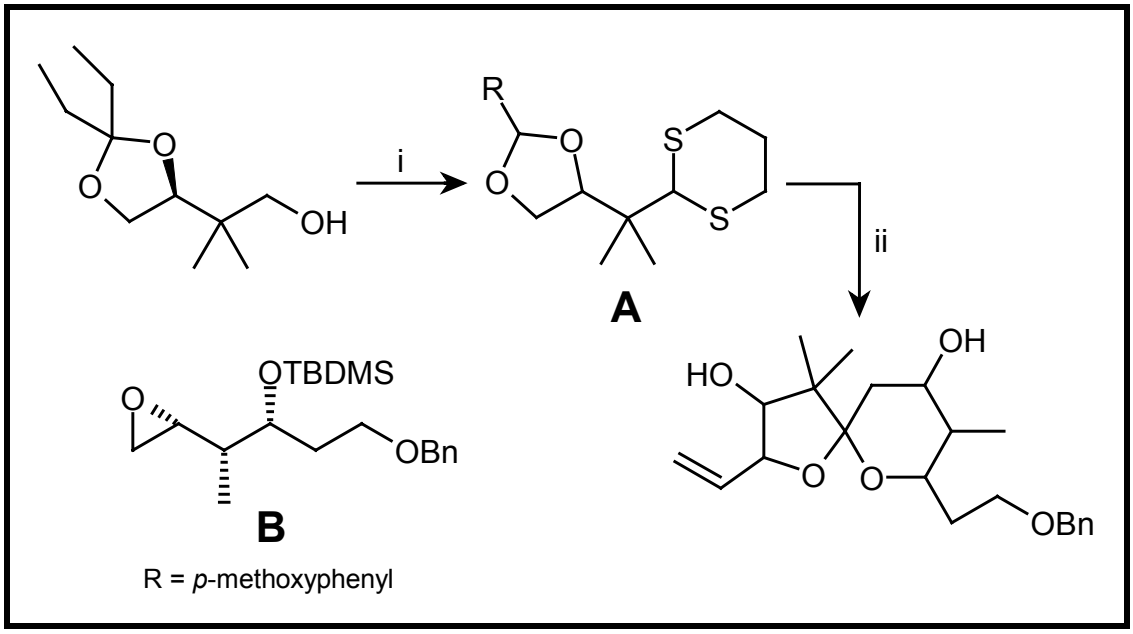
Exercises in Organic Chemistry

Exercise 1.



i: a) $Cl_2C_2O_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC; b) 1,3-Propanedithiol (2.5 equiv), $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 ºC; c) *p*-methoxybenzaldehyde dimethyl acetal, *p*-TsOH, DMF, t.a..

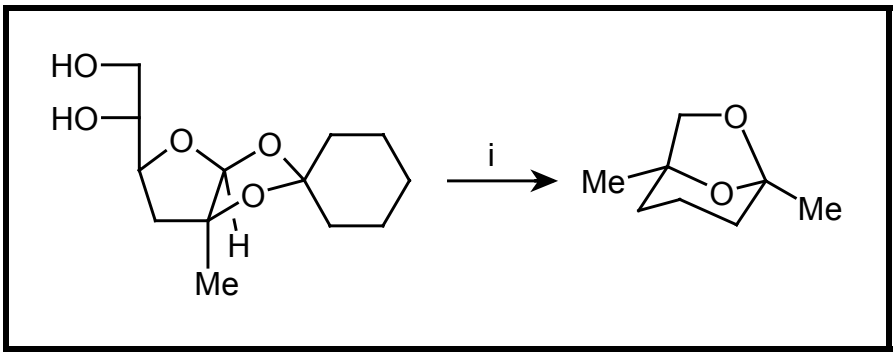
ii: a) 1º- Compound **A** (1.5 equiv), *n*-BuLi (1.5 equiv), TMEDA (6 equiv), THF, -78 → -20 ºC; 2º- DMPU (6 equiv); 3º- Compound **B** (1 equiv), THF, -20 ºC; b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC; c) DIBAL, CH_2Cl_2, -78 → 0 ºC; d) DMSO, $SO_3{\cdot}$py, Et_3N, CH_2Cl_2, t.a.; e) Vinylmagnesium bromide, THF, -78 ºC; f) HF, CH_3CN, H_2O, CH_2Cl_2, t.a..

Notes:

TMEDA is a complexating agent which withdraws the lithium cation, increasing the reactivity of the organolithium reagents.
The addition of DMPU on the step ii a) increases the reaction yield.
The reductive opening of bencylidene acetals using DIBAL yields the primary alcohol and an ether.
Conditions ii d) yield an aldehyde.
On the step ii e), the addition of the magnesium reagent produces mainly the *S* epymer.
On the step ii f), the cyclation yields the more stable acetal.

Bibliography: Smith III, A.B.; Duan, J.J.-W.; Hull, K.G.; Salvatore, B.A. *Tetrahedron Lett.* **1991**, *32*, 4855.

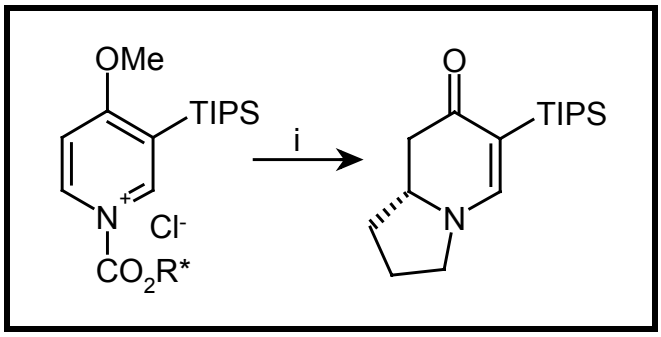
Exercise 2.



i: a) IO_4H; b) $NaBH_4$; c) BnCl, KOH; d) H_2O, H^+ cat.; e) $NaBH_4$; f) Acetone, H^+, azeotropic water removal; g) H_2, Pd/C; h) IO_4H; i) $Ph_3P{=}CHCOMe$; j) H_2, Pd/C; k) *p*-TsOH.

Bibliography: *ApSimon,* Vol. 4, 154.

Exercise 3.



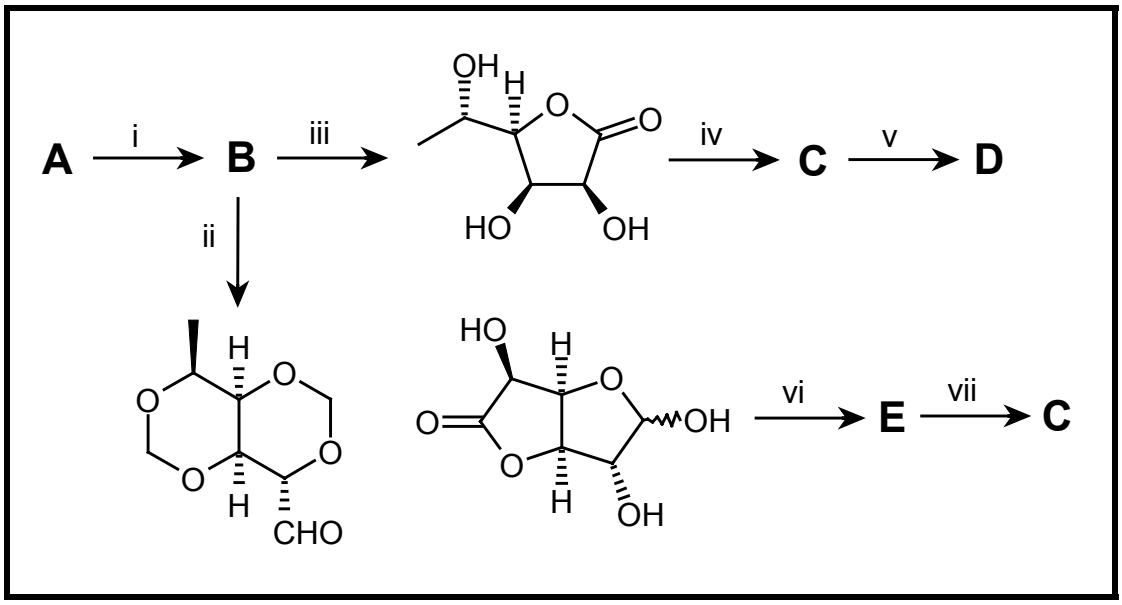
i: a) 1º- 3-buthenyl magnesium bromide; 2º- H_3O^+; b) 1º- OsO_4 (cat.), $NaIO_4$; 2º- L-Selectride®; c) Ph_3P, NCS, CH_2Cl_2; d) NaOMe, MeOH.

Notes:

R* stands for (-)-*trans*-2-(α-cumyl)cyclohexyl (TCC), a chiral auxiliary.
The mixture of Ph_3P and NCS transforms alcohols in chlorides.

Bibliography: Comins, D.L.; Chen, X. y Morgan, L.A. *J. Org. Chem.* **1997**, *62*, 7435.

Exercise 4.



A: (2*R,* 3*S,* 4*R,* 5*R*)-2,3,4,5,6-Pentahydroxyhexanal.
C: Mixture of methyl gulopyranosides.
D: 6-Deoxi-2,3-*O*-isopropylidene-4-*O*-methyl-L-gulopyranose.
E: 2-*O*-(*t*-Butyldimethylsilyl)-6-deoxi-3,5-*O*-isopropylidene-L-gulofuranose.

i: a) 1,3-Propanedithiol, H_3O^+; b) H_2, Ni Raney, Et_2O, H_2O; c) Formaldehyde, H^+; d) CrO_3.

ii: a) Diazomethane; b) DIBAL (1 equiv).

iii: H_2O, H^+.

iv: a) Na(Hg), H_3O^+; b) MeOH, H^+.

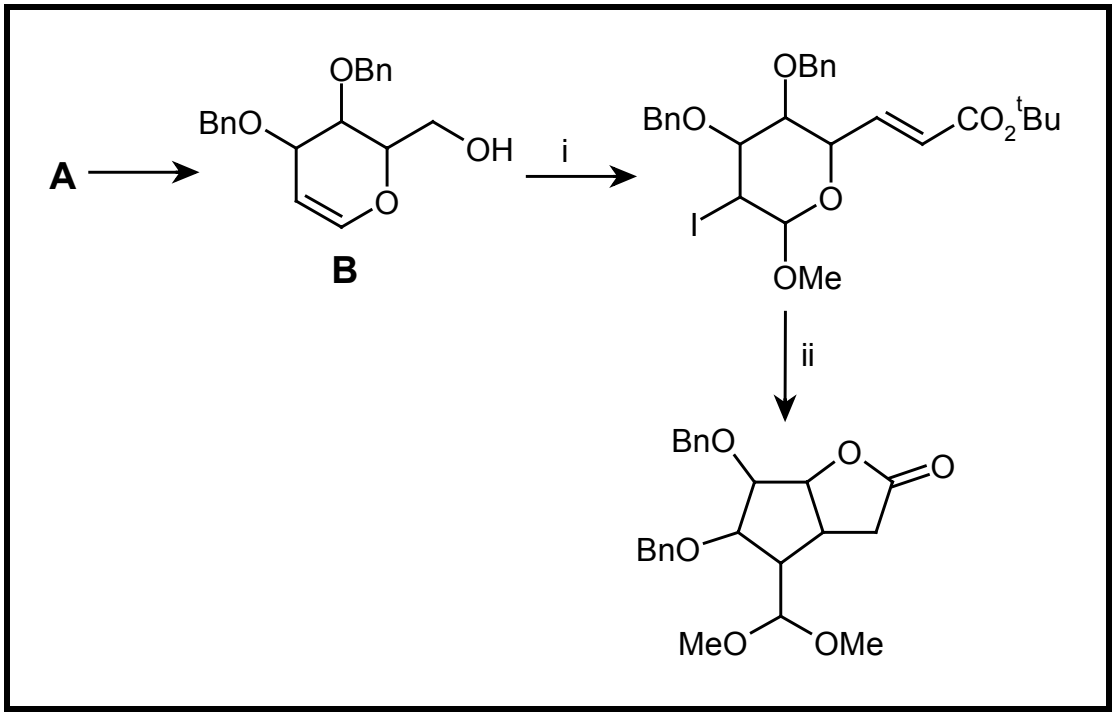
v: a) 2,2-Dimethoxypropane, acetone, H^+; b) KH, MeI, THF; c) H_2O, H^+; d) 2,2-Dimethoxypropane, acetone, H^+.

vi: a) 1,2-Ethanedithiol, H_3O^+; b) 2,2-Dimethoxypropane, acetone, H^+; c) H_2, Ni Raney, EtOH, THF; d) *t*-Butyldimethylsilyl chloride, imidazole, DMF; e) DIBAL (1 equiv), THF.

vii: MeOH, H^+.

