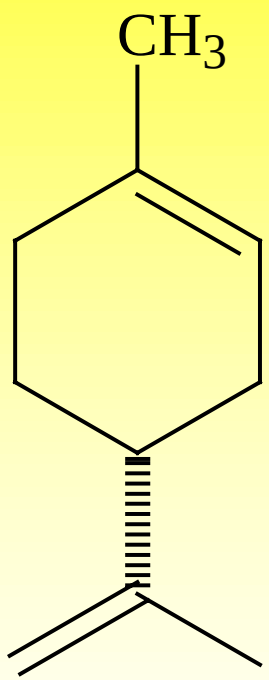
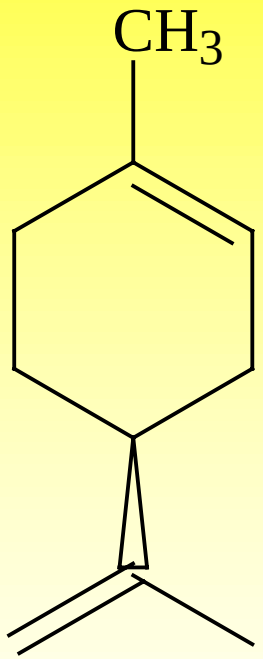
(S)/(R)-Limonene



(S)-Limonene
Lemon Odor



(R)-Limonene
Orange Odor

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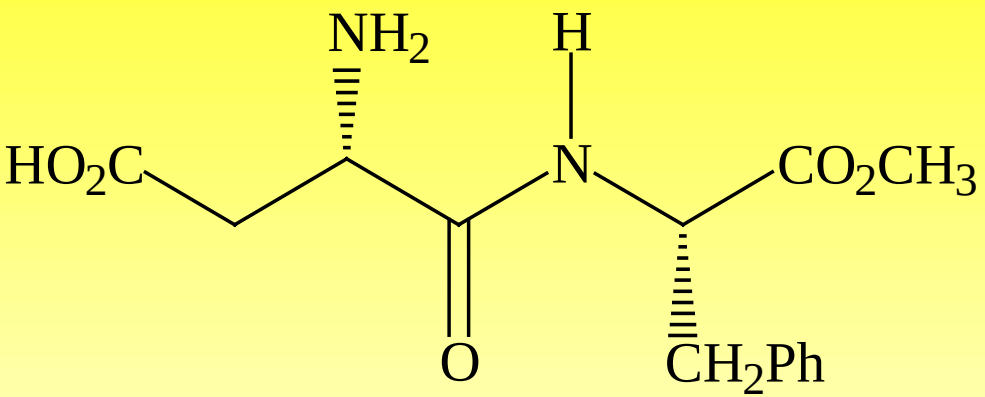
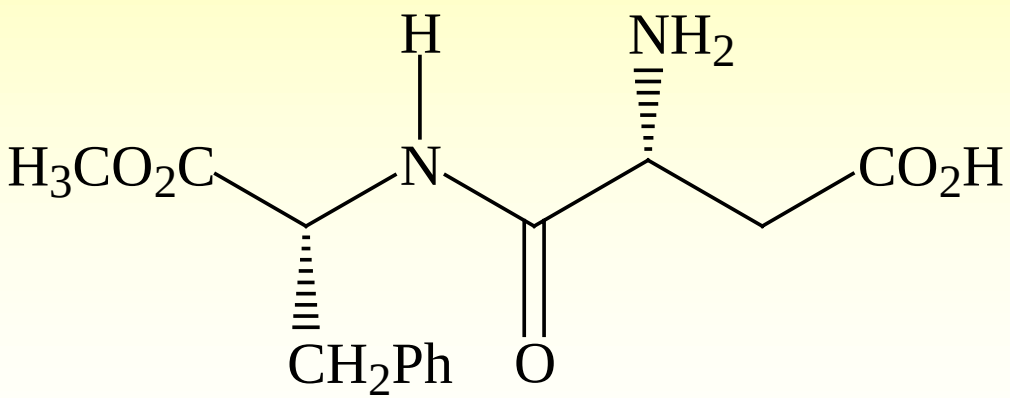
Taste Selectivity



(S,S)
Sweet
(Aspartame)



(R,R)
Bitter

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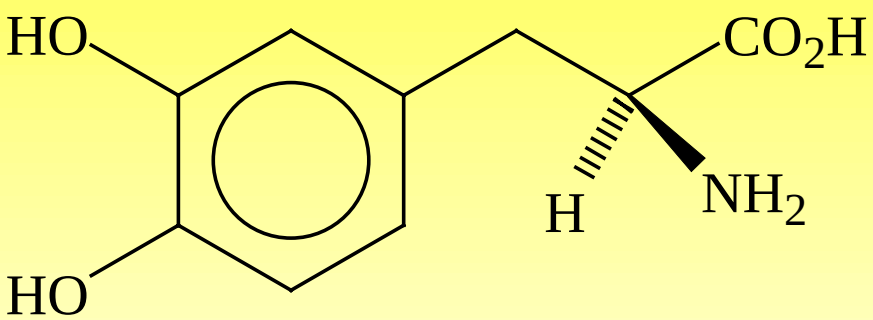
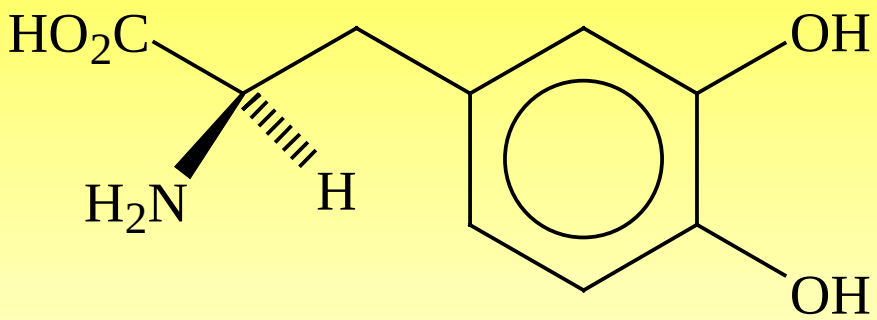
(S/R)-Dopa



(S)-Dopa
anti-Parkinson



(R)-Dopa
serious side effects

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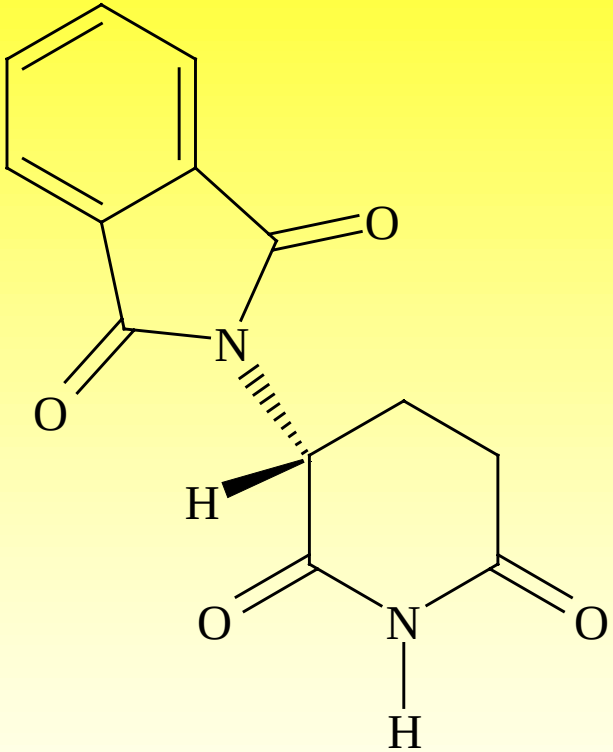
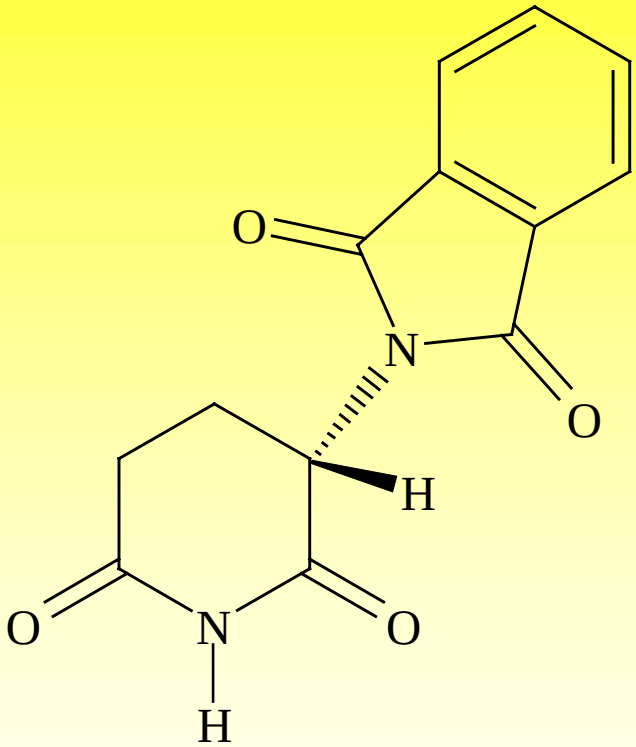
(R/S)-Thalidomide



(R)-Thalidomide
Good Sedative
No Teratogenic Effect



(S)-Thalidomide
No Sedative Effect
Potent Teratogen

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Chiral Separation Methods

- Crystallization
- Conversion to Diastereomers
- Enzymatic Transformations
- Differential Adsorption (Chromatography)

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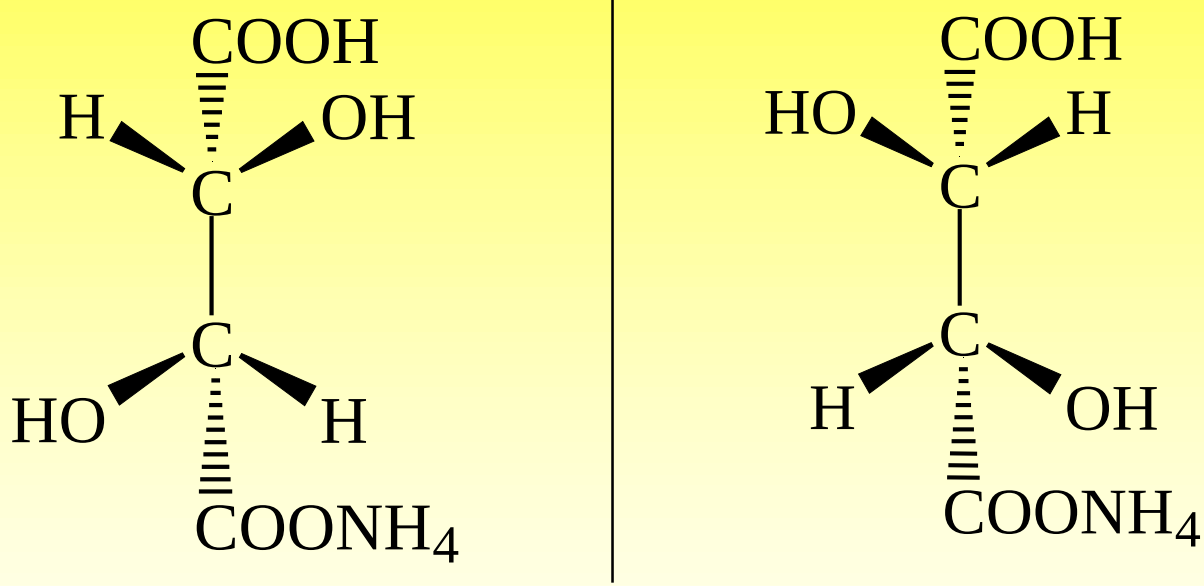
Crystallization



Pasteur, 1848

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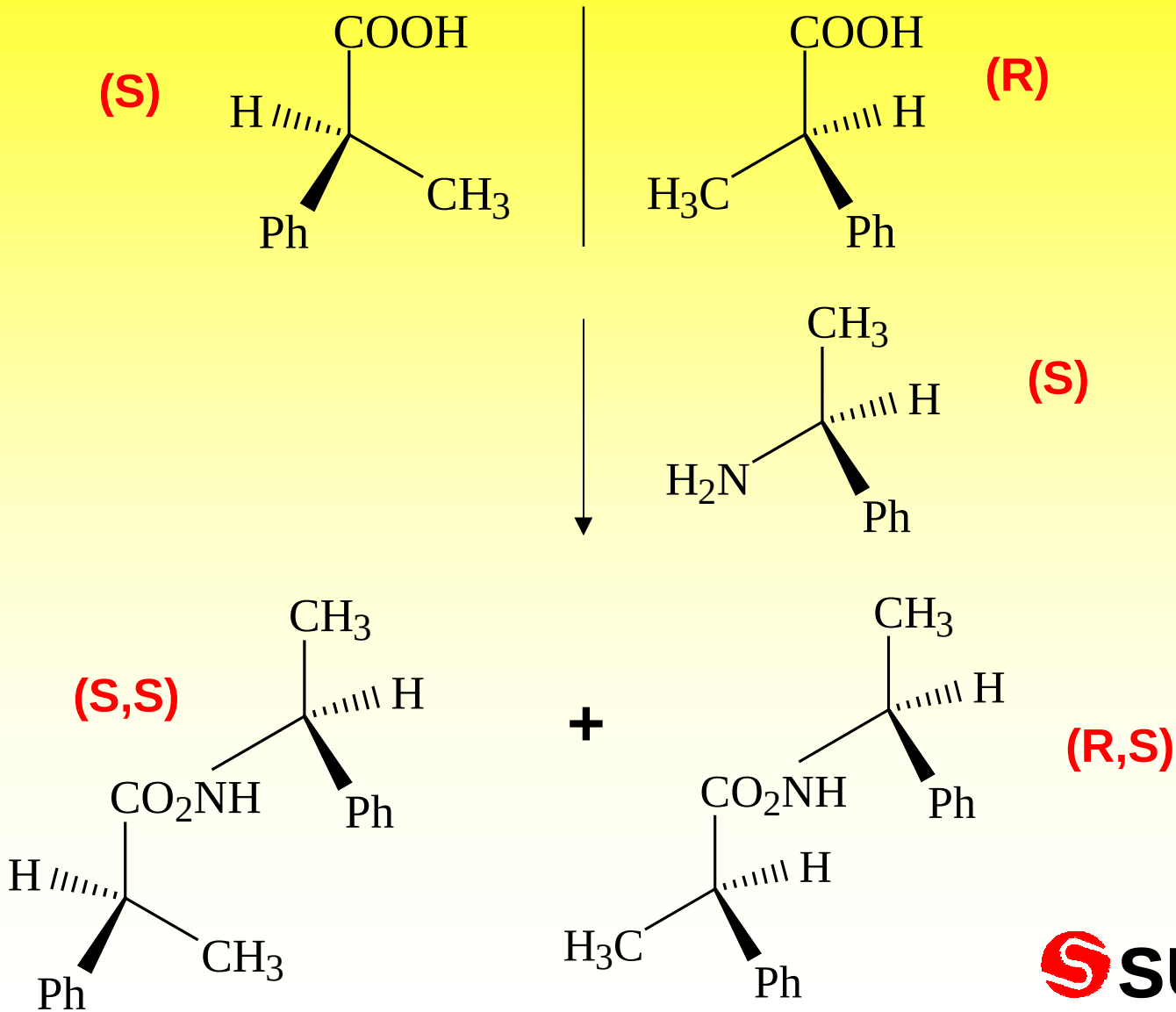
Conversion to Diastereomers