Bibliography: Ireland, R.B.; Wilcox, C.S. *J. Org. Chem.* **1980**, *45*, 197.

Exercise 5.



A: D-Glucose.

i: a) PCC; b) Ph_3=CH-CO2^{t}Bu; c) *N*-Iodosuccinimide, MeOH.

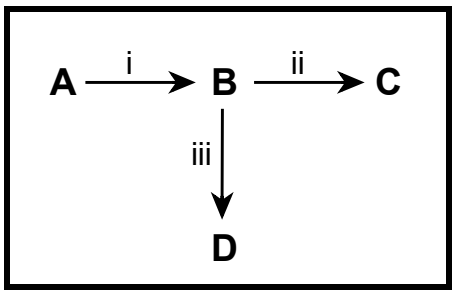
ii: a) HSn(*n*-Bu)$_3$, AIBN; b) MeOH, H^+.

Notes:

Under the conditions i c), the cyclic iodonium cation generates stereoselectively the α glucopyranoside.

Bibliography: Vite, G.D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, 2268.

Exercise 6.



A: (1*R*, 4*R*)-Byciclo[2.2.1]hept-5-en-2-one.
B: (2*R*, 3*R*, 4*R*)-2,3-Dihydroxy-2,3-*O*-isopropyliden-4-(triphenylmethoxymethyl)cyclopentan-2-one.
C: (1*S*, 2*R*, 3*R*, 4*R*)-1-Acetoxymethyl-2,3-*O*-isopropyliden-4-(triphenylmethoxy methyl)cyclopentan-1,2,3-triol.
D: (1*R*, 2*R*, 3*R*, 4*R*)-1-Acetoxymethyl-2,3-*O*-isopropyliden-4-(triphenylmethoxy methyl)cyclopentan-1,2,3-triol.

i: a) 1º- H_2O_2, NaOH, H_2O, Et_2O; 2º- MeI (1.1 equiv), DMF, t.a.; 3º- Ac_2O, py, DMAP, CH_2Cl_2, t.a.; b) 1º- OsO_4, NMO, acetone, t.a.; 2º- 2,2-dimethoxypropane, *p*-TsOH, t.a.; c) $LiAlH_4$, Et_2O, 0 ºC → t.a.; d) Br_2, Ph_3P, Et_3N, CH_2Cl_2, t.a.; e) 1º- 2-nitrophenylselenecianate, $NaBH_4$, THF, t.a.; 2º- H_2O_2, THF, t.a.; f) 1º- OsO_4, $NaIO_4$, H_2O, Et_2O, t.a.; 2º- $NaBH_4$, MeOH, t.a.; g) TrCl, py, DMAP, CH_2Cl_2, t.a.; h) PDC, CH_2Cl_2, t.a..

ii: a) 1º- $Me_3S(O)^+I^-$, NaH, DMSO, THF, t.a.; 2º- Addition of compound **B**; b) CsOAc, DMF, 80 ºC.

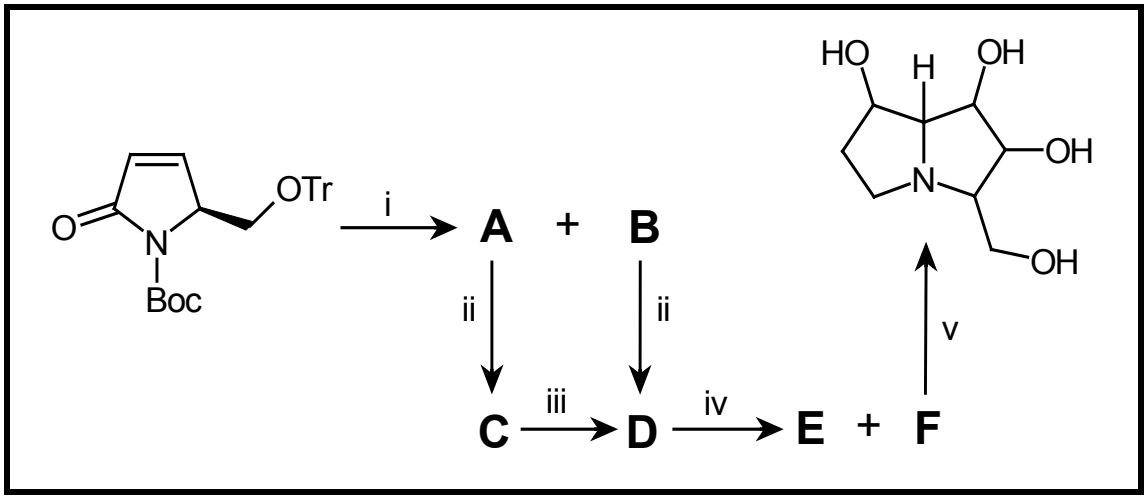
iii: a) 1º- CH_2Br_2, *n*-BuLi, THF, -80 ºC → t.a.; 2º- Addition of compound **B**; b) CsOAc, DMF, 80 ºC.

Notes:

The reaction with the sulphur ilyde occurs on the *most* hindered face.

Bibliography: Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron* **1993**, *49*, 5067.

Exercise 7.



i: a) 1º- OsO_4 cat., *N*-methylmorfoline *N*-oxide, acetone-H_2O; 2º- 2,2-Dimethoxypropane, *p*-TsOH cat., acetone; b) Vinylmagnesium bromide, THF, -50 ºC; c) $NaBH_4$, $CeCl_3{\cdot}7H_20$, MeOH; d) 1º- O_3, CH_2Cl_2, -78 ºC; 2º- $NaBH_4$, EtOH.

ii: a) *t*-Butyldimethylsilyl chloride, imidazole, DMF, 0 ºC.

iii: 1º- $Cl_2C_2O_2$, DMSO, Et_3N, CH_2Cl_2, -20 ºC; 2º- $NaBH_4$, EtOH, -78 ºC.

iv: a) 1º- MsCl, Et_3N, CH_2Cl_2; 2º- KO*t*-Bu, THF; b) TBAF, THF; c) 1º- $Cl_2C_2O_2$, Et_3N, DMSO, CH_2Cl_2, -20 ºC; 2º- Allylmagnesium chloride, THF.

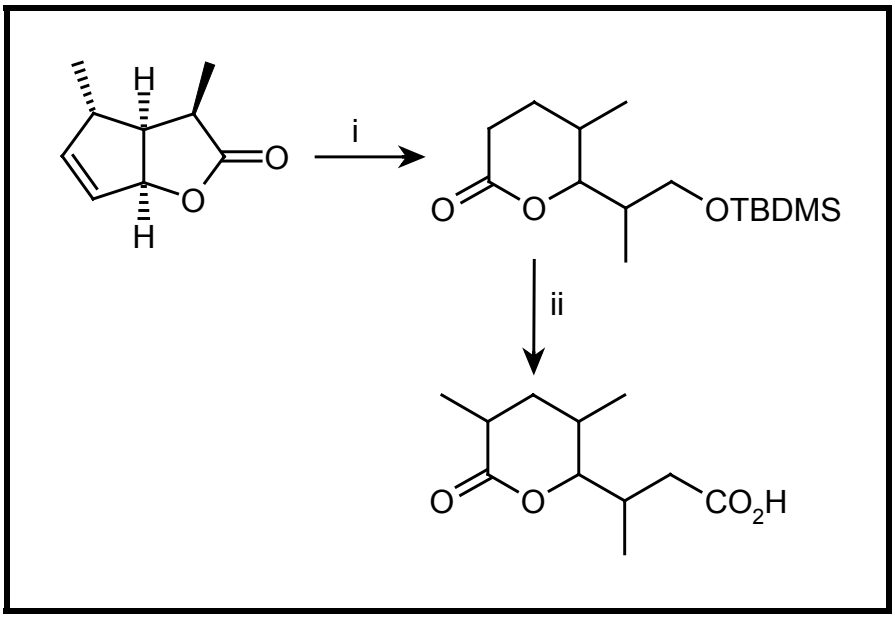
v: a) Methoxymethyl chloride, *N,N*-diethylaniline, CH_2Cl_2; b) 1º- TBDMSOTf, 2,6-lutidine, CH_2Cl_2; 2º- TBAF, THF; 3º- BnBr, K_2CO_3, acetone; c) 1º- O_3, CH_2Cl_2, -78 ºC; 2º- $NaBH_4$, EtOH; d) 1º- MsCl, Et_3N, CH_2Cl_2; 2º- Pd/C 10%, H_2, EtOH; e) HCl 10%, MeOH, 60 ºC.

Notes:

The use of Ce^{3+} salts allows the selective reduction of the carbonyl moiety in α,β-unsaturated compounds.
Compound C posses a hydroxy group on a carbon with *R* configuration.
The step iii yields a mixture of the compounds C and D in a 1:18 ratio.
Compound F is the epimer with the *S* configuration in the new chiral center.
On the step v b) occurs the selective deprotection of the *N*-Boc group and the introduction of a *N*-Bn.

Bibliography: Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553.

Exercise 8.



i: a) $LiAlH_4$; b) H_2, Pt; c) *t*-Butyldimethylsilyl chloride, imidazole; d) CrO_3, py; e) *m*-CPBA.

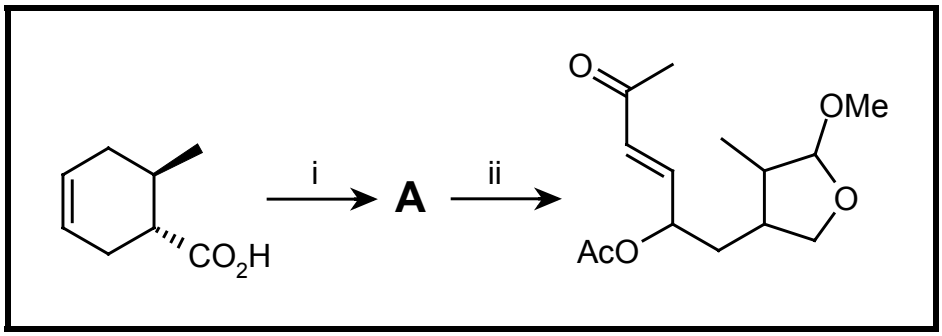
ii: a) 1º- LDA; 2º- MeI; 3º- H^+; b) CrO_3.

Notes:

On the step ii a) the methyl group is introduced with the most stable configuration.

Bibliography: Grieco, P.A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101,* 4749.

Exercise 9.



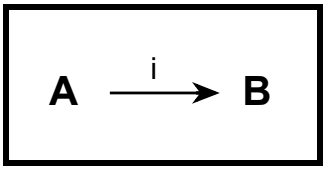
A: (2*R*)-2-Methyl-6-oxabicycle[3.2.1]octen-3-en-7-one.

i: a) I_2, $NaHCO_3$, CH_2Cl_2/H_2O; b) DBU, THF, Δ.

ii: a) $LiAlH_4$, THF; b) *t*-Butyldimethylsilyl chloride, imidazole, DMF; c) Ac_2O, py, DMAP; d) TBAF, THF; e) 1º- O_3, MeOH, -78 ºC; 2º- Me_2S; f) Ph_3P=CHCOMe, $CHCl_3$; g) PPTS, MeOH, 50 ºC.

Bibliography: Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron* **1993**, *48*, 11189.

Exercise 10.



A: Methyl 2,3-di-*O*-bencyl-α-D-glucopyranoside.
B: Uronic acid methyl esther.

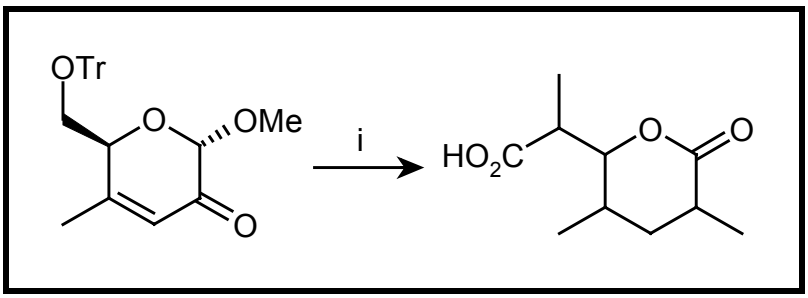
i: a) *t*-Butyldiphenylsilyl chloride, imidazole, DMF; b) Thiocarbonyldiimidazole, tolueno, ref.; c) HSn(*n*-Bu)$_3$, AIBN, toluene, ref.; d) TBAF, THF; e) PDC, DMF; f) 1º- $Cl_2C_2O_2$, DMF cat., CH_2Cl_2; 2º- CH_2N_2, Et_2O; g) hν, MeOH.

Notes:

The uronic acids are derived from aldoses by oxidation of the hydroxy group in the terminal carbon atom.

Bibliography: Kende, A.S.; Mendoza, J.S.; Fujii, Y. *Tetrahedron* **1993**, *36*, 8015.

Exercise 11.



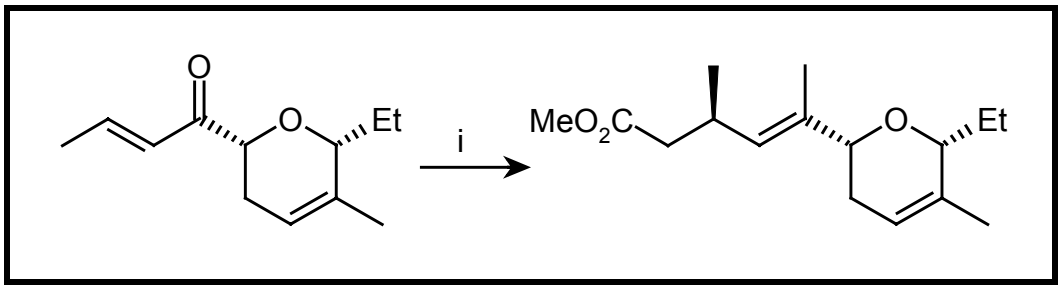
i: a) $Ph_3P=CH_2$; b) H_2, Pd/C; c) CrO_3, py; d) MeLi; e) CrO_3, py; f) 1º- $Ph_3P=CHOMe$; 2º- H_3O^+; g) CrO_3; h) Separation of the epimer with the *R* configuration on the position adjacent to the carboxy moiety.

Notes:

The catalytic hydrogenation on the step i b) yields mainly the diastereoisomer with the substituents affected by the reaction in equatorial disposition. The synthesis is carried out with this diastereoisomer.

Bibliography: Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 2533.

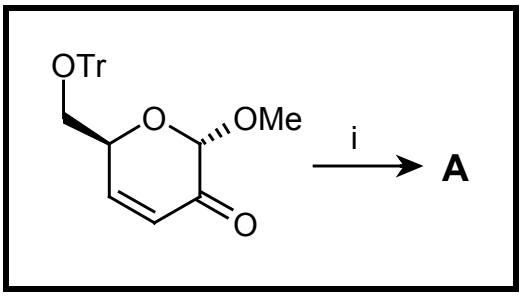
Exercise 12.



i: a) 1º- BrMgMe, THF, 0 ºC; 2º- Ac_2O, DMAP, Et_3N, CH_2Cl_2; b) 1º- LDA, THF, -78 ºC; 2º- *t*-Butyldimethylsilyl chloride, imidazole, DMF, -78 ºC → -60 ºC; 3º- H_3O^+; c) CH_2N_2, Et_2O.

Bibliography: Kende, A.S.; Mendoza, J.S.; Fujii, Y. *Tetrahedron* **1993**, *36*, 8015.

Exercise 13.



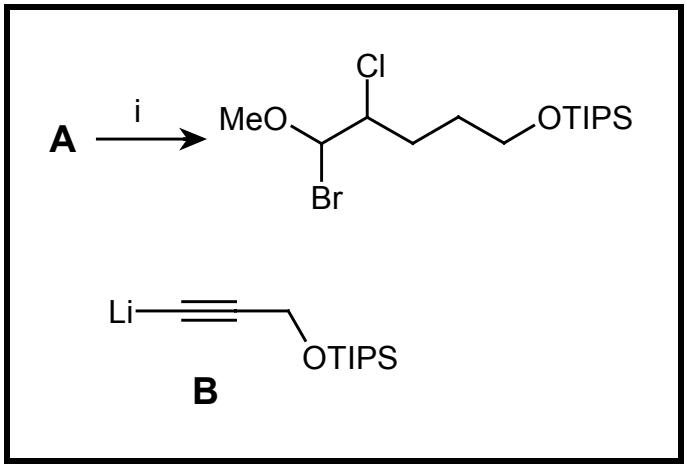
i: a) 1º- MeLi; 2º- Ac_2O; b) Me_2CuLi; c) H_2, Pt; d) $Cl_2C_2O_2$, DMSO, Et_3N; e) $MeNO_2$, KF; f) Ac_2O, DMAP.

Notes:

The addition of the cuprate on the step i b) yields the compound with the methyl in equatorial disposition.
The catalytic hydrogenation on the step i c) yields a 4:1 mixture of the equatorial/axial products; the equatorial is isolated and used.
The KF is used as base.

Bibliography: Kawachi, N.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1441.

Exercise 14.



A: 2-Hydroxyacetaldehyde dimethyl acetal.

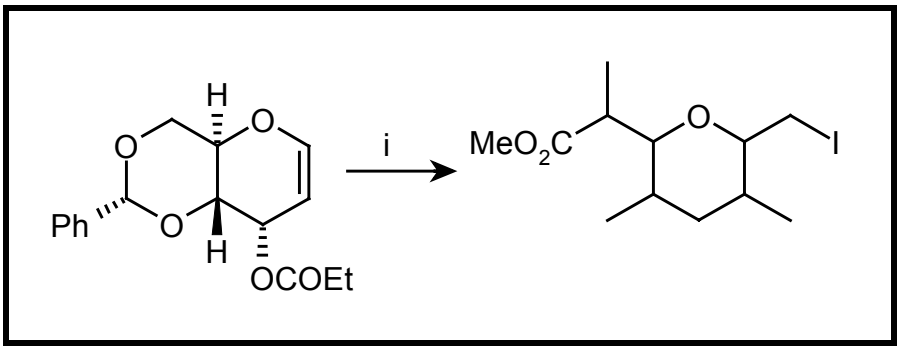
i: a) $Cl_2C_2O_2$, DMSO, Et_3N; b) Addition of compound **B**; c) CrO_3, H_2O, H_2SO_4, acetone; d) (R)-Binal-H; e) H_2, $Pd/BaSO_4$; f) Tf_2O, py; g) TBAC, CH_2Cl_2, 25 ºC; h) Me_2BBr, -78 ºC.

Notes:

The reduction with (*R*)-Binal-H yields an alcohol of *S* configuration.

Bibliography: Berger, D.; Overman, L.E.; Renhowe, P.A. *J. Am. Chem. Soc.* **1993**, *115*, 9305.

Exercise 15.



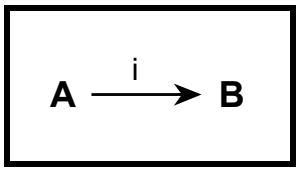
i: a) 1º- $LiN(TMS)_2$; 2º- *t*-Butyldimethylsilyl chloride, imidazole; 3º- Δ; b) CH_2N_2; c) H_3O^+; d) *t*-Butyldimethylsilyl chloride, imidazole; e) PDC; f) Me_2CuLi; g) $Ph_3P{=}CH_2$; h) H_2, Pt; i) TBAF; j) TsCl, py; k) NaI.

Notes:

The conditions used on the step i a) yield the *E* enolate.
The catalytic hydrogenation on the step i h) generates a new asymmetric center with the *R* configuration.

Bibliography: Ireland, R.E.; Daub, J.P. *J. Org. Chem.* **1981**, *46*, 479.

Exercise 16.

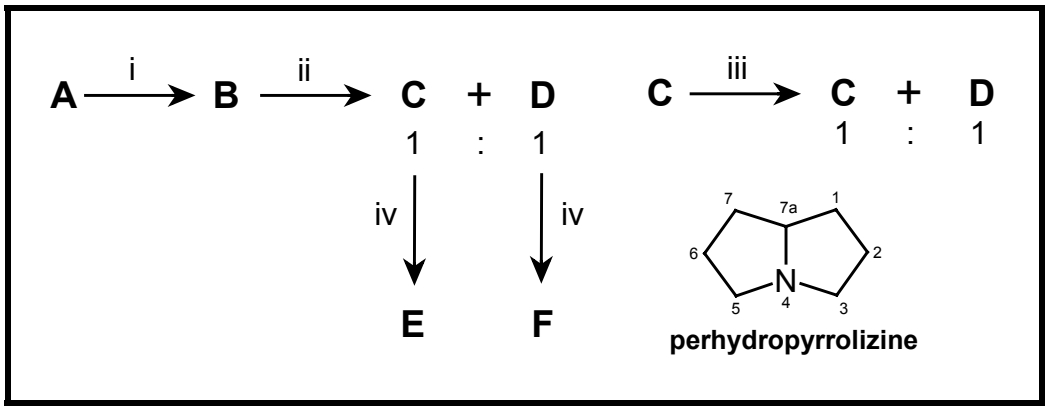


A: (*S*)-*N*-Phenylsulfonylserine.
B: (2*S*, 3*S*, 4*R*)-2-(Hydroxymethyl)-3-methyl-3,4-pyrrolidinediol.

i: a) MeLi; b) 1º- NaH; 2º- Triphenylvinylphosphonium bromide; c) *t*-Butyldimethylsilyl chloride, imidazole; d) OsO_4 cat., *N*-methylmorfoline *N*-oxide; e) TBAF; f) *N*-sulphonamide deprotection.

Bibliography: Burley, I.; Hewson, A.T. *Tetrahedron Lett.* **1994**, *35*, 7099.

Exercise 17.



A: D-Glucose.
B: Methyl 2-azido-3-*O*-bencyl-2-deoxi-α-D-mannofuranoside.
C: $C_{23}H_{27}NO_4$.
E: (1*R*, 2*R*, 3*R*, 7*S*, 7a*S*)-3-(Hydroxymethyl)perhydro-1,2,7-pyrrolizinetriol.

i: a) Acetone, H^+; b) NaH, BnBr; c) H_2O, H^+ (mild); d) CO_3Me_2, NaOMe; e) MeOH, H^+; f) Tf_2O, py; g) NaN_3; h) NaOMe, MeOH.

ii: a) *t*-Butyldimethylsilyl chloride, imidazole, DMF, 0 ºC; b) Tf_2O, py, -30 ºC; c) 1º- H_2, Pd/C 10%, AcOEt; 2º- BnBr, KOH, DMF; d) TBAF, THF; e) 1º- $Cl_2C_2O_2$, DMSO; 2º- Et_3N; f) Vinylmagnesium bromide, THF.

iii: a) MnO_2; b) $NaBH_4$.

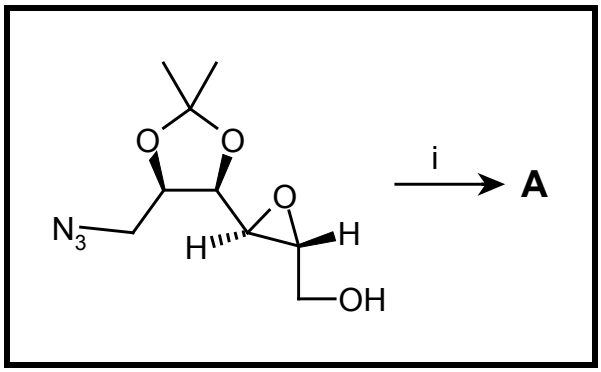
iv: a) *t*-Butyldimethylsilyl chloride, imidazole, DMF; b) 1º- $BH_3{\cdot}SMe_2$, THF; 2º- H_2O_2, OH^-; c) TsCl, py, CH_2Cl_2; d) H_2, Pd/C 10%; e) TFA, H_2O, 36 h; f) $NaBH_4$, EtOH.

Notes:

The compound **C** is the *S* epimer.
The step iv c) yields a salt.

Bibliography: a) Fleet, G.W.J.; Smith, P.W. *Tetrahedron* **1987**, *43*, 971. b) Fleet, G.W.J.; Haraldsson, M.; Nash, R.J.; Fellows, L.E. *Tetrahedron Lett.* **1988**, *29*, 5441.

Exercise 18.



A: (1*S*, 2*R*, 7*R*, 7a*R*)perhydro-1,2,7-pyrrolizinetriol.

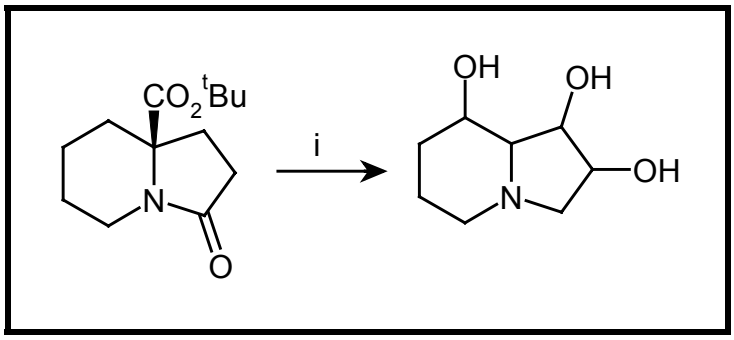
i: a) Tf_2O; b) LiCN; c) H_2, Pd/C, EtOH; d) Benzyl chloroformate; e) H_2O_2, MeOH; f) *t*-Butyldimethylsilyl chloride, imidazole; g) H_2, Pd/C; h) $NaHCO_3$; i) $BH_3{\cdot}SMe_2$; j) TFA, H_2O.