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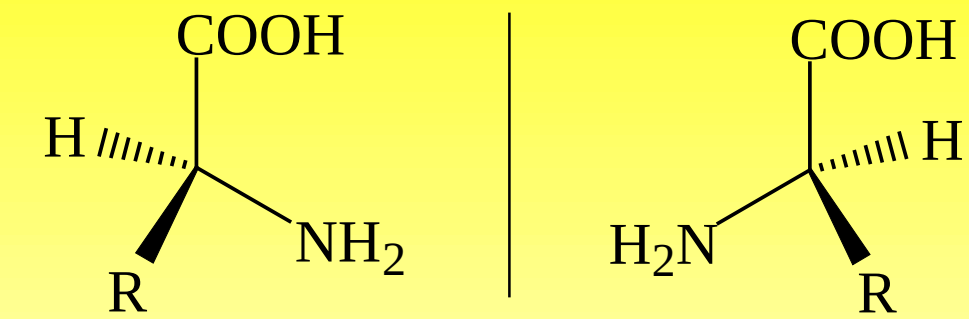
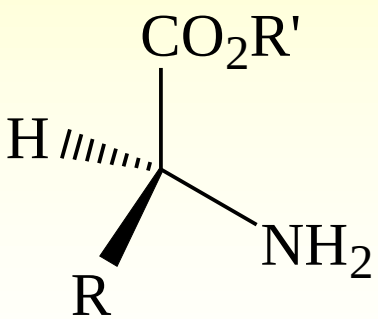
Enzymatic Transformations



Esteraze / R^1OH



Very Slow Reaction

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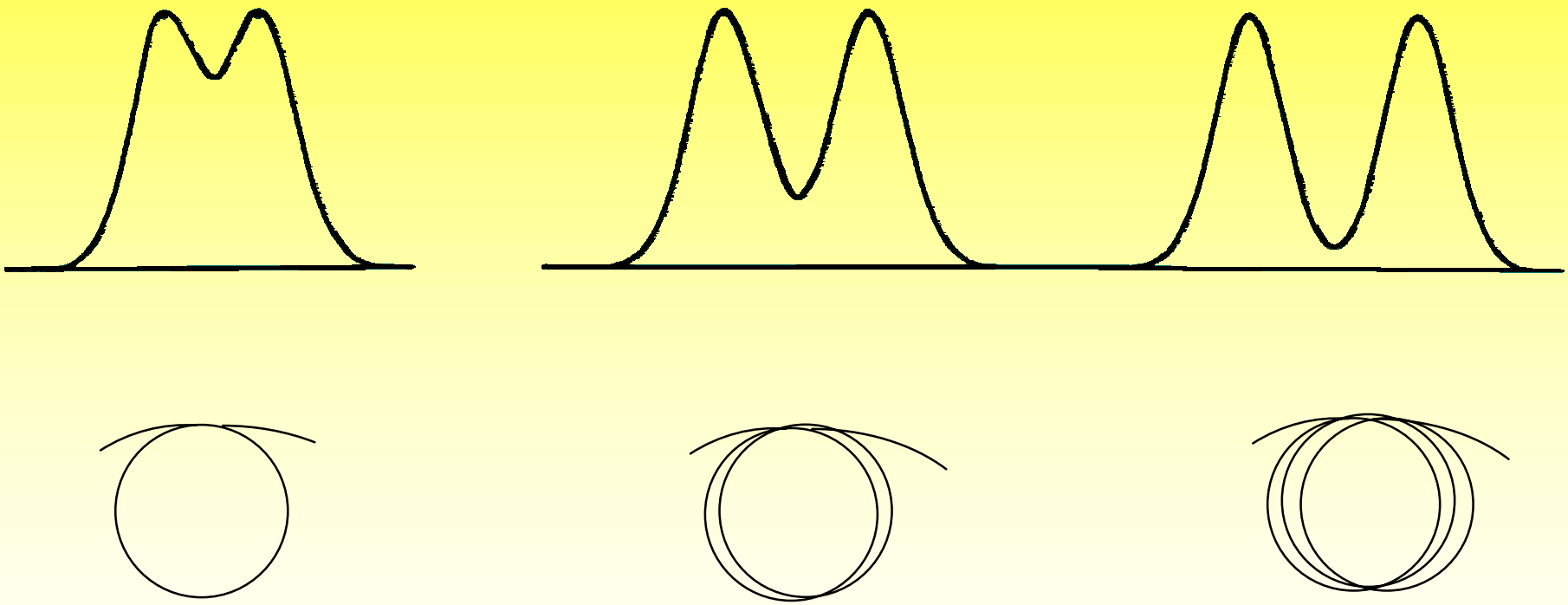
Chromatographic Separation



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Chiral GC Stationary Phases

- Amino Acid Derivatives/Analogues
- Metal Complexes
- Native and Derivatized Cyclodextrins

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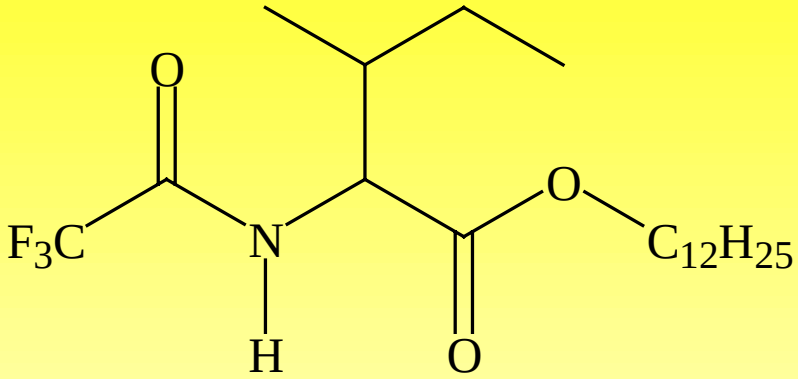
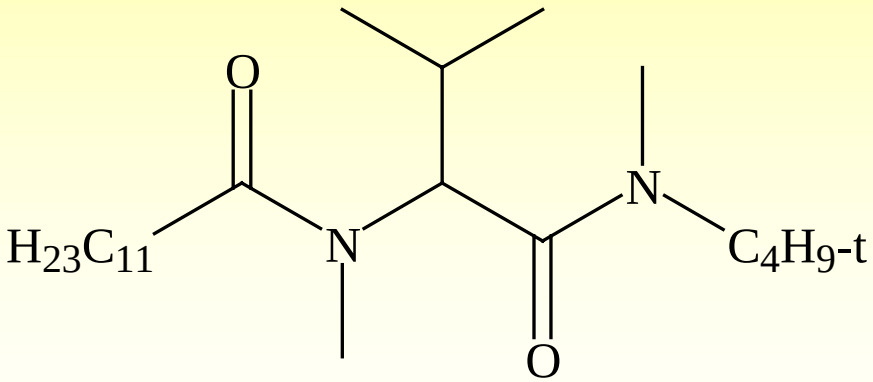
Amino Acid Derivatives/Analogues



N-Trifluoroacetyl-(L)-isoleucine lauryl ester (Gil-Av, 1966)



N-Lauroyl-(L)-valine tert-butylamide (SP-300)

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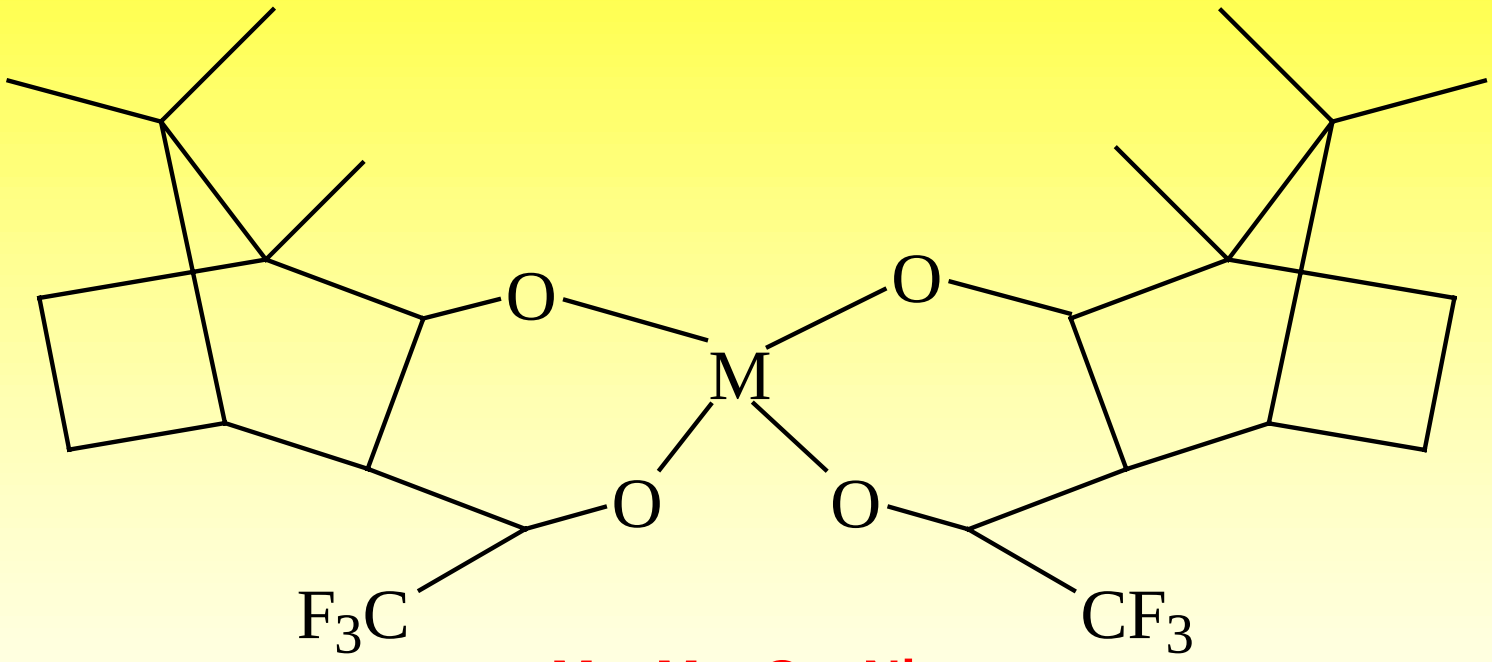
Metal Complexes



M = Mn, Co, Ni

Schurig, 1988

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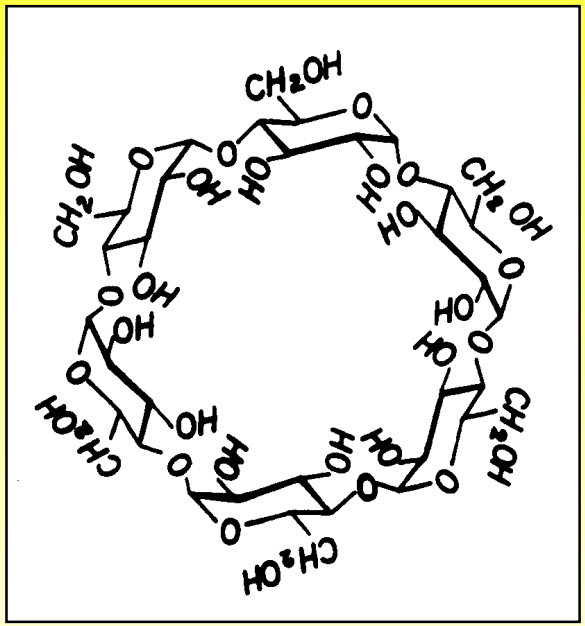
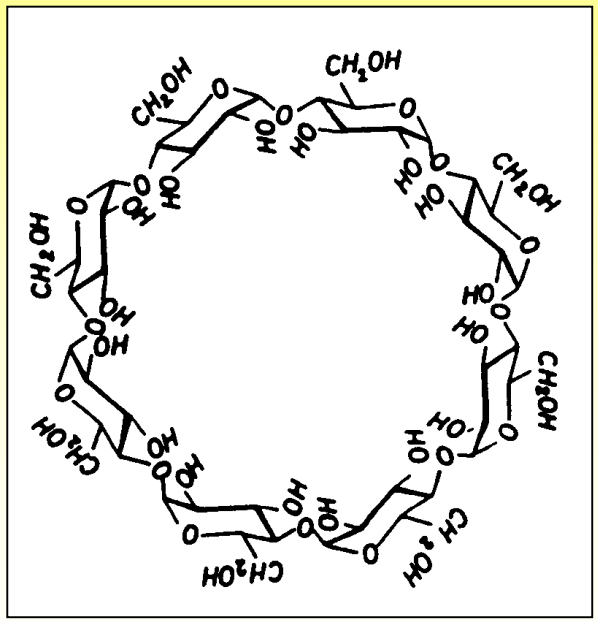
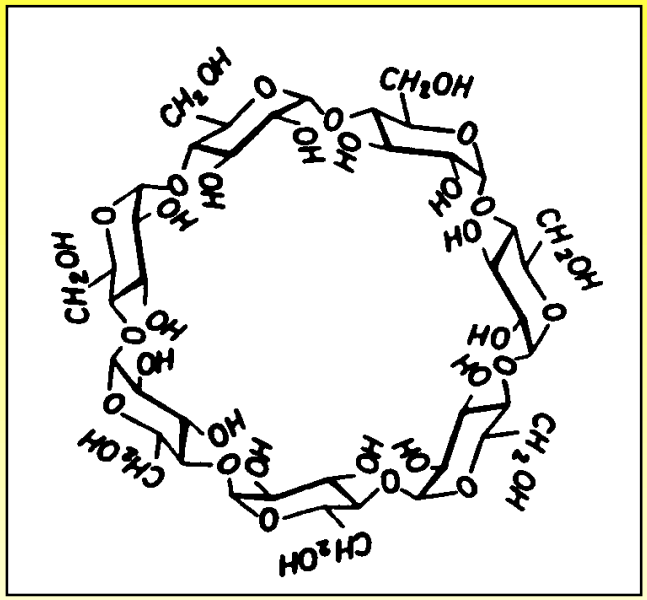
Cyclodextrins