Notes:

The conditions used on the step i e) transform nitriles into amides.

Bibliography: Carpenter, N.M.; Fleet, G.W.J.; Cenci di Bello, I.; Winchester, B.; Fellows, L.E.; Nash, R.J. *Tetrahedron Lett.* **1989**, *30*, 7261.

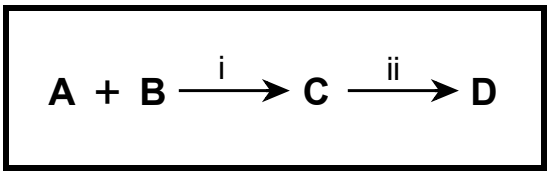
Exercise 19.



i: a) 1º- LDA; 2º- PhSeCl; b) H_2O_2, AcOH; c) OsO_4 cat., *N*-methylmorfoline *N*-oxide; d) 2,2-Dimethoxypropane, H^+; e) TFA, H_2O; g) $Cl_2C_2O_2$; h) Xylene, ref.; i) 1º- B_2H_6; 2º- H_2O_2, OH^-; j) HCl, H_2O.

Bibliography: Martín-López, M.J.; Bermejo-González, F. *Tetrahedron Lett.* **1994**, *35*, 8843; Martín-López, M.J.; Bermejo-González, F. *Tetrahedron Lett.* **1994**, *35*, 4235.

Exercise 20.



A: 2-*O*-Benzyl-D-glyceraldehyde.
B: 2-Nitroacetaldehyde diethyl acetal.
C: 1:1 Mixture of 5-*O*-tosyl-2-Benzyloxycarbonylamine-D-arabinose diethyl acetal and 5-*O*-tosyl-2-Benzyloxycarbonylamine-D-ribose diethyl acetal.
D: (2*R*, 3*S*, 4*R*)-2-(Hydroxymethyl)-3,4-pyrrolidinediol.

i: a) TBAF, H_2O; b) H_2, Pd/C, MeOH; c) Benzyl chloroformate, $NaHCO_3$; d) TsCl, py.

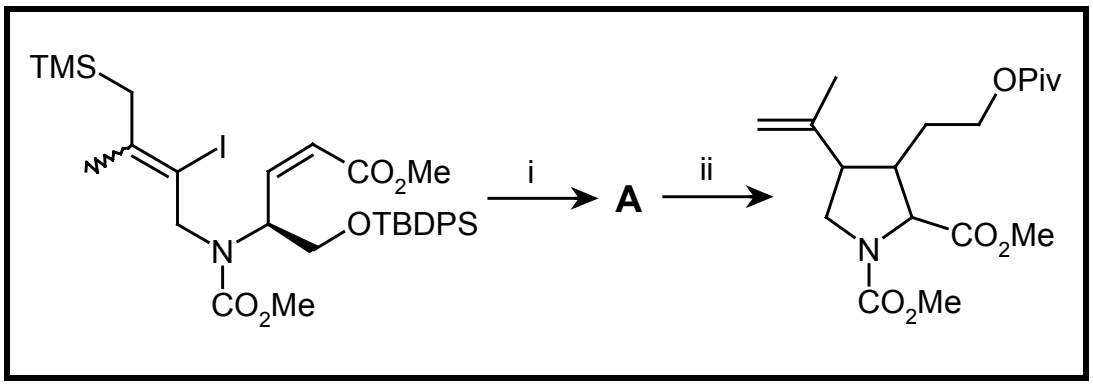
ii: a) H_2, Pd/C, MeOH; b) Benzyl chloroformate, $NaHCO_3$; c) Separation of epimers; d) HCl; e) $NaBH_4$; f) H_2, Pd/C.

Notes:

The use of the fluoride on the step i a) avoids the epimerization on the aldehyde α position.
The step ii a) yields a salt.

Bibliography: a) Wehner, V.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169. b) Jäger, V.; Hümer, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1182. c) Müller, R.; Leibold, T.; Pätzel, M.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1295.

Exercise 21.



i: a) $HSn(n\text{-}Bu)_3$, AIBN, bencene, ref.; b) $LiAlH_4$; c) Pivaloyl chloride, Et_3N; d) TBAF.

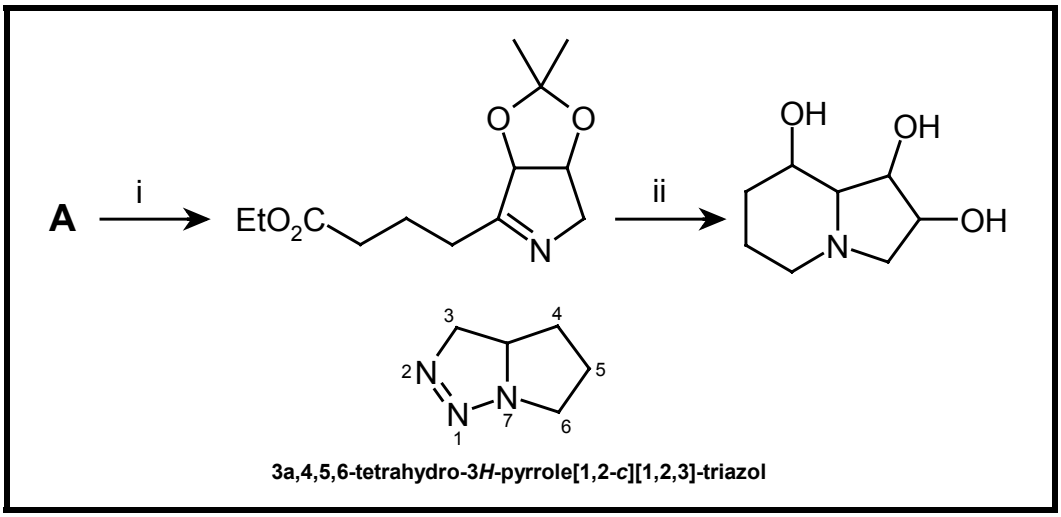
ii: a) $Cl_2C_2O_2$, DMSO, Et_3N; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; c) $BF_3{\cdot}Et_2O$; d) CH_2N_2.

Notes:

The conditions used on the step ii b) oxidize aldehydes to carboxilic acids.

Bibliography: Takano, S.; Inomata, K.; Ogasawara, K.J. *J. Chem. Soc. Chem. Commun.* **1992**, 169.

Exercise 22.



3a,4,5,6-tetrahydro-3*H*-pyrrole[1,2-*c*][1,2,3]-triazol

A: 2,3-*O*-Isopropyliden-D-erithrofuranose.

i: a) $BrPh_3P(CH_2)_3CO_2Et$, KHMDS, THF; b) TsCl, Et_3N; c) NaN_3, DMF, Δ.

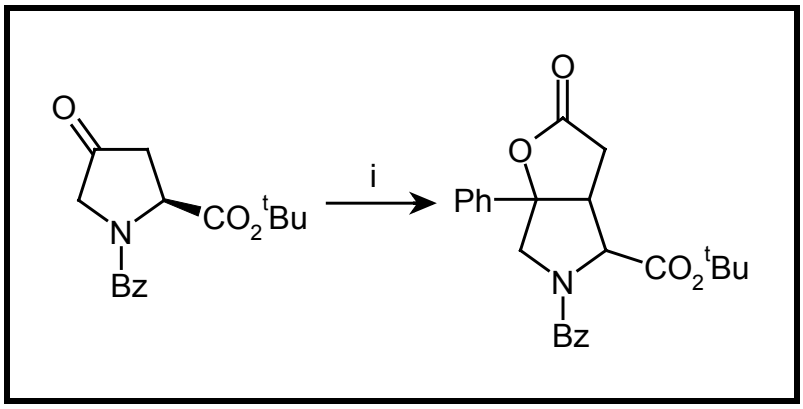
ii: a) K_2CO_3, H_2O, MeOH; b) Toluene, ref.; c) 1º- $BH_3{\cdot}THF$; 2º- H_2O_2, OH^-; d) HCl, THF.

Notes:

On the step i c) a 3a,4,5,6-tetrahydro-3*H*-pyrrole[1,2-*c*][1,2,3]-triazol is produced as intermediate.

Bibliography: Bennett III, R.B.; Choi, J.-R.; Montgomery, W.D.; Cha, J.K.; *J. Am. Chem. Soc.* **1989**, *111*, 2580.

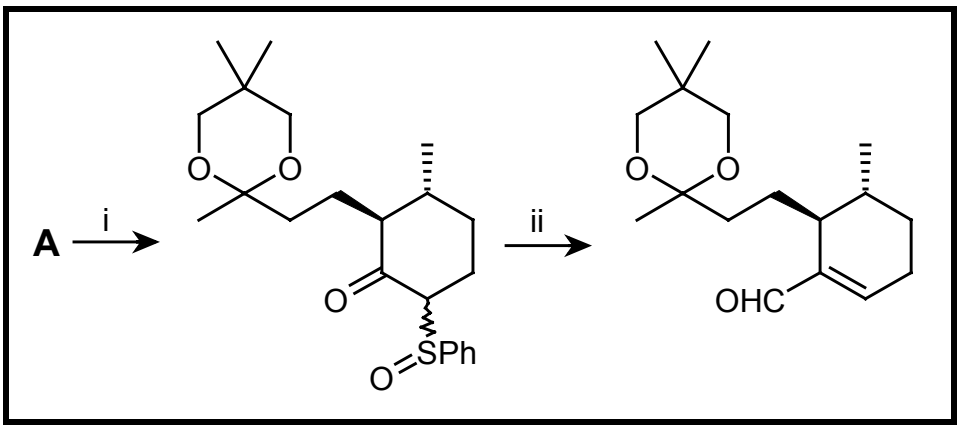
Exercise 23.



i: a) Pyrrolidine, bencene; b) 1º- *t*-Butyl 2-bromoacetate, K_2CO_3, CH_3CN; 2º- AcOH, H_2O; c) Phenylmagnesium bromide, Et_2O; d) TFA.

Bibliography: Baldwin, J.E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163.

Exercise 24.



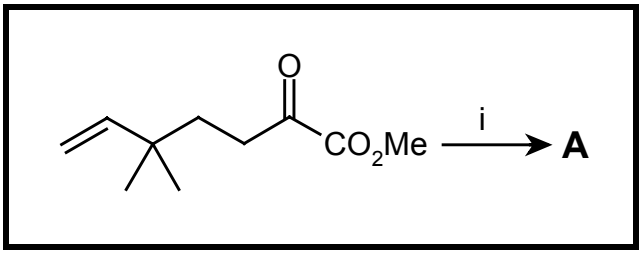
A: (5*R*)-2-Isopropyliden-5-methylcyclohexanone.

i: a) H_2O_2, OH^-, THF; b) NaSPh, THF; c) *m*-CPBA, CH_2Cl_2, -78 ºC; d) 1º- LDA (2 equiv), HMPT, THF, -35 ºC; 2º- 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane.

ii: a) Al(Hg), THF, H_2O; b) *p*-$TsNHNH_2$, water distillation; c) 1º- *n*-BuLi (4 equiv), TMEDA, 0 ºC; 2º- DMF.

Bibliography: Avery, M.A.; Chong, W.K.M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114,* 974.

Exercise 25.



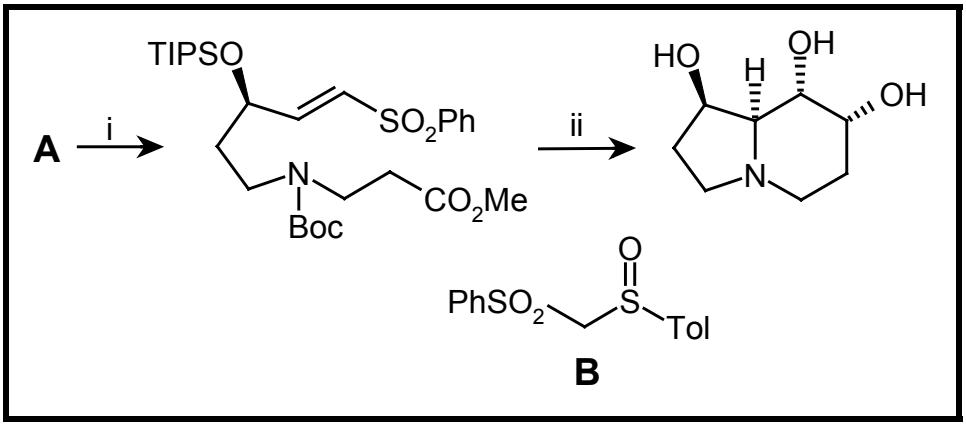
i: a) *N*-methylhydroxylamine hydrochloride, Et_3N, MeOH/toluene (6:94), 60 ºC, 12 h; b) H_2, 5% Rh/C, MeOH, 5 h.