α-Cyclodextrin



γ-Cyclodextrin



β-Cyclodextrin

712-0575,0576,0577

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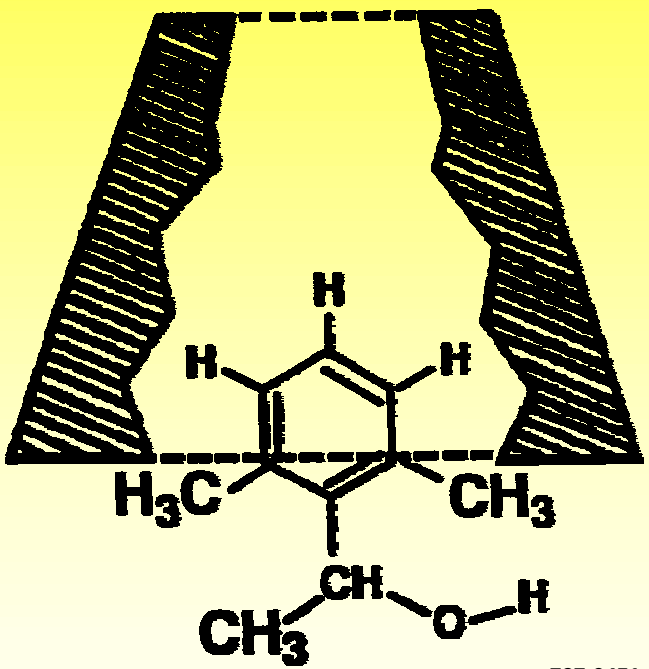
Possible Orientations of Enantiomers



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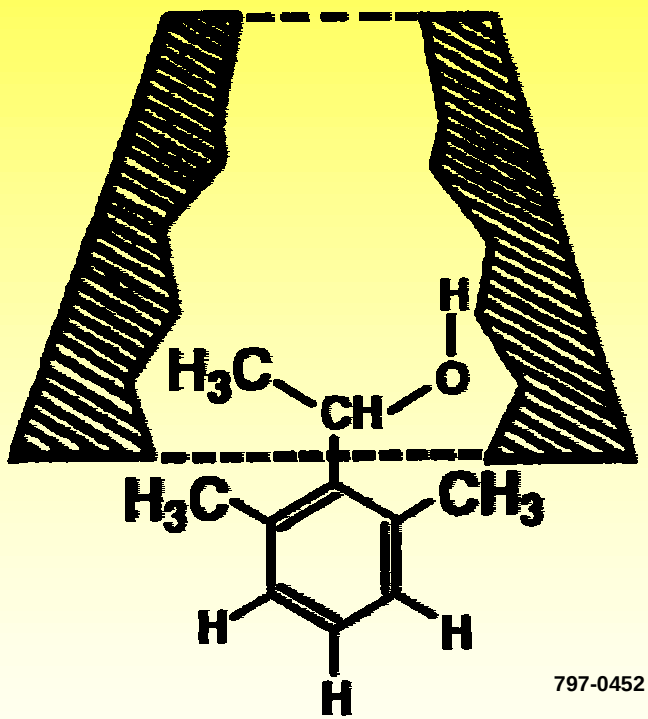
Tail Complex



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Head Complex

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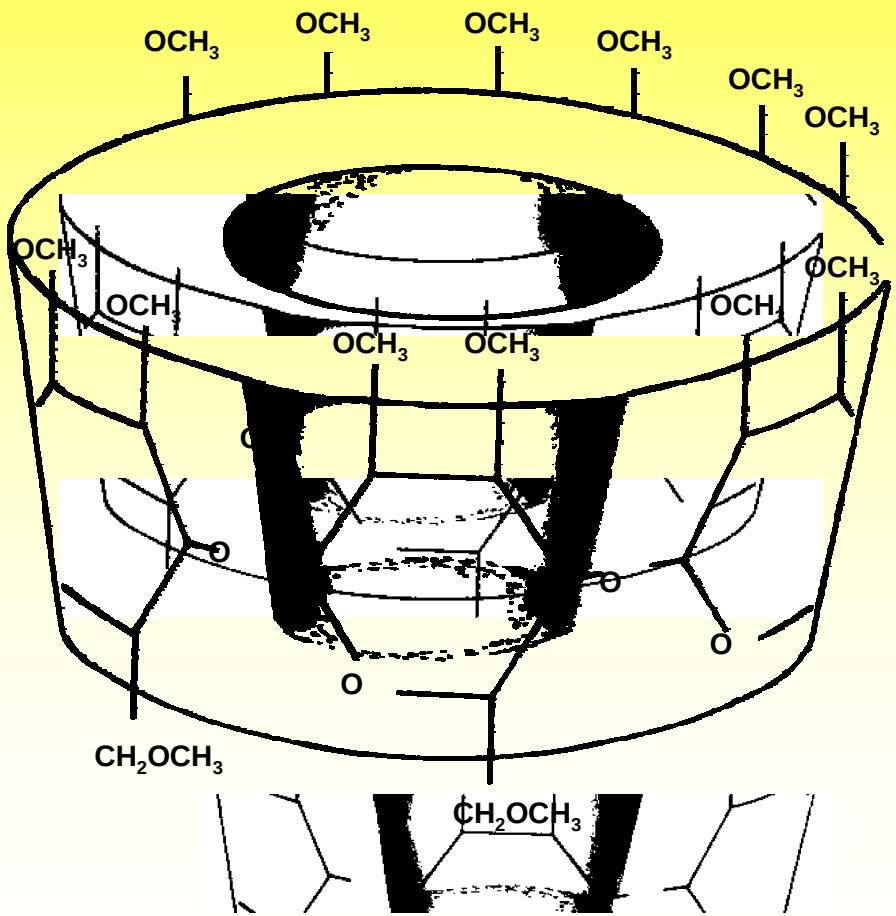
Per-O-methyl-α-cyclodextrin



712-0090

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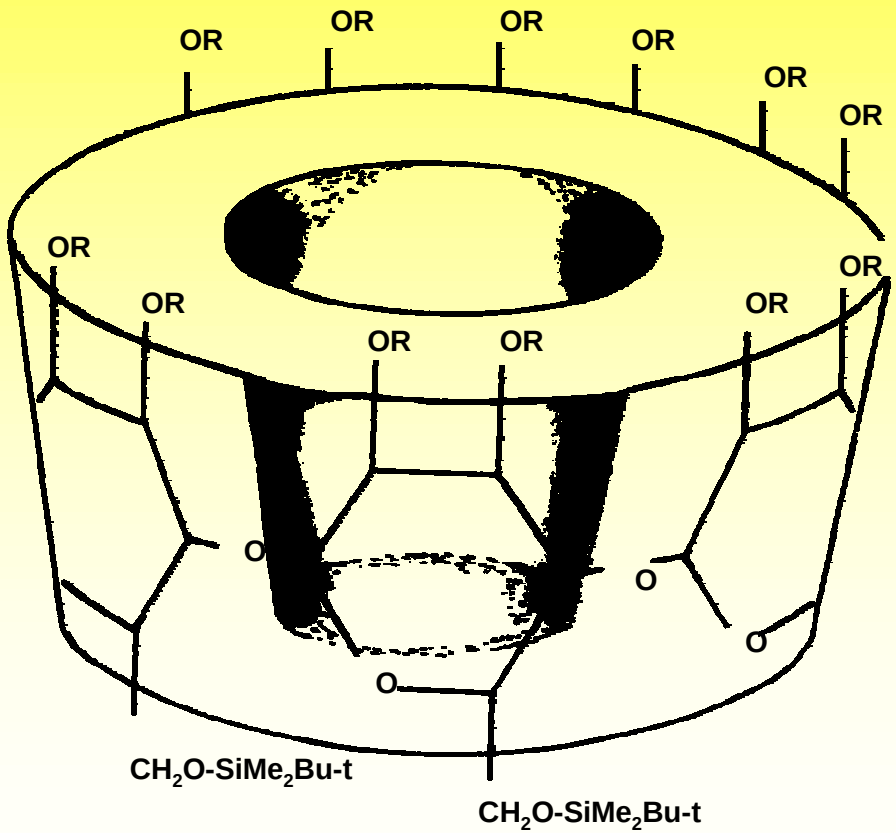
Chiral Stationary Phases

DEX™ 225
R = CH_3CO

DEX 325
R = CH_3



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DEX™ Columns

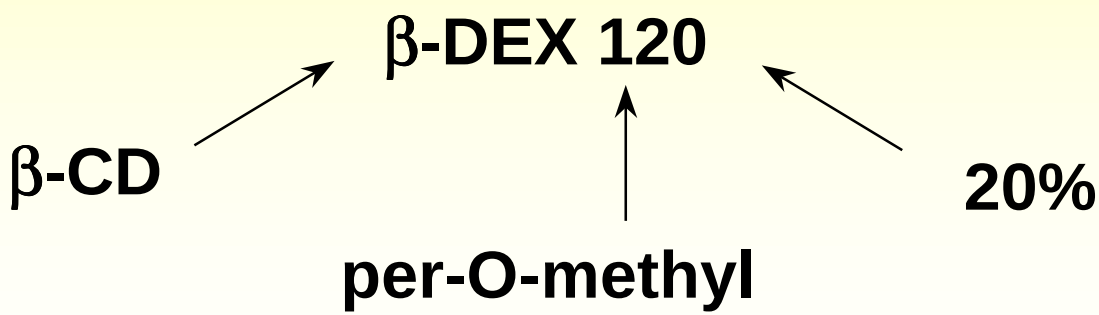
Chiral Stationary Phase:

Cyclodextrin derivative in polysiloxane
SPB™-20 or SPB-35

Cyclodextrin Derivative:

Series 100: per-O-methyl-CD
Series 200: 2,3-di-O-acetyl-6-tert-butyldimethylsilyl-CD
Series 300: 2,3-di-O-methyl-6-tert-butyldimethylsilyl-CD

Example:



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Enantioseparations on DEX Columns

α-DEX™	β-DEX	γ-DEX
Menthols Substituted benzenes and phenols Epoxides Small molecules	Largest number of analytes	Carvone α -Ionone Menthone Methamphetamine Large molecules

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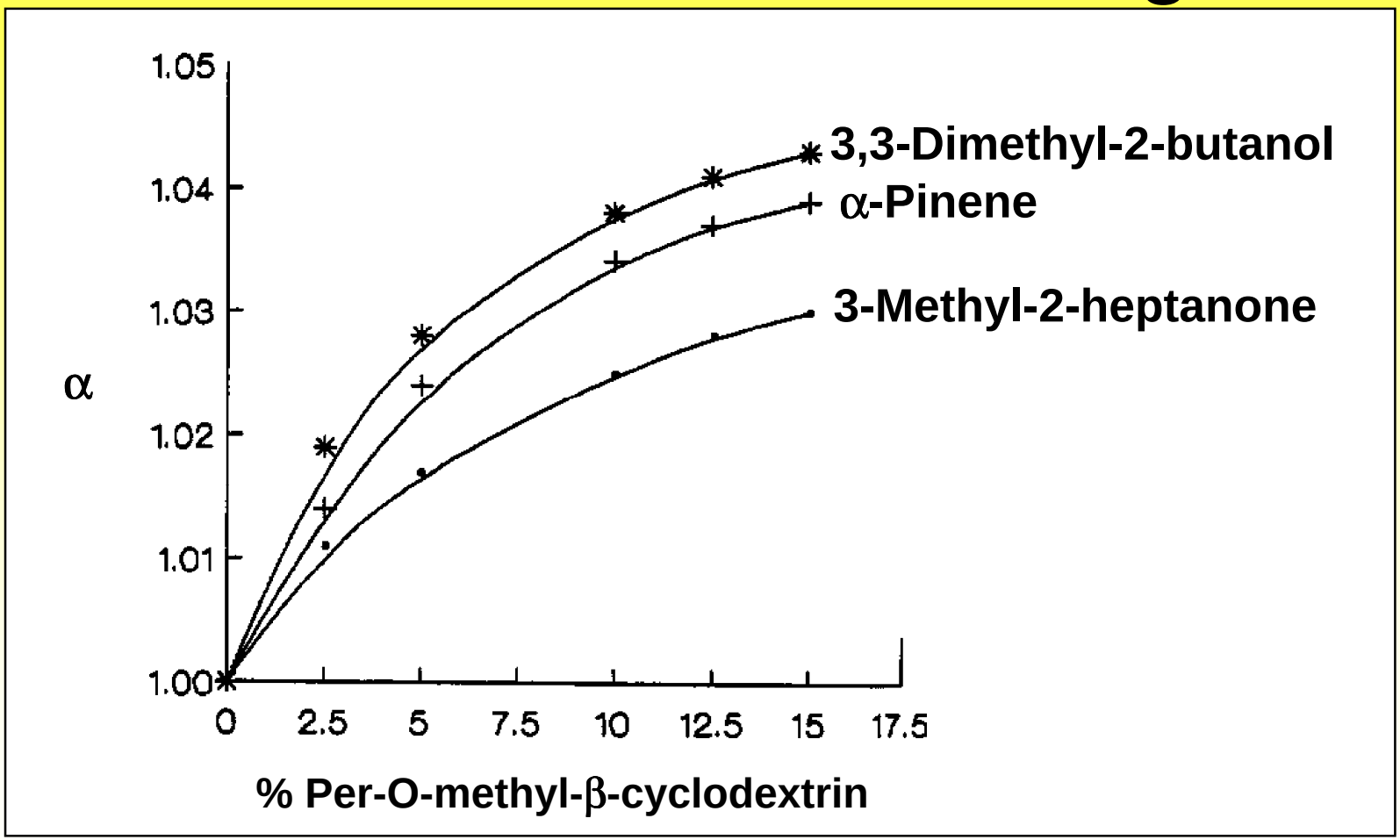
Enantioselectivity: Chiral Selector Percentage