Notes:

The product **A** is obtained as a mixture of enantiomers. Suggest one method to carry out the enantioselective synthesis of **A**.

Bibliography: Toy, A.; Thompson, W.J. *Tetrahedron Lett.* **1984**, *33*, 3533.

Exercise 26.



A: 4-aminebutanol.

i: a) Methyl acrylate, EtOH, 0 ºC; b) Boc_2O, CH_2Cl_2, t.a.; c) $Cl_2C_2O_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC; d) Compound **B**, piperidine, CH_2Cl_2, 0 ºC, 10 h; e) TIPSOTf, 2,6-lutidine, CH_2Cl_2.

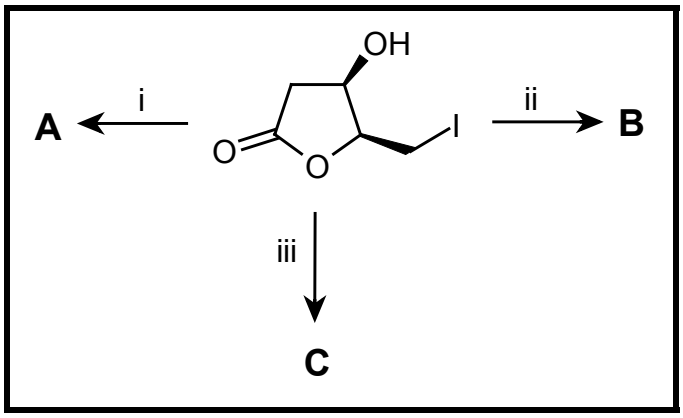
ii: a) TFA, CH_2Cl_2, t.a.; b) Et_3N, -78 ºC; c) Separation of diastereoisomers; d) LHMDS, THF, 0 ºC; e) $NaBH_4$; f) Na(Hg), MeOH; g) OsO_4, Me_3NO; h) HCl.

Notes:

The conditions on the step i d) yield an α,β–unsaturated γ-hydroxysulfone.
On the step ii b) the *cis/trans* isomers are obtained in a 10/90 ratio.

Bibliography: Carretero, J.C.; Gómez-Arrayás, R. *J. Org. Chem.* **1995**, *60,* 6000.

Exercise 27.



A: (4*S*, 5*R*)-4-Methyl-5-butyltetrahydro-2-furanone [(+)-Lactone of whisky].
B: (4*S*, 5*R*)-4-Methyl-5-pentyltetrahyidro-2-furanone [(+)-Lactona of cognac].
C: (2*R*, 3*S*, 4*S*)-4-Methyl-5-oxo-2-dodecyltetrahydro-3-furancarboxylic acid.

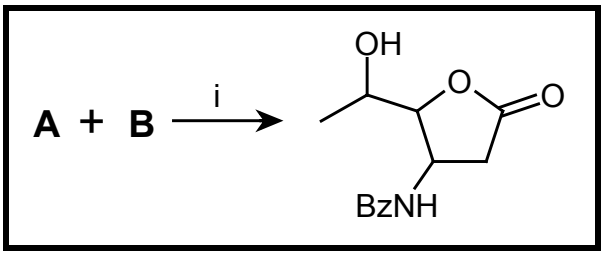
i: a) Propylmagnesium bromide, $CuBr{\cdot}Me_2S$; b) Benzoyl chloride, py; c) NH_3, MeOH; d) Me_2CuLi, THF.

ii: a) Butylmagnesium bromide, $CuBr{\cdot}Me_2S$; b) Benzoyl chloride, py; c) NH_3, MeOH; d) Me_2CuLi, THF.

iii: a) $C_{11}H_{23}MgBr$, $CuBr{\cdot}Me_2S$; b) Benzoyl chloride, py; c) NH_3, MeOH; d) 1º- $(PhS)_3CLi$; 2º- MeI; e) HgO, $BF_3{\cdot}Et_2O$, THF, H_2O.

Bibliography: Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60,* 5628.

Exercise 28.



A: Methyl 3-nitropropanoate.
B: (*R*)-2-Benzyloxypropanal.

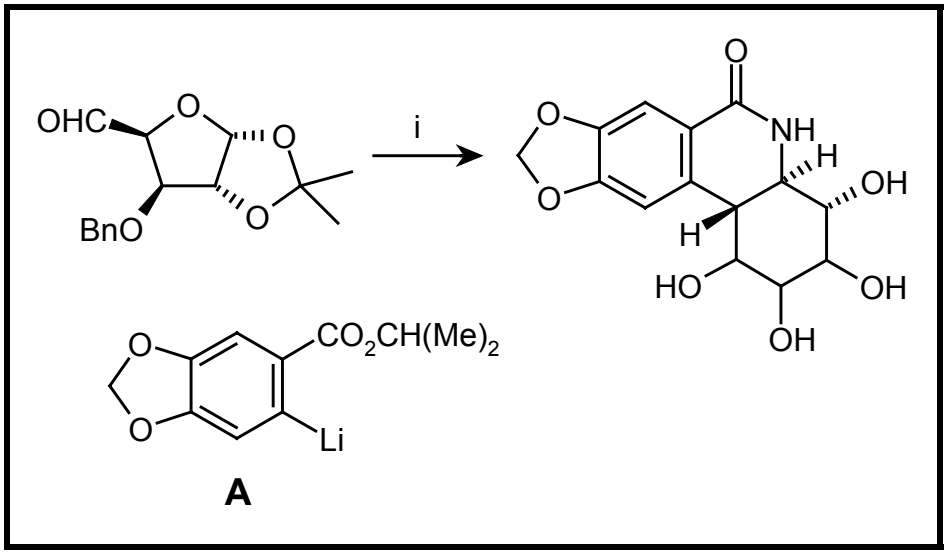
i: a) Al_2O_3; b) HCl, CH_2Cl_2; c) H_2, Ni Raney, Bz_2O, MeOH; d) H_2, Pd/C, H^+, MeOH; e) MsCl, py; f) NaOBz, DMF; g) NaOMe (0.1 equiv), MeOH.

Notes:

The alumine (Al_2O_3) acts as basic catalyst.
The product obtained on the step i a) is an alose derivative.

Bibliography: Hanessian, S.; Kloss, J.; *Tetrahedron Lett.* **1985**, *26,* 1261.

Exercise 29.



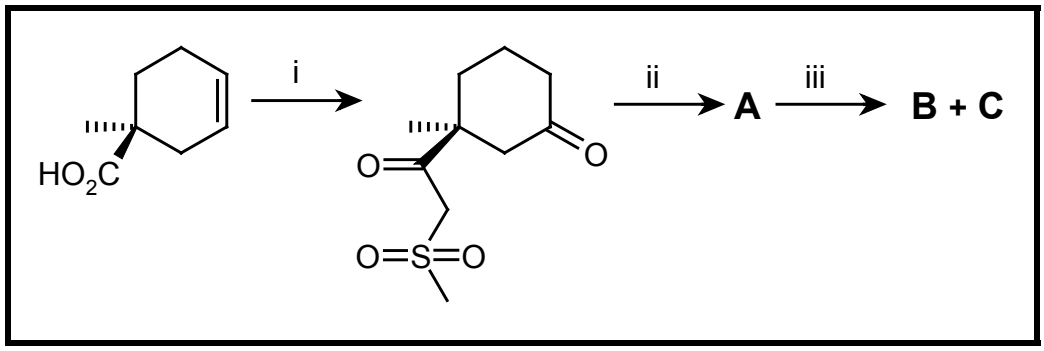
i: a) $MeNO_2$, KF; b) Ac_2O, *p*-TsOH; c) $NaHCO_3$, bencene, 80 ºC; d) Compound **A**, THF, -110 ºC; e) AcOH (50%), ref.; f) $NaHCO_3$ (2.25%), MeOH; g) H_2 (1 atm), Pd/C 10%; h) K_2CO_3, MeOH.

Notes:

The product obtained on the step i f) is the lactone derived from the epimer with the aromatic ring in equatorial disposition.

Bibliography: Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, *23,* 3171.

Exercise 30.



A: (1*S*,5*S*)-1-Hydroxy-5-methylbycicle[3.2.1]octan-6-one.
B: $C_{13}H_{16}O_2$.

i: a) I_2, $NaHCO_3$, H_2O, THF; b) $HSn(n\text{-}Bu)_3$, AIBN, bencene, ref.; c) 1º- $LiCH_2SO_2CH_3$, DME; 2º- H_2CrO_4.

ii: a) NaOH, H_2O, THF; b) Na(Hg), K_2HPO_4, MeOH.

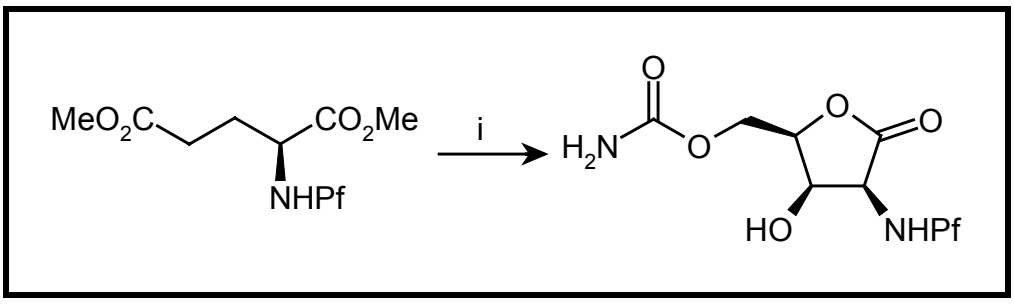
iii: a) MsCl, py; b) Et_3N, furane, ref..

Notes:

The products **B** and **C** are obtained in 4:1 ratio.

Bibliography: House, H.O.; Haack, J.L.; McDaniel, W.C.; Vanderveer, D. *J. Org. Chem.* **1983**, *48,* 1643-1654.

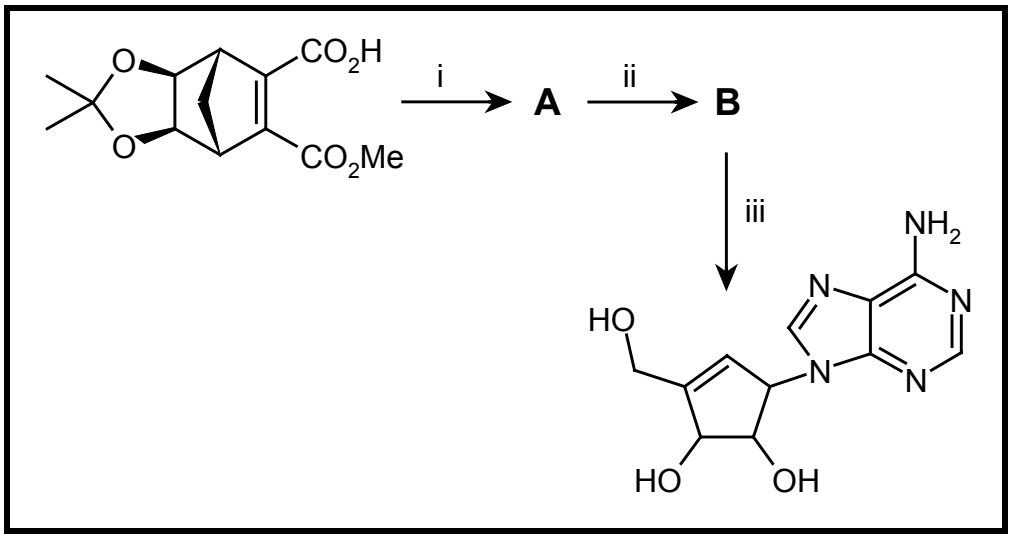
Exercise 31.



i: a) 1º- KHMDS; 2º- PhSeCl; b) *m*-CPBA; c) DIBAL (2 equiv); d) *p*-NO_2-PhOCOCl; e) NH_3; f) OsO_4; g) Et_3N.

Bibliography: Paz, M.M.; Sardina, F.J. *J. Org. Chem.* **1993**, *58,* 6090.

Exercise 32.



A: (1*R*, 5*R*, 6*S*, 7*R*)- 6,7-Dihydroxy-6,7-*O*-isopropyliden-3-oxabycicle[3.2.1]octan-2-one.
B: (1*S*, 2*R*, 5*R*)-5-Amino-1,2-*O*-isopropyliden-3-[(methoxymethoxy)methyl]-3-cyclopentene-1,2-diol.

i: a) O_3, AcOEt, -78 ºC; b) $NaBH_4$; c) $NaIO_4$, HCl 2 N; d) $NaBH_4$; e) Ac_2O, py.

ii: a) NaSePh, DMF; b) 1º- $ClCO_2Et$, Et_3N; 2º- NaN_3; 3º- Δ, bencene; 4º- MeOH, c) 1º- O_3, CH_2Cl_2; 2º- py (cat.); d) *m*-CPBA, CH_2Cl_2; e) 1º- TMSOTf, 2,6-lutidine, toluene; 2º- DBU; 3º- K_2CO_3; f) MOMCl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, 0º C; g) KOH, H_2O.

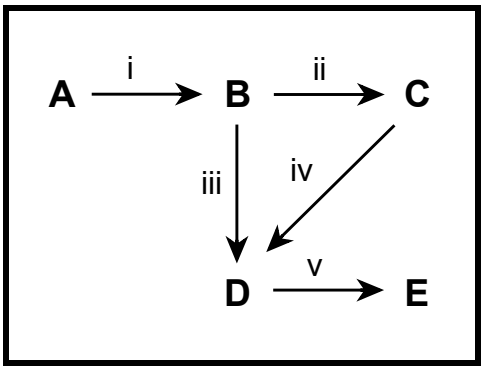
iii: a) 5-Amino-4,6-dichloropyrimidene, Et_3N; b) 1º- Triethoxymethyl, Ac_2O; 2º- NH_3; c) HCl 2 M.

Notes:

On the step i a) the 1,2,4-trioxolane intermediate of the ozonolysis evolves through a decarboxylation. Conditions on the step ii e) yield an allylic alcohol.

Bibliography: Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105,* 4049-4055.

Exercise 33.



A: Methyl 6-deoxy-α-L-mannopyranoside.
B: Methyl 2,4-*O*-Acetyl-3,6-dideoxy-3-*C*-methyl-3-nitro-α-L-glucopyranoside.
C: Methyl *N*-Acetyl-3,6-dideoxy-3-*C*-methyl-3-amino-α-L-glucopyranoside.
D: (2*S*, 3*R*, 4*S*)-4-Acetamido-3-acetoxy-2,4-dimethyl-3,4-dihydro-1*H*-pirane.
E: Mixture of methyl 3-Acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-L-glucopyranoside.

i: a) $NaIO_4$, H_2O; b) NO_2Et, NaOMe, MeOH; c) Ac_2O, py.

ii: a) H_2 (30 atm), Ni Raney, MeOH; b) Ac_2O, MeOH.

iii: a) HCl, H_2O; b) Ac_2O, py; c) H_2 (30 atm), Pd/C, MeOH; d) Ac_2O, py; e) Ac_2O, AcOH, HBr, 0º C; f) Zn, AcOH, NaOAc, H_2O.

iv: a) HCl, H_2O; b) Ac_2O, py; c) Ac_2O, AcOH, HBr, 0º C; d) Zn, AcOH, NaOAc, H_2O.

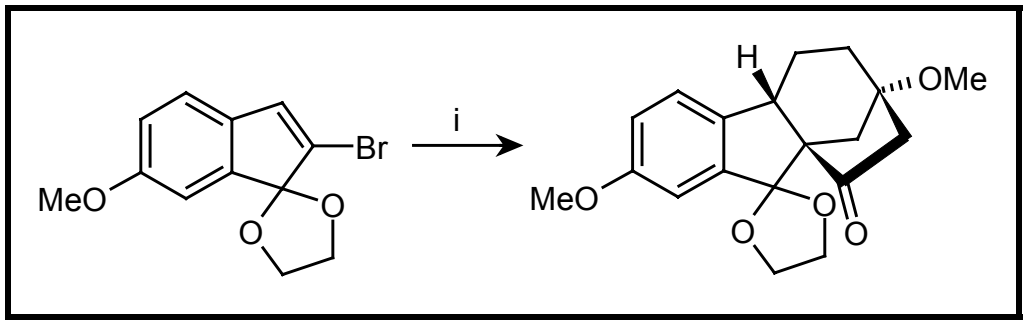
v: a) $BF_3{\cdot}Et_2O$, MeOH, CH_2Cl_2.

Notes:

On the step iii b) the α epimer is obtained selectively.
Conditions on the step iii f) yield an alkene trough a reductive elimination of an acetobromo derivative.

Bibliography: a) Brimacombe, J.S.; Doner, L.W. *J. Chem. Soc. Perkin Trans. I,* **1974**, 62; b) Brimacombe, J.S.; Mengech, A.S. *J. Chem. Soc. Perkin Trans. I,* **1980**, 2054.

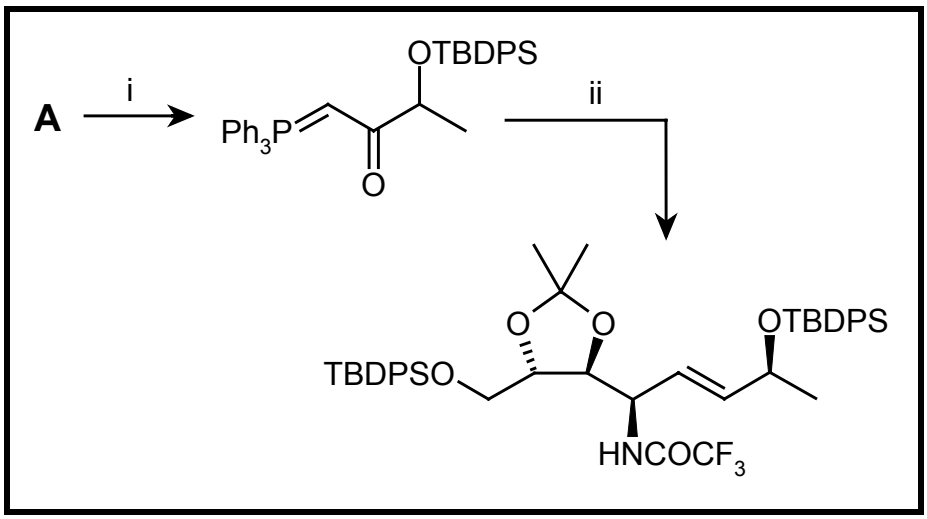
Exercise 34.



i: a) 1º- *n*-BuLi, Me_2O, hexane; 2º- CO_2; 3º- H_2O; b) CH_2N_2; c) 1,3-Butadiene, 130-140 ºC; d) NaOH 4 M, MeOH; e) 1º- I_2, $NaHCO_3$, H_2O, THF; 2º- $HSn(n\text{-}Bu)_3$, AIBN, bencene, ref.; f) 1º- $LiCH_2P(O)(OMe)_2$, DME, -78 ºC; 2º- H_2O; g) H_2CrO_4; h) Na_2CO_3, MeOH, ref.

Bibliography: House, H.O.; Haack, J.L.; McDaniel, W.C.; Vanderveer, D. *J. Org. Chem.* **1983**, *48,* 1643-1654.

Exercise 35.



A: Ethyl (2*S*)-2-hydroxypropanoate.
B: (4*R*, 5*S*)-2,2-Dimethyl-4-formyl-5-[(*terc*-butyldiphenylsilyloxy)methyl]-1,3-dioxolane.

i: a) *t*-Butyldiphenylsilyl chloride, imidazole; b) KOH, MeOH; c) 2-Pyridinethiol, DCC; d) $Ph_3P{=}CH_2$.

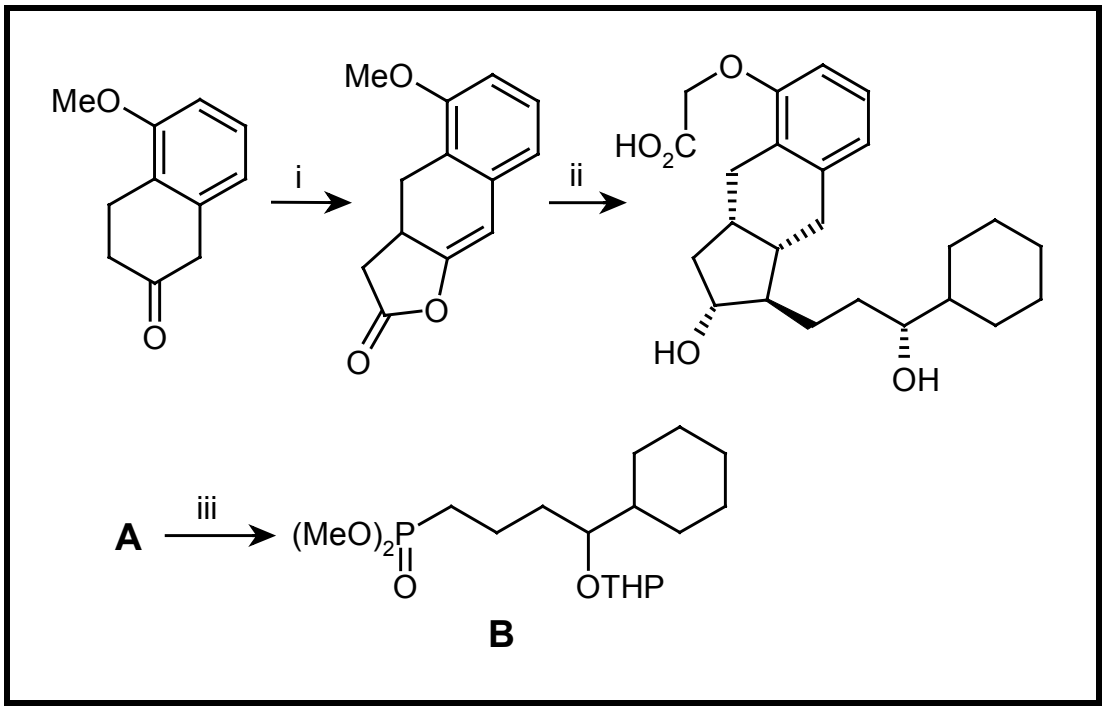
ii: a) Compound **B**, bencene, ref.; b) L-Selectride; c) 1º- *n*-BuLi; 2º- CF_3CN; d) Xilene, ref..

Notes:

L-Selectride® reduction yields the *S* epimer.

Bibliography: Savage, I.; Thomas, E.J. *J. Chem. Soc. Chem. Commun.* **1989**, 717.

Exercise 36.



A: Cyclohexanecarbaldehyde.

i: a) NaOMe, CO_3Me_2, 70 ºC; b) 1º- LDA, THF, -78 ºC; 2º- Allyl bromide; c) LiCl, H_2O, DMSO, 150 ºC; d) Ethylen glycol, $(EtO)_3CH$, *p*-TsOH, CH_2Cl_2, 25 ºC; e) 1º- $NaIO_4$, $KMnO_4$, H_2O, 25 ºC; 2º- HCl 3 M, acetone, 60 ºC; f) Ac_2O, $HClO_4$ (cat.), AcOEt.

ii: a) 1º- Compund **B** (2 equiv), *n*-BuLi (2 equiv), THF, -78 ºC → -10 ºC; 2º- AcOH; b) H_2 (3 atm), Pd/C 10%, EtOH; c) $NaBH_4$, NaOH, H_2O, EtOH, -10 ºC; d) 1º- AcOH, H_2O, THF, 45 ºC; 2º- Separation of diastereoisomers; e) $LiPPh_2$, THF, 75 ºC; f) K_2CO_3, $ClCH_2CN$, acetone, 60 ºC; g) KOH, H_2O, MeOH, 90 ºC.