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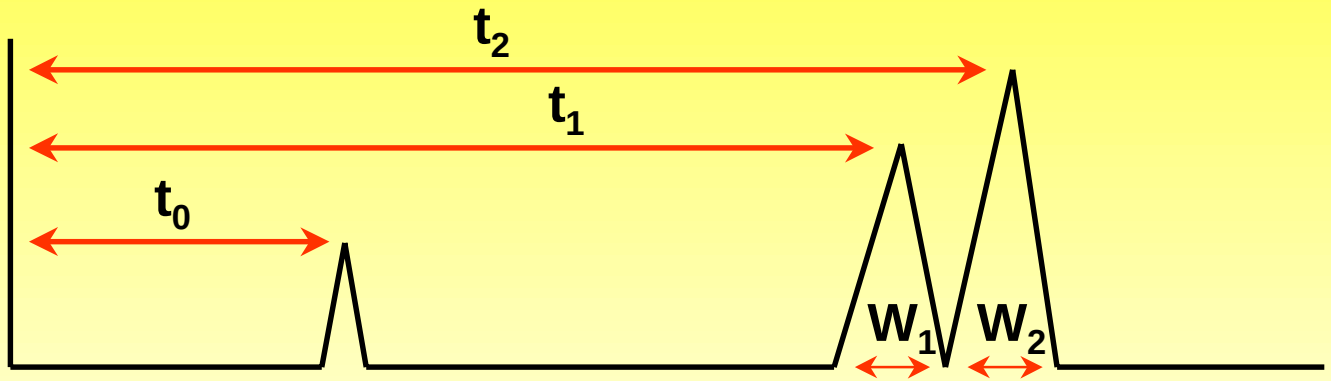
Peak Resolution (Rs) can be expressed via chromatographic factors of retention (k'), efficiency (N), and enantioselectivity (α)



$$R_s = 2\,\frac{t_2 - t_1}{W_1 + W_2} = \left(\frac{\sqrt{N_2}}{4}\right)\left(\frac{\alpha - 1}{\alpha}\right)\left(\frac{k'_2}{1 + k'_2}\right)$$

where:

$N_2 = 16(t_2 / W_2)^2$

$\alpha = (t_2 - t_0) / (t_1 - t_0)$

$k'_2 = (t_2 - t_0) / (t_0)$

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Effect of Column ID on Efficiency and Resolution

Column: β-DEX™ 120, 30m

Column ID	N	α	Rs
100µm	5580	1.021	1.90
200µm	3550	1.020	1.53
320µm	2180	1.022	1.26
530µm	1310	1.023	1.04

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Column Selection: Chiral Column Kit II

- 30m, 0.25mm ID, 0.25um Film
  - 20% Per-O- methyl-β-cyclodextrin
  - 25% 2,3-O-Diacetyl-6-O-TBDMS-β-cyclodextrin
  - 25% 2,3-O-Diacetyl-6-O-TBDMS-γ-cyclodextrin
  - 25% 2,3-O-Dimethyl-6-O-TBDMS-β-cyclodextrin

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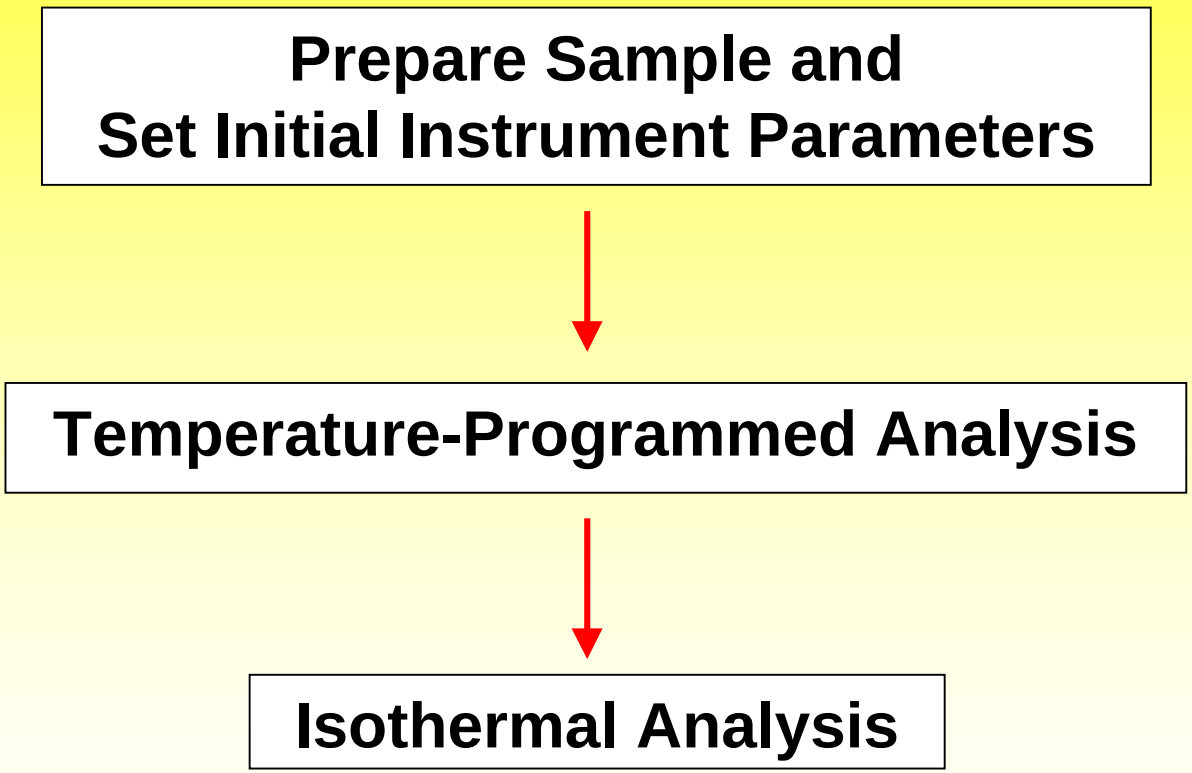
Column Selection: Overall Approach



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Sample & Instrument Parameters

- Sample Concentration:
  - 10mg/mL in Dichloromethane or Methanol
- Injection Volume: 1uL, Split (100:1)
- Injector: 230°C
- Detector: FID, 250°C
- Carrier Gas: Helium (25cm/sec at 180°C) or
  Hydrogen (50cm/sec at 180°C)

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Temperature Programmed Analysis

- Initial Temperature: 50°C
- Program Rate: 10°C/minute
- Final Temperature: 230°C
- Hold Time: 60 minutes

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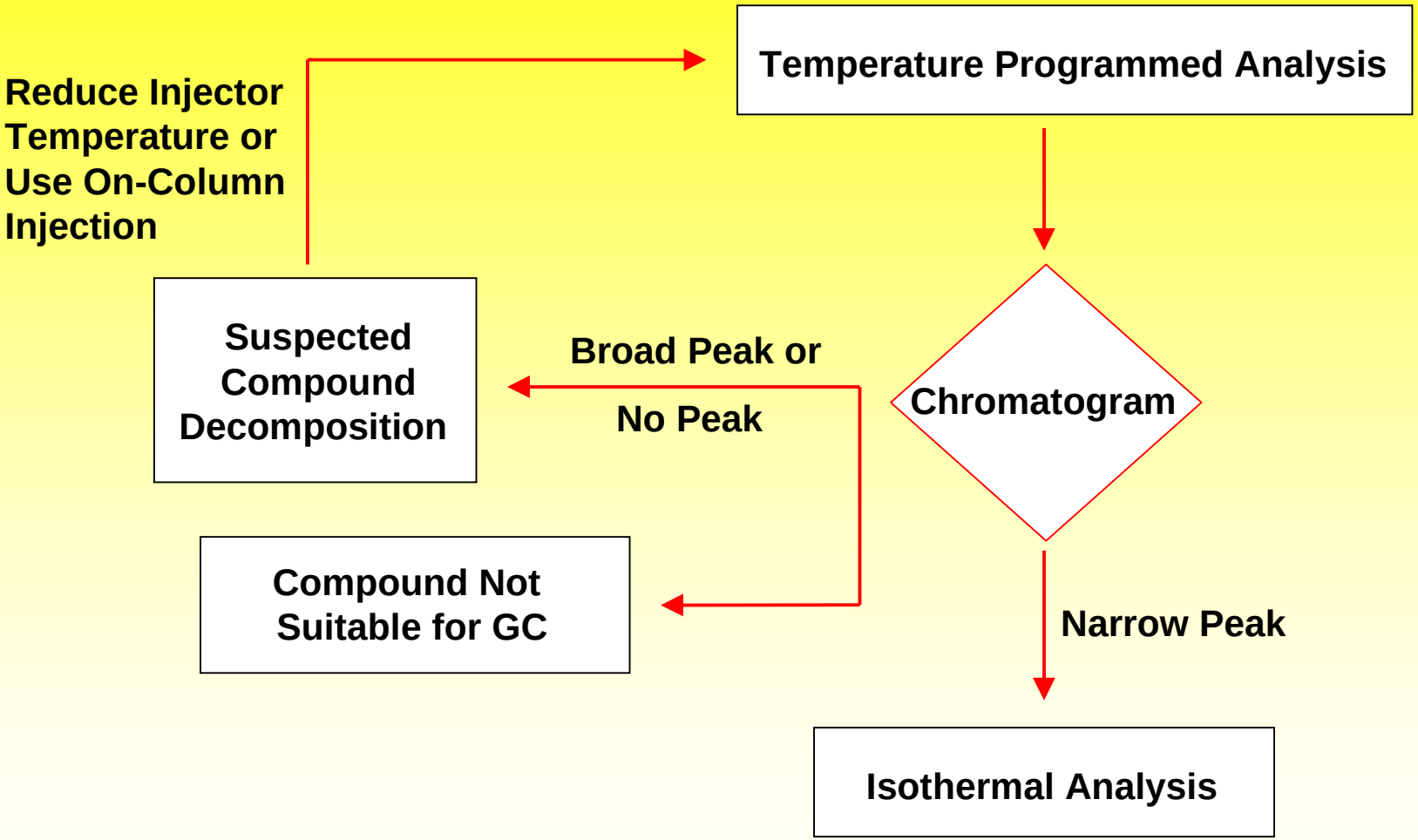

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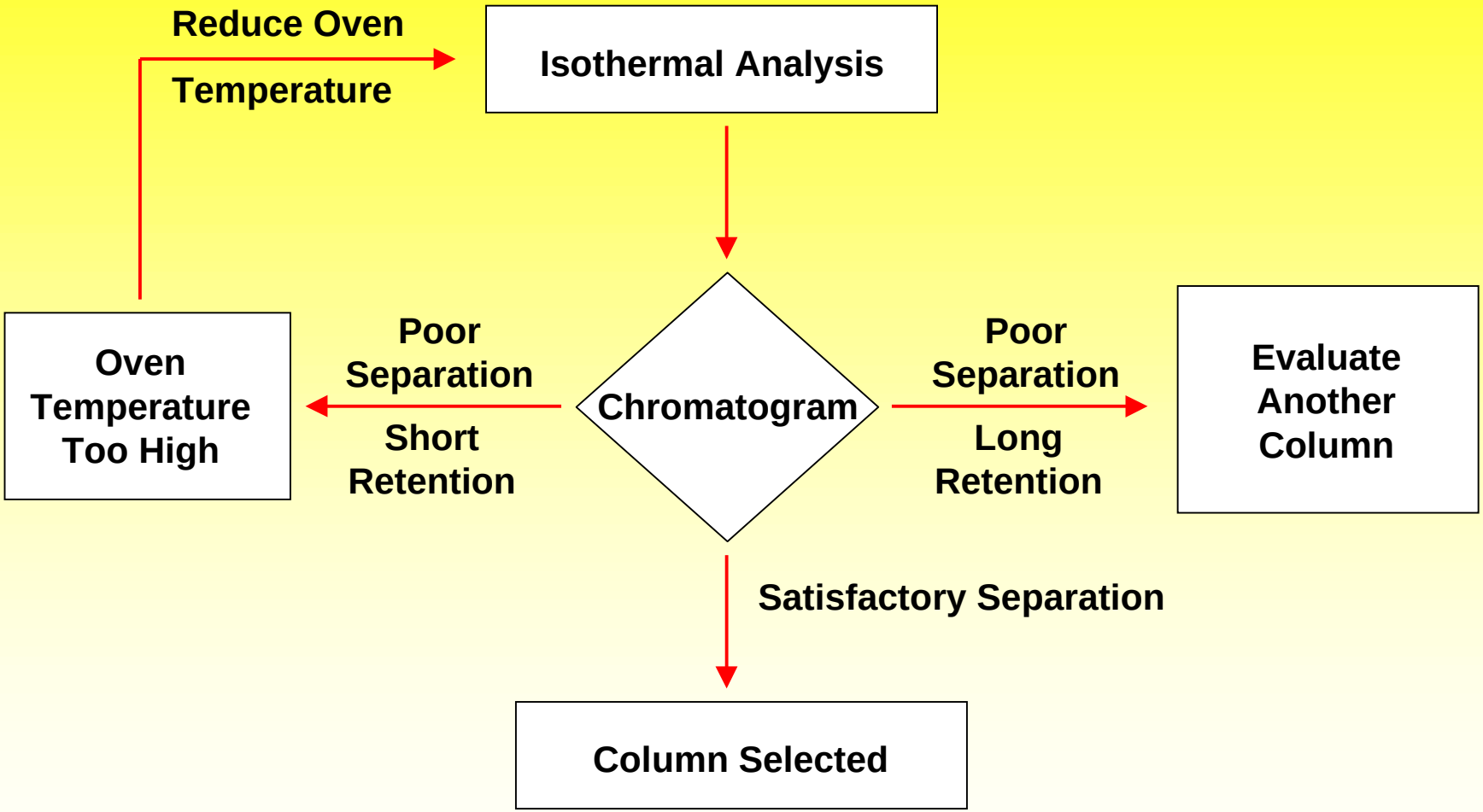

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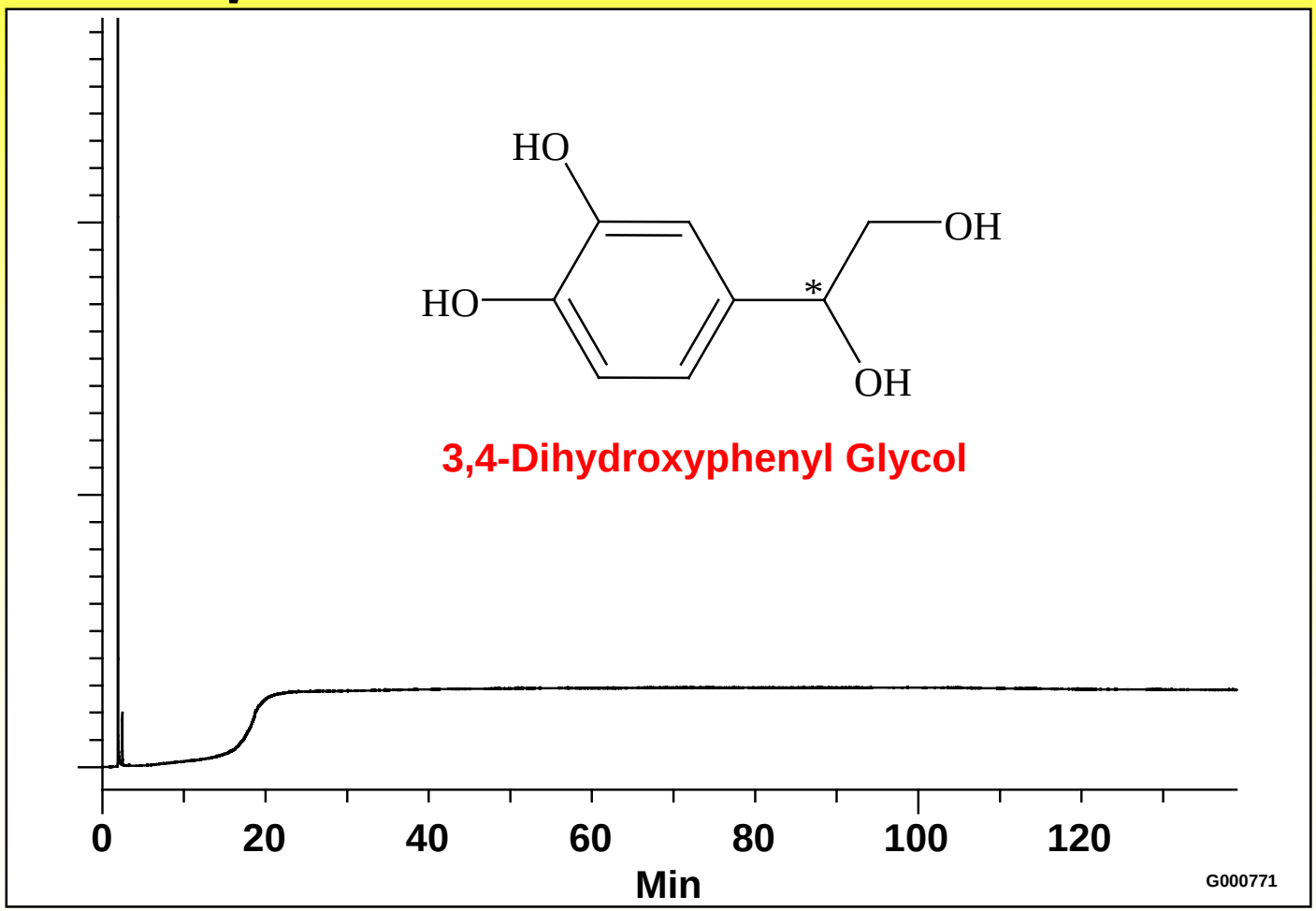
Temperature Programmed Analysis
β-DEX™ 120 Column



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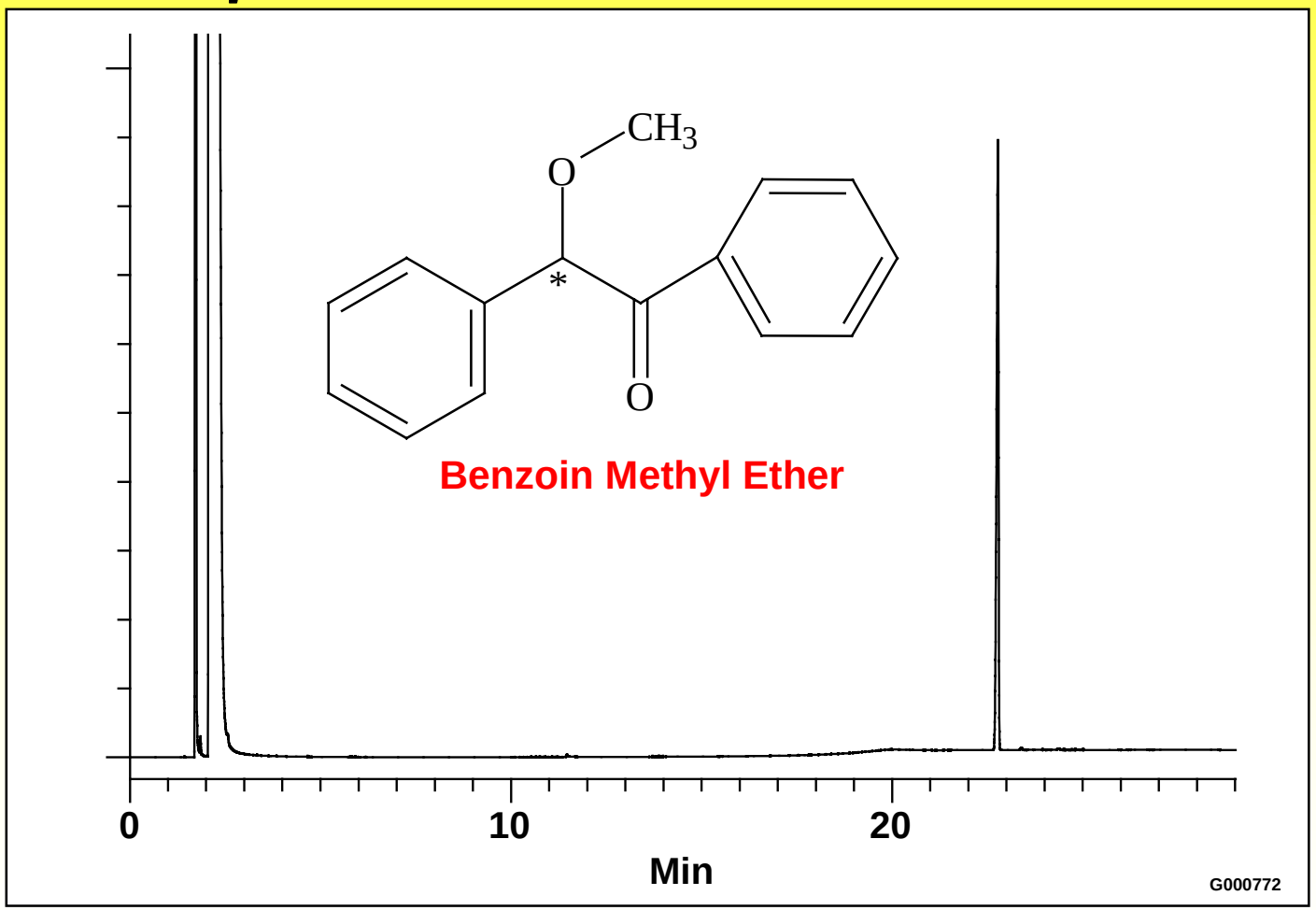
Temperature Programmed Analysis
β-DEX™ 120 Column



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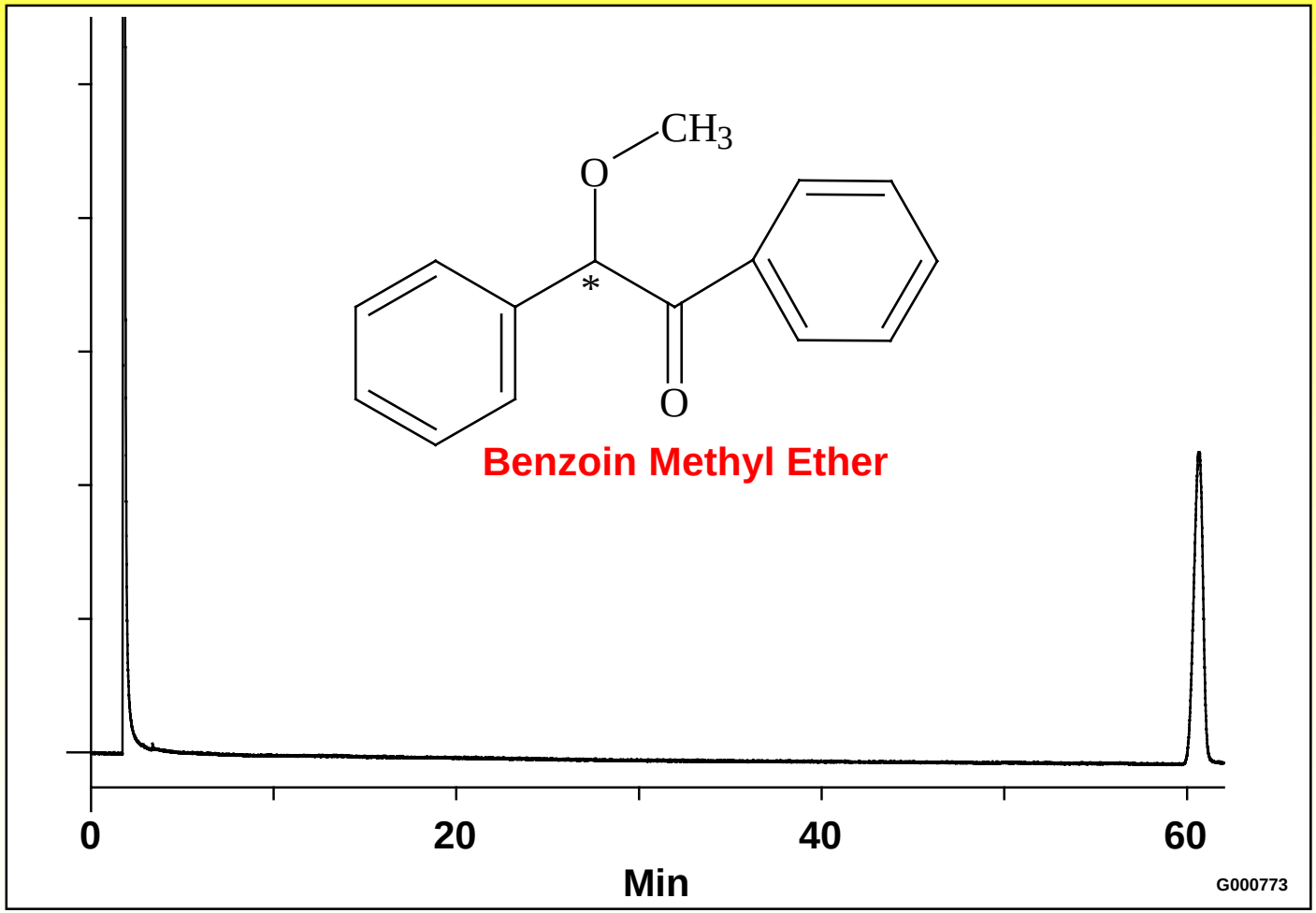
Isothermal Analysis
β-DEX™ 120 Column