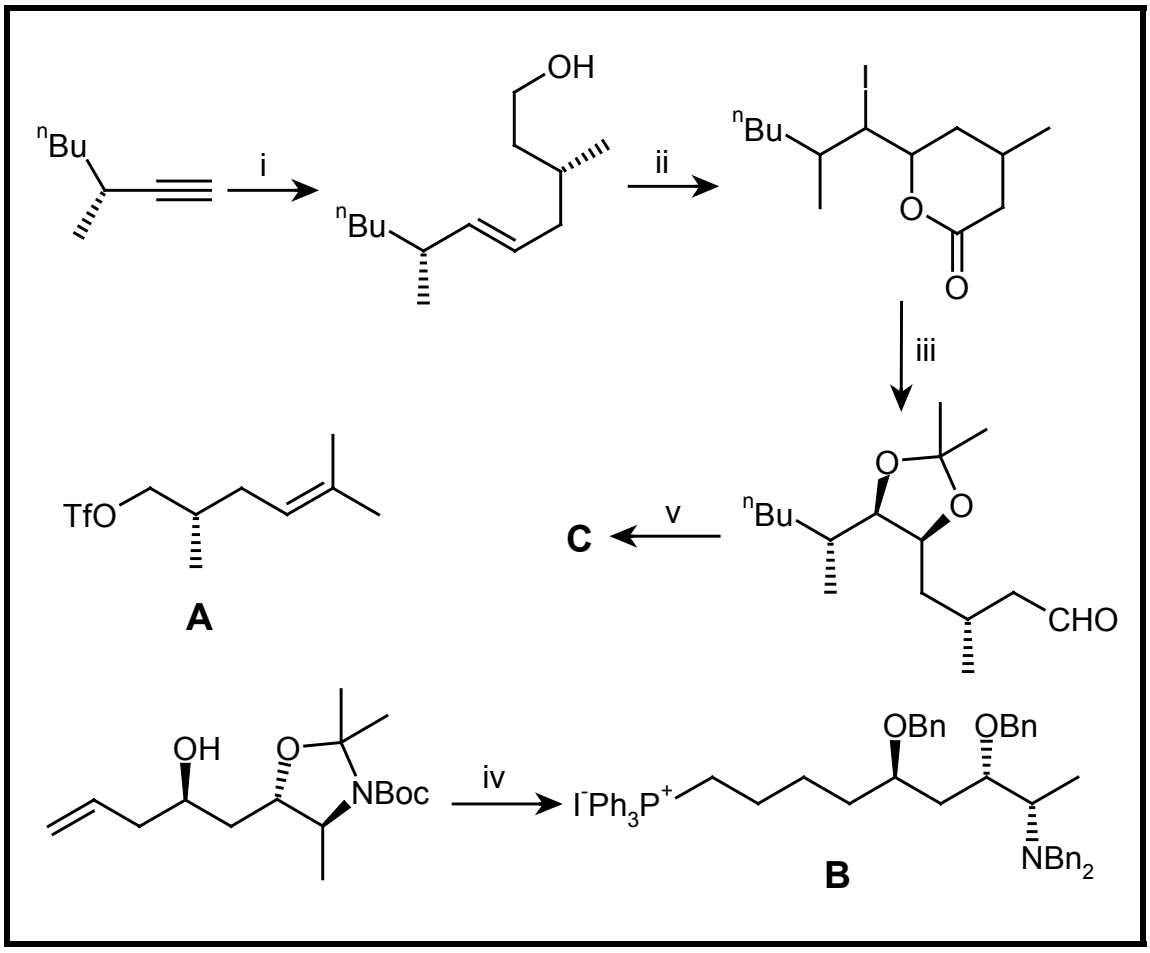
iii: a) Vinylmagnesium bromide, THF, 0 ºC; b) Separation of *R* enantiomer; c) DHP, H^+, CH_2Cl_2; d) 1º- 9-BBN, THF; 2º- H_2O_2, KOH; e) *p*-TsCl, py, 0 ºC; f) NaI, $(i\text{-}Pr)_2EtN$, acetone; g) $(MeO)_2P(O)CH_2Li$, THF, -78 ºC → -10 ºC.

Notes:

$LiPPh_2$ is used as demethylating agent.

Bibliography: Aristoff, P.A.; Johnson, P.D.; Harrison, A.W. *J. Am. Chem. Soc.* **1985**, *107*, 7971.

Exercise 37.



C: $C_{50}H_{69}NO_4$.

i: a) 1º- *n*-BuLi; 2º- Addition of compound **A**; b) $K_2OsO_4 \cdot 2H_2O$; c) $Pb(OAc)_4$; d) $NaBH_4$; e) Na, liquid NH_3.

ii: a) $Cl_2C_2O_2$, DMSO, Et_3N; b) $NaClO_2$; c) I_2, CH_3CN, -30 ºC.

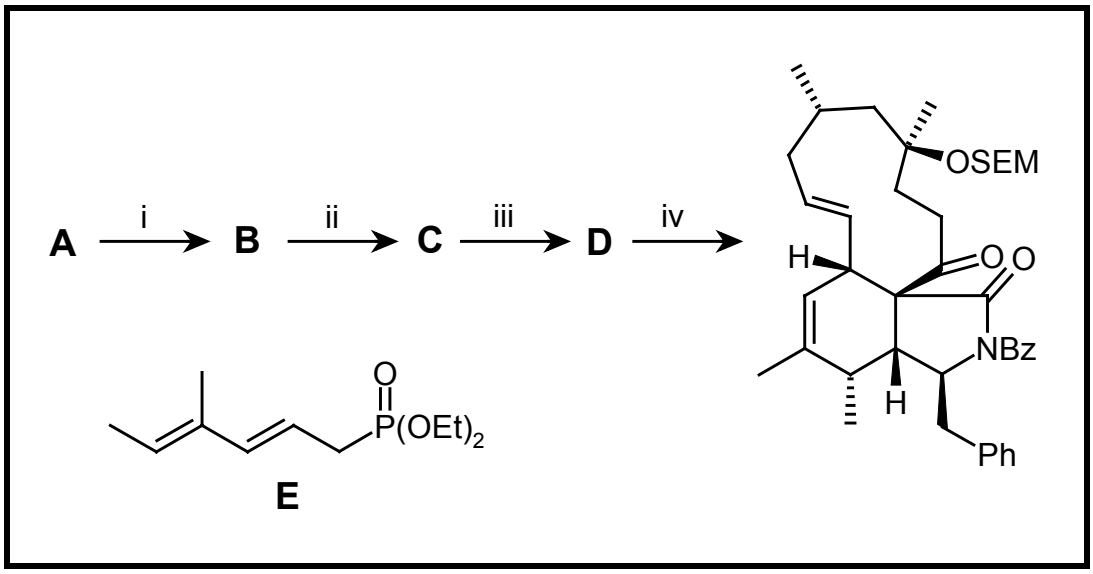
iii: a) NaOBn; b) H_2, Pd/C, *p*-TsOH cat.; c) $LiAlH_4$; d) *p*-TsOH cat., acetone; e) $Cl_2C_2O_2$, DMSO, Et_3N.

iv: a) *p*-TsOH cat., MeOH; b) NaH, BnBr (excess), TBAI; c) 1º- O_3; 2º- Me_2S; d) $(MeO)_2P(O)CH_2CO_2Me$, NaH; e) H_2, cat. Lindlar; f) TFA, CH_2Cl_2; g) BnBr (1 equiv), K_2CO_3; h) DIBAL; i) I_2, PPh_3, imidazole; j) PPh_3, CH_3CN, ref..

v: a) 1º- *n*-BuLi; 2º- Addition of compound **B**; b) TFA, H_2O.

Bibliography: Shi, Y.; Peng, Lee F.; Kishi, Yoshito, *J. Org. Chem.* **1997**, *62*, 5666.

Exercise 38.



A: Methyl (2*S*)-3-hydroxy-2-methylpropanoate.
B: (2*R*, 4*R*)-2,4-Dimethyl-5-*O*-(*t*-butyldimethylsilyl)pentane-1,2,5-triol.
C: Methyl (4*R*, 6*R*)-4,7-dihydroxy-4,6-dimethyl-4-*O*-[(2-trimethylsilyloxy)ethoxymethyl] heptanoate.
D: (4*S*, 6*S*, 8*E*, 10*E*, 12*E*)-4-Hydroxy-1-(1*H*-1-imidazolyl)-4,6,12-trimethyl-4-*O*-[(2-trimethylsilyloxy)ethoxy]methyl-8,10,12-tetradecatrien-1-one.

i: a) *t*-Butyldimethylsilyl chloride, imidazole; b) DIBAL; c) $Cl_2C_2O_2$, DMSO, Et_3N; d) $Ph_3P{=}C(Me)CO_2Et$; e) DIBAL; f) *m*-CPBA; g) $LiAlH_4$.

ii: a) NCS, Me_2S; b) $Ph_3P{=}CHCO_2Me$; c) SEMCl, imidazole; d) Dowex 50W-X8, MeOH; e) H_2, Pd/C.

iii: a) $Cl_2C_2O_2$, DMSO, Et_3N; b) $Ph_3P{=}CH_2$; c) 1º- 9-BBN; 2º- H_2O_2, OH^-; d) $Cl_2C_2O_2$, DMSO, Et_3N; e) Compound **E**, base; f) KOH; g) $C(O)Im_2$.

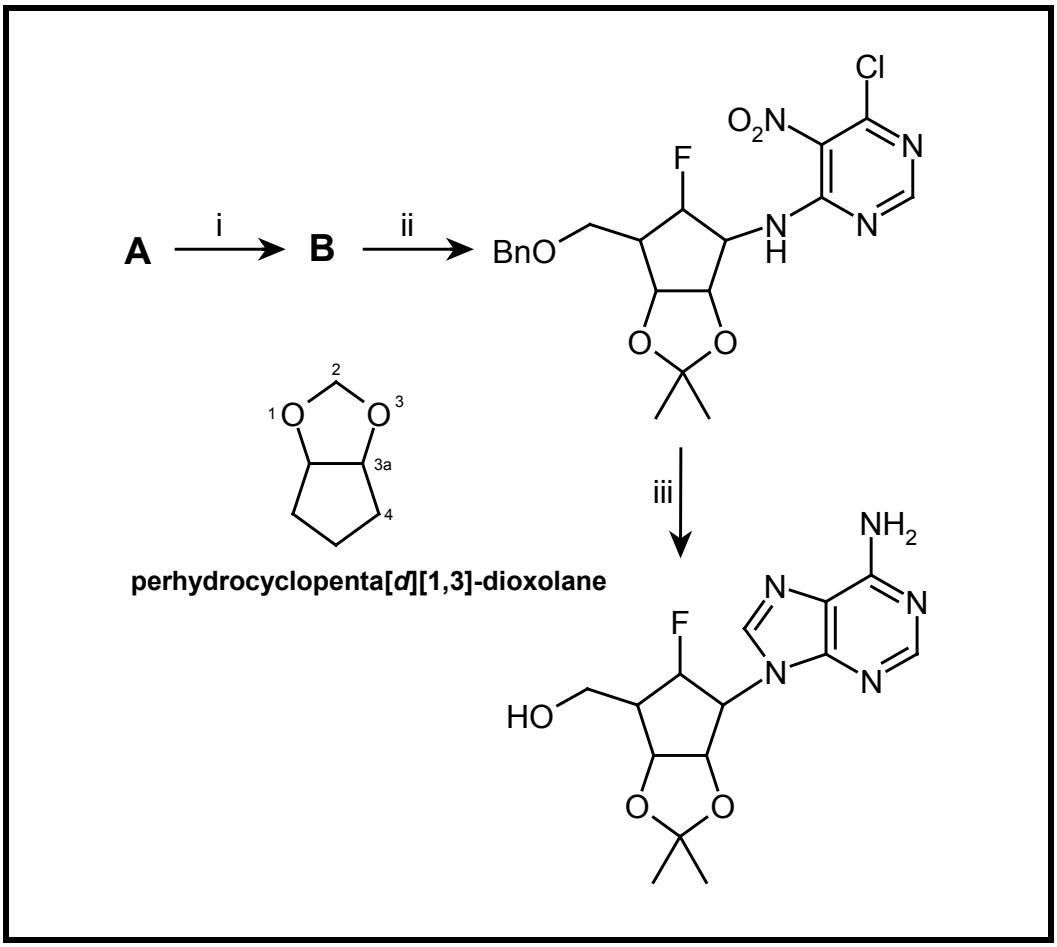
iv: a) 1º- (*5R*)-*5*-Benzyl-*N*-benzoyl-2-pyrrolidinone, LHMDS; 2º- Compound **D**; b) 1º- Base; 2º- PhSeCl; c) *m*-CPBA; d) Toluene, 100 ºC, 5 h.

Notes:

The $NCS{\cdot}SMe_2$ system is used as selective oxidating agent for primary hydroxy groups.
The Dowex 50W-X8 is an ion exchange resine. Use handbooks of fine chemicals to find out if this resine is anionic or cationic.

Bibliography: Thomas, Eric J.; Whitehead, John W.F. *J. Chem. Soc. Perkin Trans. I,* **1989**, 507.

Exercise 39.



A: (1*S*, 4*R*, 5*S*)-5-[(Benzyloxy)methyl]-4-hydroxy-2-cyclopentenyl acetate.
B: (3a*S*, 4*R*, 5*S*, 6*S*, 6a*R*)-4-Azido-6-(benzyloxymethyl)-5-[(methoxyethoxy)methoxy]-2,2-dimethylperhydrocyclopenta[*d*][1,3]-dioxolane.

i: a) *m*-CPBA, CH_2Cl_2, 0 ºC, 24 h; b) MEMCl, (*i*-Pr)$_2$EtN, CH_2Cl_2, t.a., 48 h; c) K_2CO_3, MeOH, t.a., 2 h; d) 1º- NaN_3, NH_4Cl, EtOH/H_2O (4:1), ref., 3 días; 2º- 2,2-dimethoxypropane, *p*-TsOH cat., 2 h.

ii: a) Me_2BBr, CH_2Cl_2/Et_2O (10:1), -78 ºC, 2 h; b) Tf_2O, py, CH_2Cl_2, 0 ºC, 30 min.; c) LiOBz, DMF, t.a., 30 min.; d) K_2CO_3, MeOH, t.a., 2 h; e) DAST, CH_2Cl_2, 0º C, 2 h; f) H_2, cat. Lindlar, EtOH, t.a., 3 h; g) 4,6-Dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2, t.a., 3 h.