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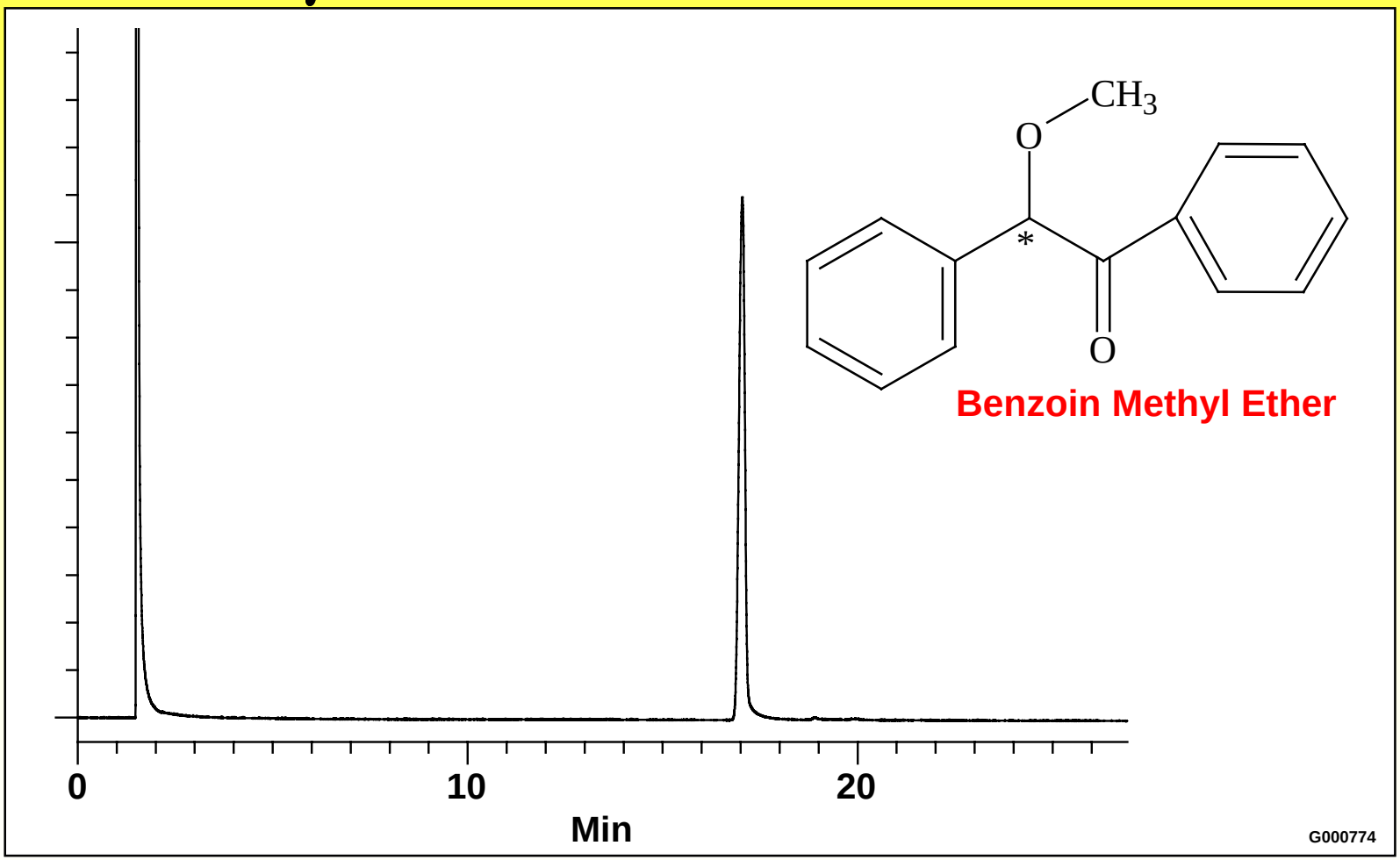
Isothermal Analysis (180°C)
γ-DEX™ 225 Column



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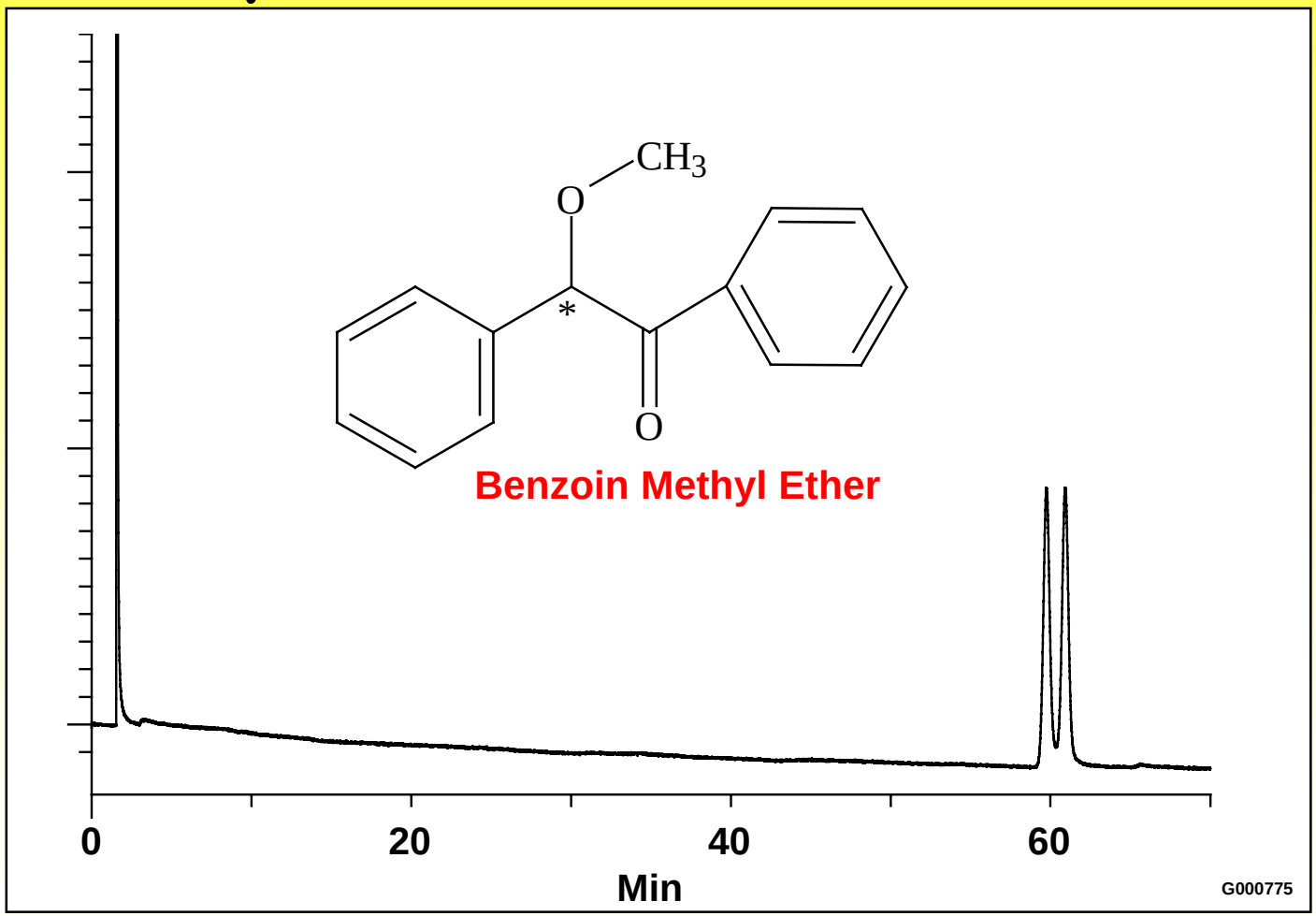
Isothermal Analysis (150°C)
γ-DEX™ 225 Column



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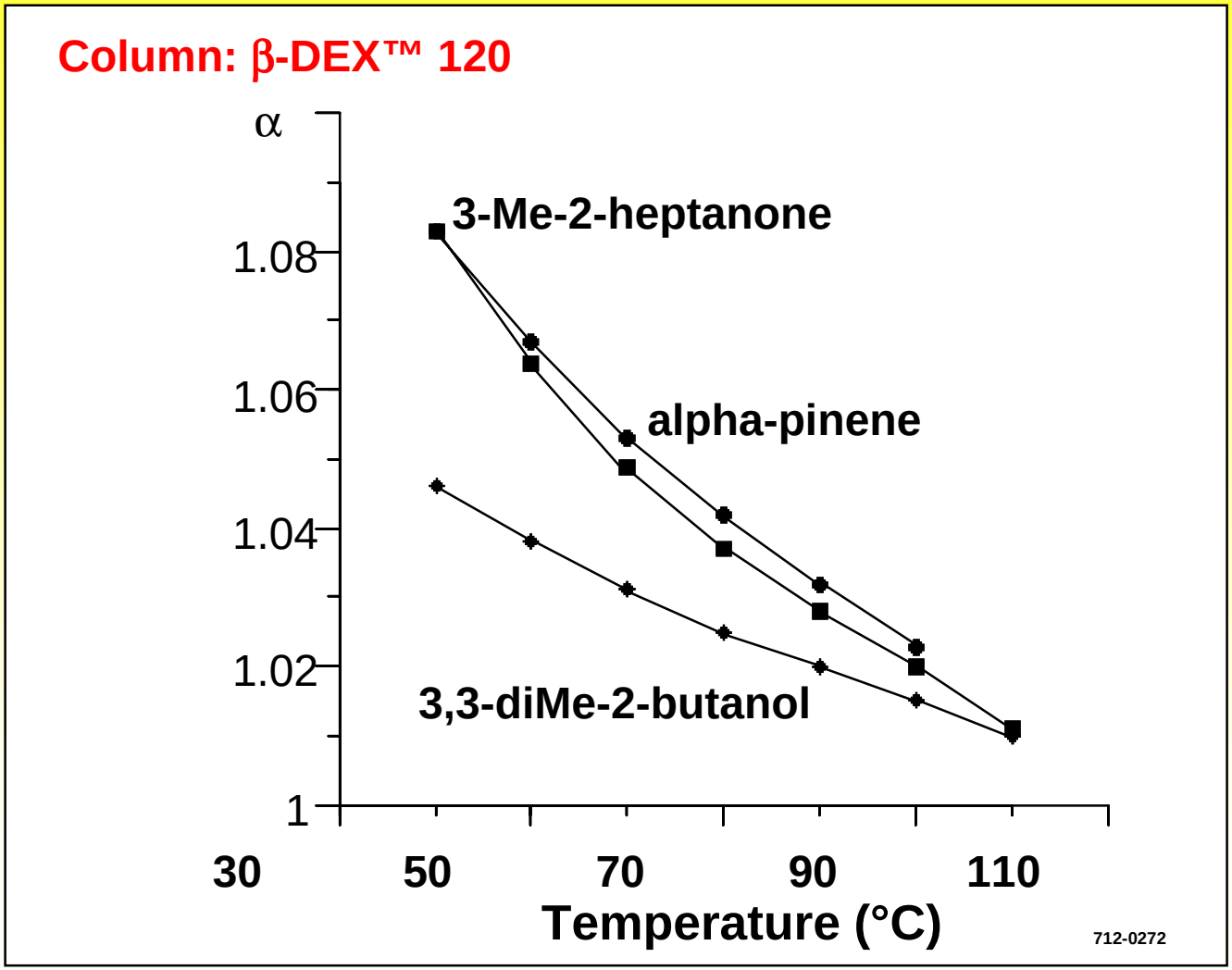
Effect of Temperature on Enantioselectivity



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Temperature-Dependent Enantioreversal

T (°C)	k'_R	k'_S	k'_R / k'_S	R_S
90	163	166	0.978	1.5
100	86.3	87.3	0.989	0.8
120	27.6	27.6	1	0.0
140	10.8	10.7	1.008	0.7
150	7.0	6.9	1.010	0.8

Analyte: Ethyl mandelate
Column: β-DEX™ 120, 30m x 0.25mm x 0.25µm film

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Isoenantioselective Temperature

$$RT \ln \alpha = -\delta(\Delta H) + T\delta(\Delta S)$$

where:

$\delta(\Delta H)$ = difference in enthalpy of sorption of the enantiomers

$\delta(\Delta S)$ = difference in entropy of sorption of the enantiomers

$$T_{isoen} = \delta(\Delta H) / \delta(\Delta S)$$

T_{isoen}: enantioseparation is impossible

97-0432

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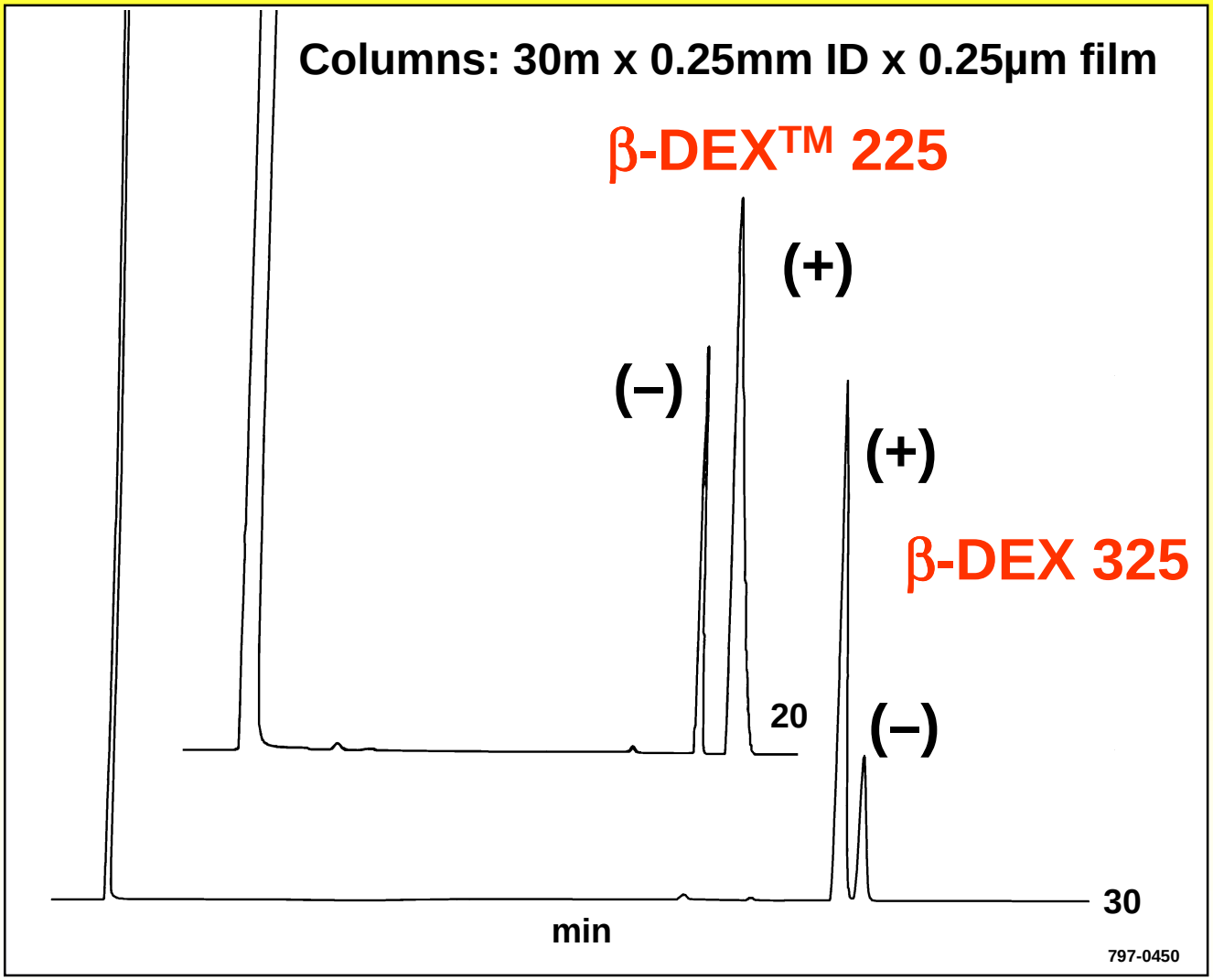
Enantioseparation of Terpinen-4-ol at 100°C



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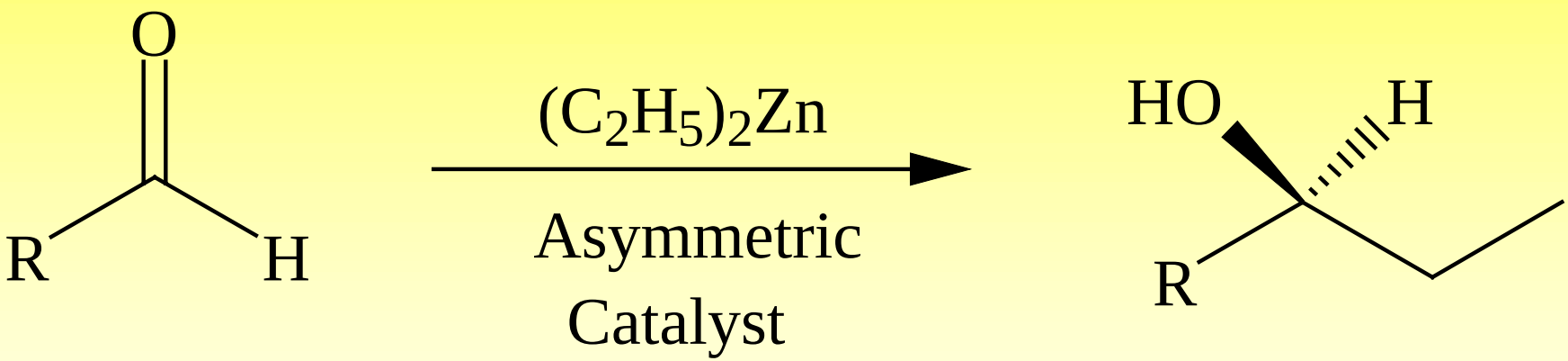
Enantiomeric Excess Determination: β-DEX™ 120



Jun, Guo, and Zhang* J. Org. Chem.

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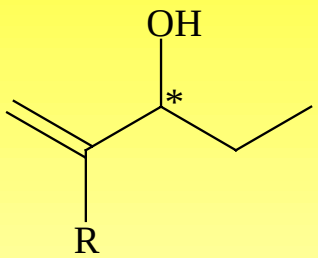
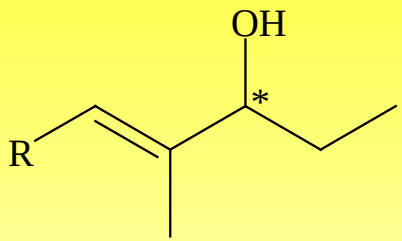
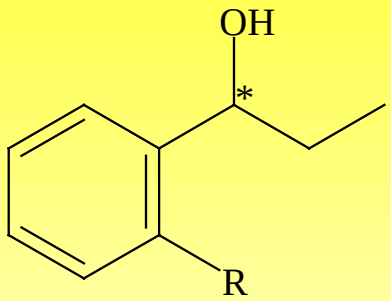
Enantiomeric Excess Determination: β-DEX™ 120



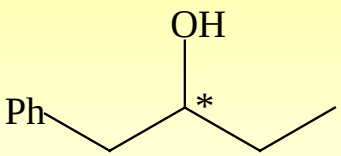
R = CH_3, C_2H_5, C_4H_9-n

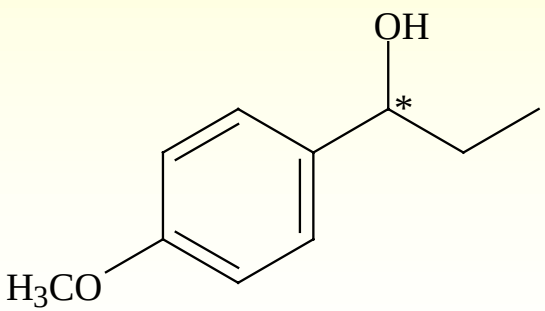


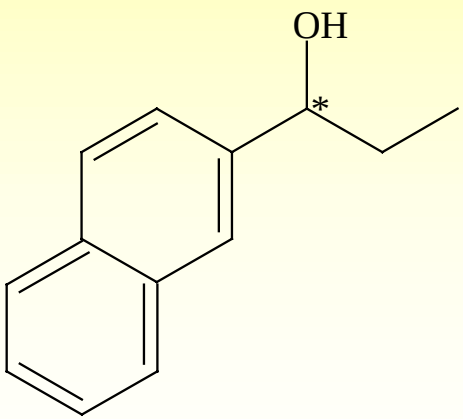
R = CH_3, C_6H_5

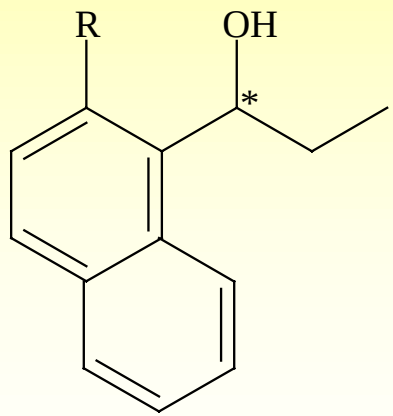


R = H, CH_3, OCH_3, Cl





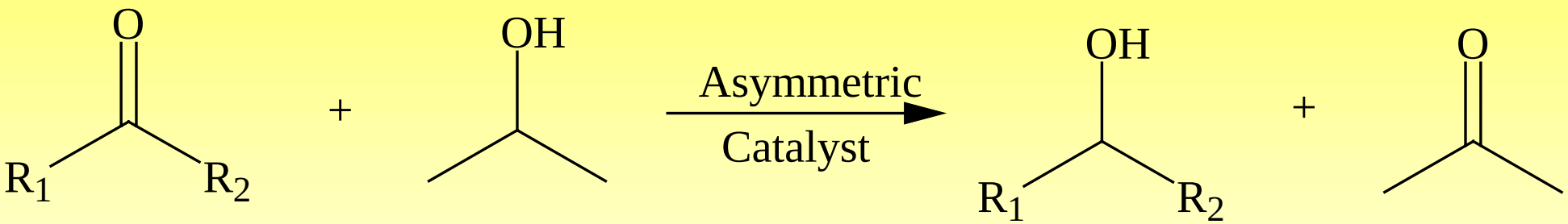




R = H, OCH_3

SUPELCO

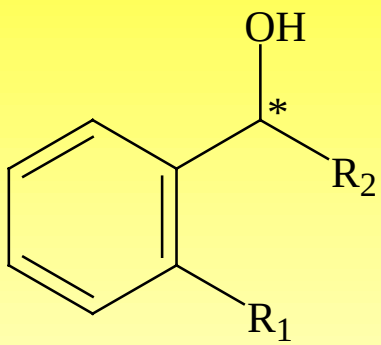
Enantiomeric Excess Determination: β-DEX™ 120



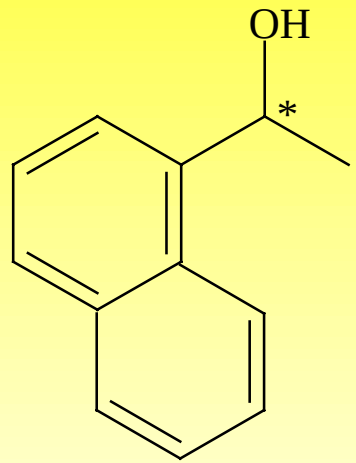
Jiang, Jiang, Zhu, and Zhang* Tetrahedron Letters 1997, *38*, 6565

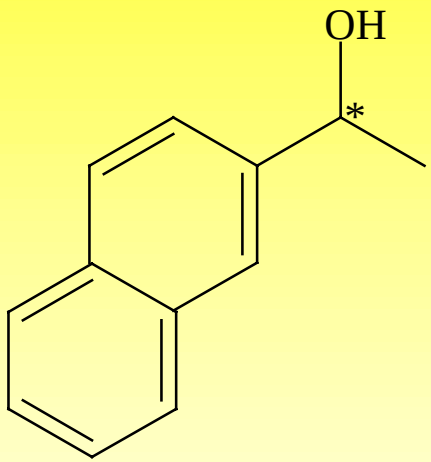
SUPELCO

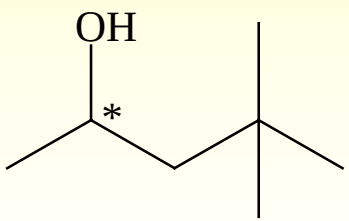
Enantiomeric Excess Determination: β-DEX™ 120

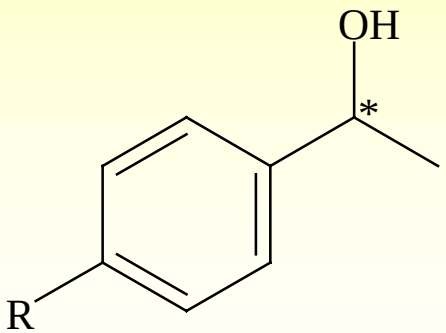


R_1 = H, R_2 = CH_3
R_1 = H, R_2= C_2H_5
R_1 = R_2 = CH_3

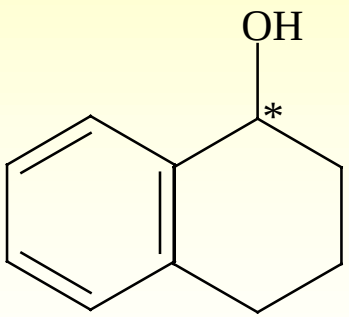






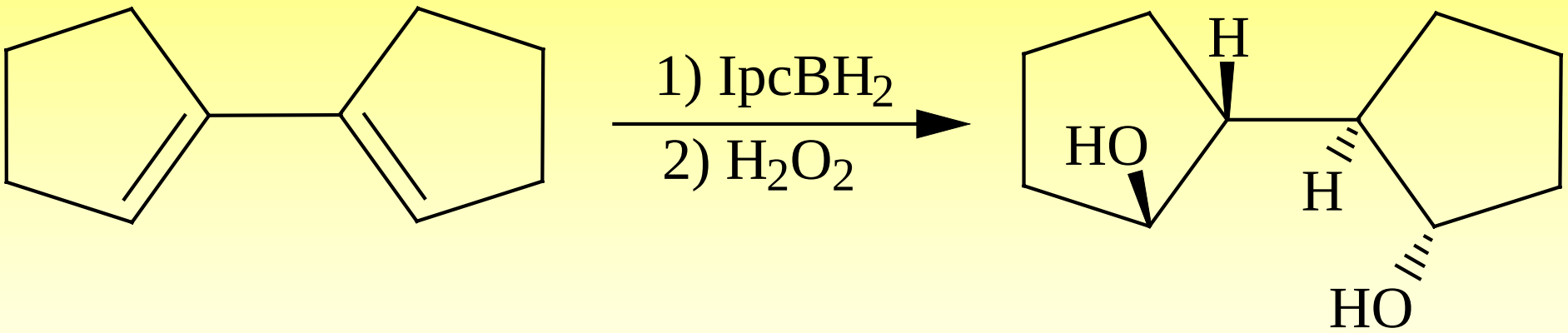


R = OCH_3, Br



SUPELCO

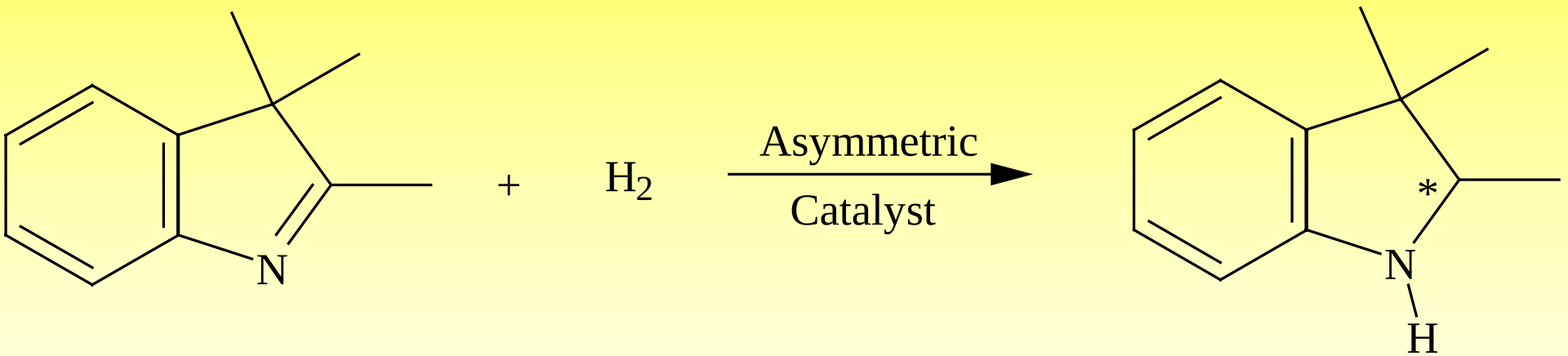
Enantiomeric Excess Determination: γ-DEX™ 225



Zhu, Cao, Jiang, and Zhang* J. Am. Chem. Soc. 1997, 119, 1799

SUPELCO

Enantiomeric Excess Determination: β-DEX™ 225



Zhu and Zhang* Tetrahedron: Asymmetry 1998, 9, 2415

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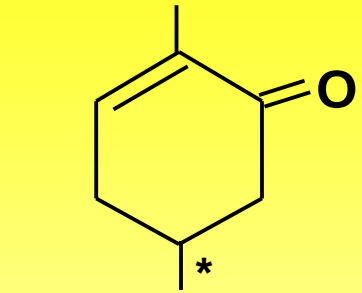
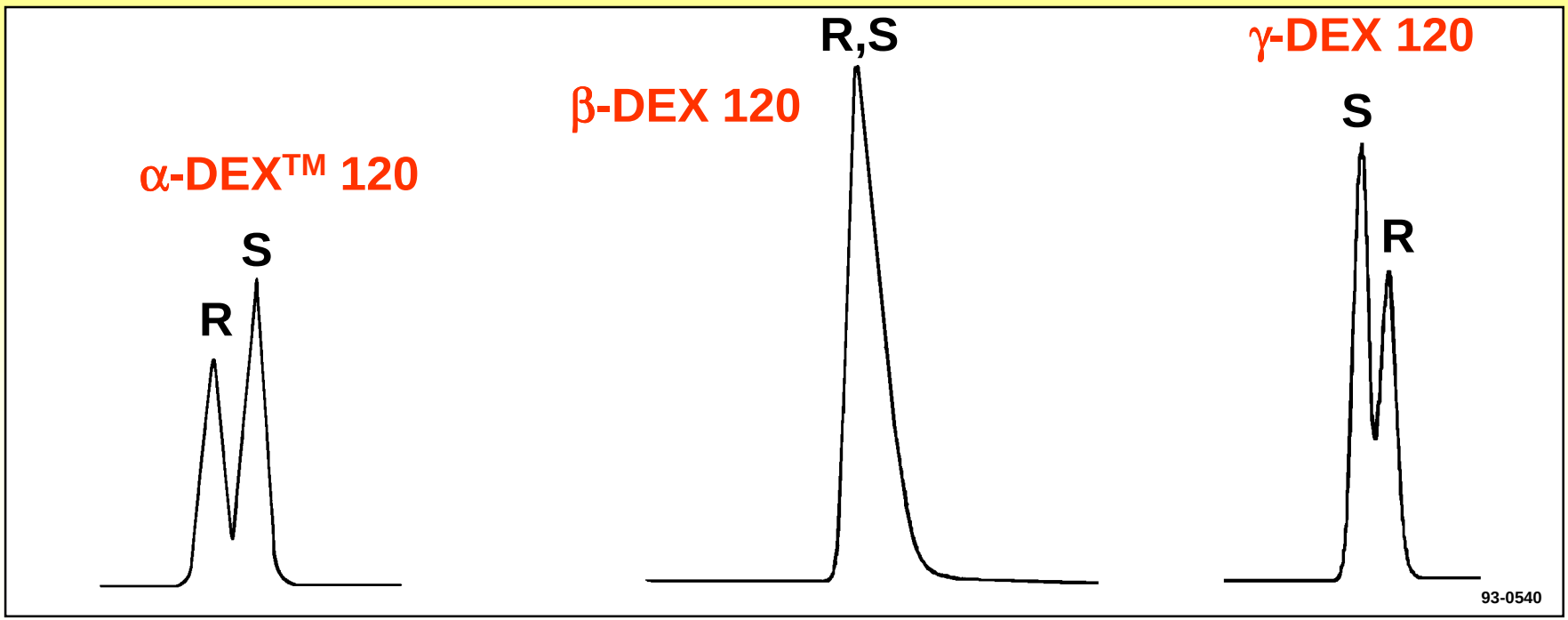
Carvone (Enantioreversal)



Columns: 30m x 0.25mm ID x 0.25µm film
Oven: 90°C

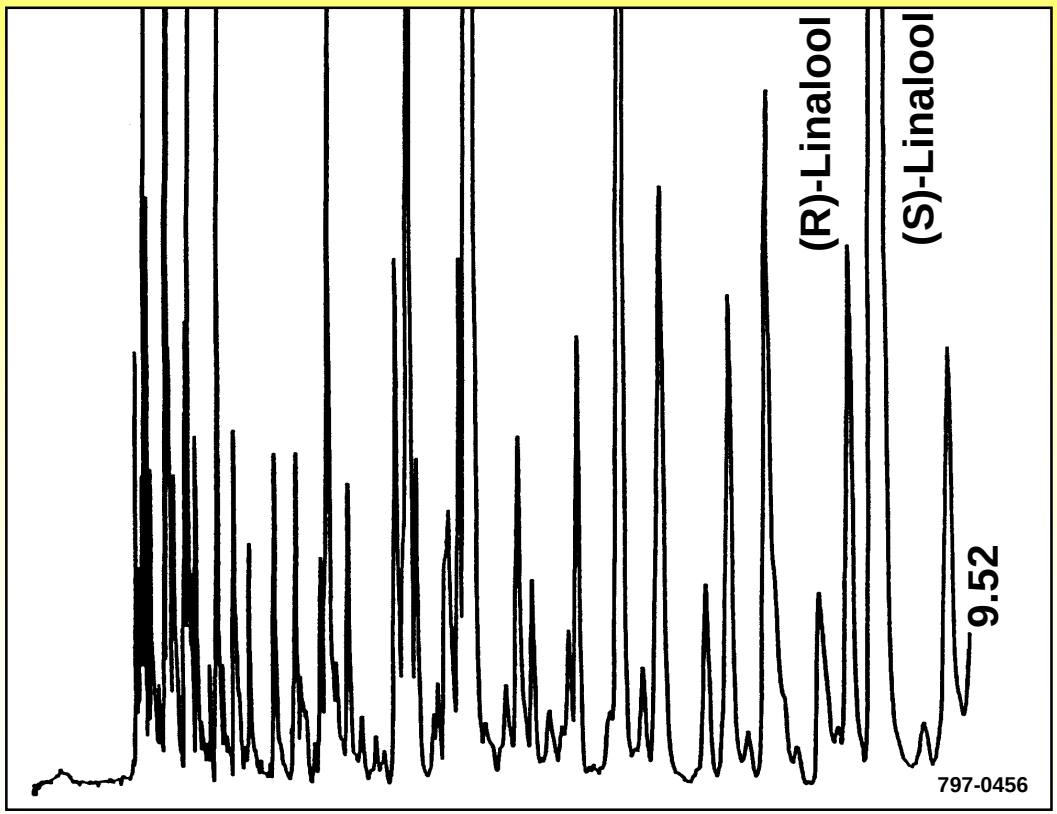


97-0473

SUPELCO

Linalool Enantiomers in Tea

Sample: Gao-sun tea (Taiwan)
SPME Fiber: 65µm polydimethylsiloxane / divinylbenzene
Column: β-DEX™ 325, 30m x 0.25mm ID x 0.25µm film
Oven: 100°C



97-0486

SUPELCO

Enantiomeric Ratio of Linalool in Teas

can be used to identify / control quality of tea

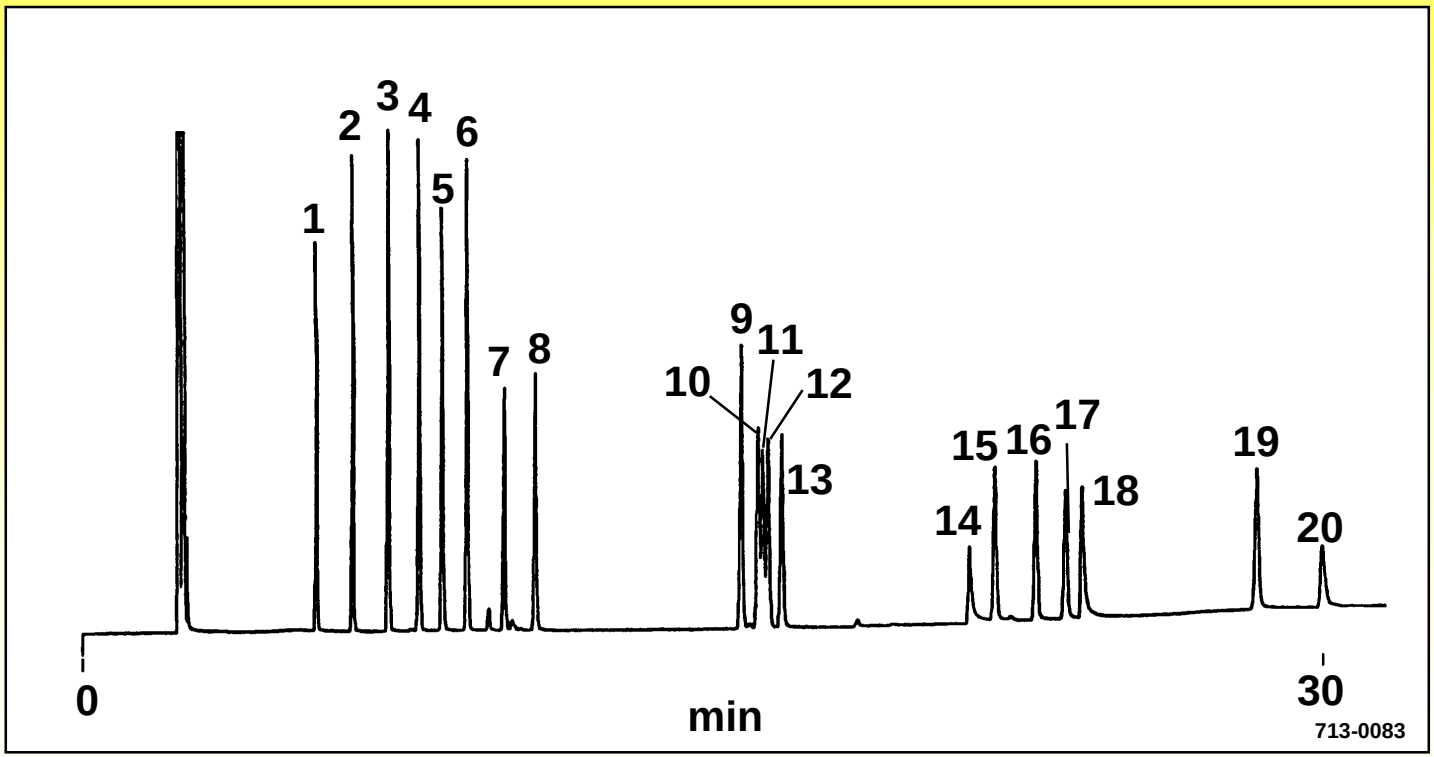
Type of Tea (Source)	R/S Ratio
Gao-sun (Taiwan)	9:91
Assam (Yamamoto, Orient, Los Angeles)	34:66
Spring Harvest, Lichee's Black (China)	36:64
Arati (Tea Packs Specialty Ltd., Calcutta)	40:60
Darjeeling (Jacksons of Picadilly)	44:56
Green Label (Lipton)	47:53
Hoji-cha (Yamamotoyama, Japan)	50:50
Yunnan Tuo (Xiaguan Tea Factory, China)	56:44
Red Label (Brooke Bond Lipton India, Calcutta)	58:42
Lapsang Souchong (China)	65:35

97-0437

SUPELCO

Environmental Phenols

Column: α-DEX™ 120, 30m x 0.25mm ID x 0.25µm film
Oven: 130°C to 220°C at 3°C/min



1. 2-Chlorophenol
2. Phenol
3. o-Cresol
4. p-Cresol
5. m-Cresol
6. 2,4-Dimethylphenol
7. 2,4-Dichlorophenol
8. 2,6-Dichlorophenol
9. 4-Chloro-3-methylphenol
10. 2,3,5-Trichlorophenol
11. 2,4,6-Trichlorophenol
12. 2,3,4-Trichlorophenol
13. 2,4,5-Trichlorophenol
14. 4-Nitrophenol
15. 2,3,5,6-Tetrachlorophenol
16. 2,3,4,6-Tetrachlorophenol
17. 2,3,4,5-Tetrachlorophenol
18. 4,6-Dinitrophenol
19. 2,4-Dinitrophenol
20. Pentachlorophenol

97-0489

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Conclusions

- Derivatized cyclodextrins are the most useful chiral selectors for enantioselective capillary GC
- A broad range of volatile and semi-volatile enantiomers can be resolved using cyclo-dextrin-based capillary columns
- Selecting the appropriate DEX™ column is an empirical process

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