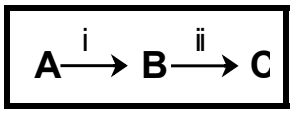
iii: a) H_2, Ni Raney, EtOH, t.a., 30 min.; b) $(EtO)_3CH$, ref., 5 h; c) NH_3 liq., 24 h; d) H_2, $Pd(OH)_2$, cyclohexane/EtOH (1:2), ref., 12 h.

Notes:

DAST stands for diethylamino sulfide trifluoride, a reagent used for the conversion of alcohols into alkyl fluorides with configuration inversion.
The MEM group can be selectively deprotected by using dimethylborane bromide.

Bibliography: Cotterill, I.C.; Cox, P.B.; Drake, A.F.; Le Grand, D.M.; Hutchinson, E.J.; Latouche R.; Pettman, R.B.; Pryce, R.J.; Roberts, S.M.; Ryback, G.; Sik, V.; Williams, J.O. *J. Chem. Soc. Perkin Trans. I,* **1991**, 3071.

Exercise 40.



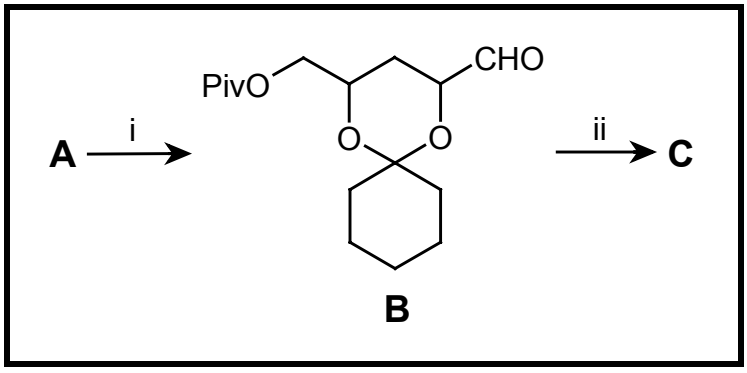
A: (1*R*, 5*S*)-5-Isopropenyl-2-methyl-2-cyclohexen-1-ol.
B: (3a*R*, 4*R*, 6*R*, 7a*R*)-4-Chloro-6-isopropenyl-3a-methylperhydrobenzo[*b*]furan-2-one.
C: (1*R*, 2*R*, 3*R*, 5*R*)-2-[(1*R*)-1-Bromo-2-hydroxyethyl]-3-chloro-5-isopropenyl-2-methylcyclohexan-1-ol.

i: a) 1º- MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, -30 ºC; 2º- *p*-$AcNHC_6H_4SO_2N_3$, DBU, CH_3CN, 23 ºC; b) Cu(II)bis(salyciliden-*t*-butylamine), CH_2Cl_2, 70 ºC, 8 h; c) LiCl, CSA, DMF, 140 ºC.

ii: a) 1º- LDA, -78 ºC, THF; 2º- CBr_4, -78 ºC → 23 ºC; b) 1º- DIBAL, -78 ºC, CH_2Cl_2; 2º- $NaBH_4$, EtOH, 23 ºC.

Bibliography: Fukuyama, Tohru e Chen, Xiaoqi, *J. Am. Chem. Soc.* **1994**, *116*, 3125.

Exercise 41.



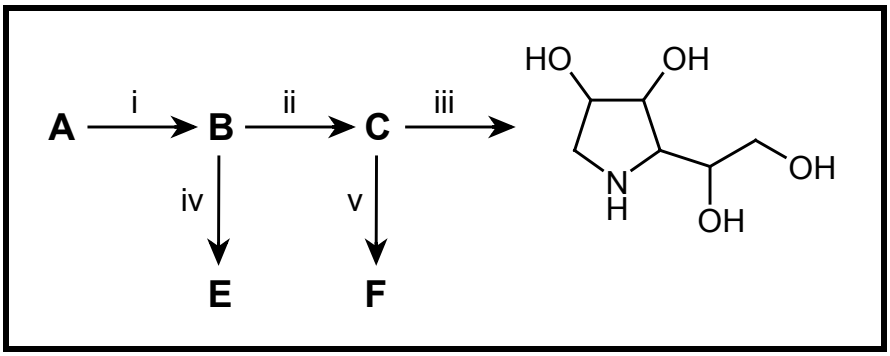
A: D-(+)-Xilose.
C: $C_{20}H_{34}O_5$.

i: a) Acetone, $CuSO_4$, H_2SO_4; b) HCl 0.2%; c) Me_3COCl, py, 0 ºC → t.a.; d) 1º- NaH, CS_2, THF; 2º- MeI, 0 ºC → t.a.; e) $HSn(n\text{-}Bu)_3$, AIBN, toluene, 80 ºC; f) EtSH (10 equiv), HCl 6N; g) Cyclohexanone dimethyl acetal, *p*-TsOH, 16 h, t.a.; h) $HgCl_2$, $CaCO_3$, CH_3CN/H_2O (4:1), 0 ºC → t.a..

ii: 1º- [(2*S*)-3-Hydroxy-2-methylpropyl]triphenylfosfonium bromide (2 equiv), *n*-BuLi (4 equiv), THF, -78 ºC → t.a., 2 h; 2º- TMSCl (2 equiv), 0 ºC → t.a., 30 min.; 3º- Addition of compound **B**, THF, -78 ºC → t.a.; 4º- NH_4F, THF/H_2O (1:1).

Bibliography: White, James D.; Jeffrey, Scott C. *J. Org. Chem.* **1996**, *61*, 2600.

Exercise 42.



A: D-Mannose.
C: (1*S*)-1-[(2*R*, 3*S*, 4*R*)-3,4-Dihydroxy-3,4-*O*-isopropylidentetrahydro-1*H*-2-pyrrolyl]-1,2-ethanediol.
E: (2*R*, 3*S*, 4*R*)-2-[(1*R*)-2-Amino-1-hydroxyethyl]-3,4-pyrrolidinediol.
F: (2*R*, 3*S*, 4*R*)-2-(Hydroxymethyl)-3,4-pyrrolidinediol.

i: a) BnOH, H^+; b) *t*-Butyldimethylsilyl chloride, imidazole; c) 2,2-Dimethoxypropane, H^+; d) PCC; e) $NaBH_4$; f) Tf_2O; g) NaN_3; h) TBAF.

ii: a) H_2, Pd/C, MeOH; b) H_2, Pd/C, AcOH.

iii: TFA, H_2O.

iv: a) MsCl, Et_3N; b) NaN_3; c) H_2, Pd/C, MeOH; d) H_2, Pd/C, AcOH; e) H^+, MeOH.

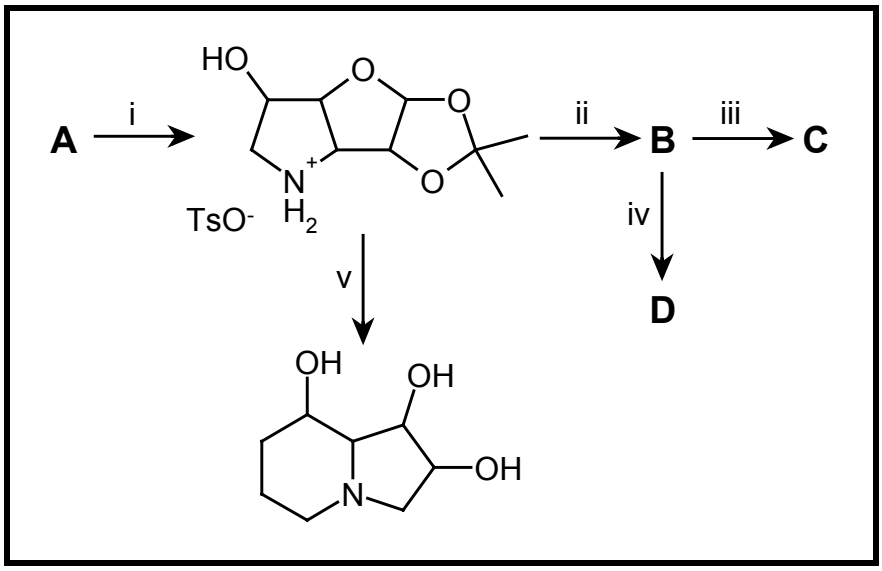
v: a) $(Boc)_2O$, py; b) $NaIO_4$, EtOH; c) $NaBH_4$; d) TFA, H_2O.

Notes:

Compound **B** is an α-D-mannopyranoside.

Bibliography: Fleet, G.W.J.; Nicholas, S.J.; Smith, P.W.; Evans, S.V.; Fellows, L.E.; Nash, R.J. *Tetrahedron Lett.* **1985**, *26,* 3127; Bashyal, B.P.; Fleet, G.W.J.; Gough, M.J.; Smith, P.W. *Tetrahedron* **1987**, *25,* 1853; Bashyal, B.P.; Fleet, G.W.J.; Gough, M.J.; Smith, P.W. *Tetrahedron* **1987**, *43*, 3083; Farr, R.A.; Holland, A.K.; Huber, E.W.; Peet, N.P.; Weintraub, P.M. *Tetrahedron* **1994**, *50*, 1033.

Exercise 43.



A: 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropyliden-α-D-glucofuranose.
B: (2*S*, 3*S*, 4*R*)-4-Benzyloxy-*N*-benzyloxycarbonil-3-hydroxy-2-pyrrolidinecarbaldehyde.
C: (2*S*, 3*S*, 4*R*)-2-(Hydroxymethyl)-3,4-pyrrolidinediol.
D: (2*S*, 3*S*, 4*R*)-3,4-Dihydroxy-2-pyrrolidinecarboxylic acid.

i: a) MeOH, H^+ (mild cat.); b) TsCl, py; c) H_2, Pd/C.

ii: a) CbzCl; b) NaH, BnBr; TBAI; c) TFA, H_2O; d) $NaIO_4$, EtOH, H_2O.

iii: a) $NaBH_4$; b) H_2, Pd/C, AcOH.

iv: a) $NaClO_2$, KH_2PO_4, H_2O; b) H_2, Pd/C, AcOH.

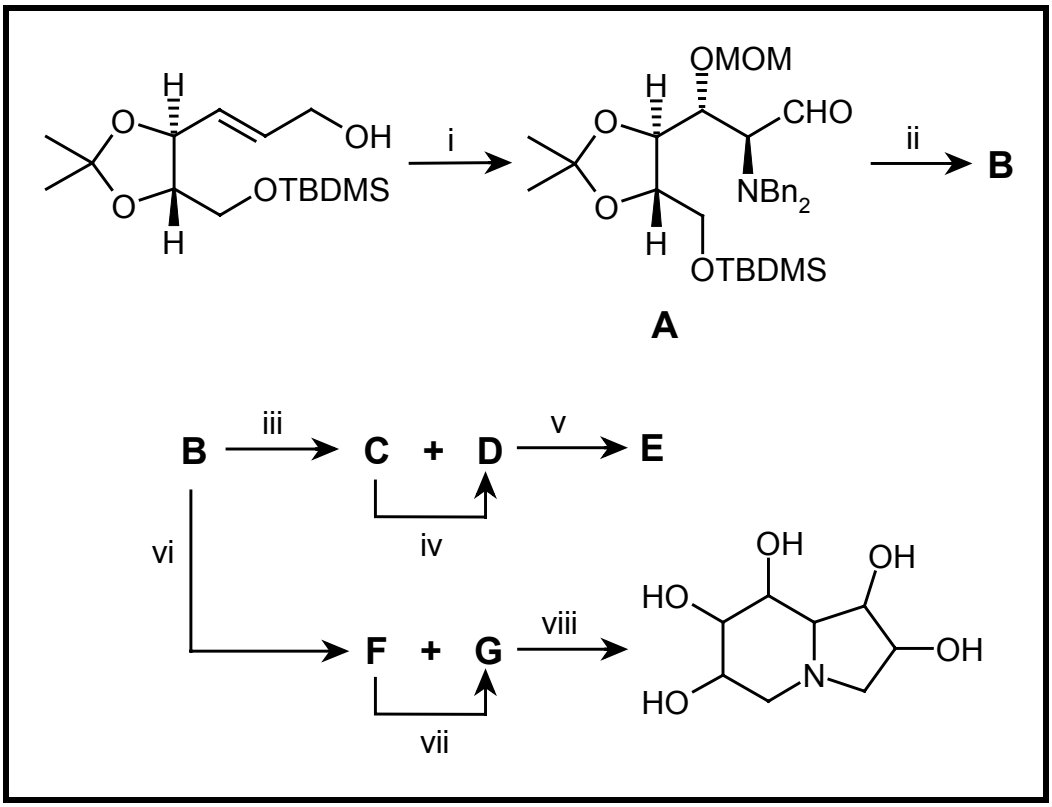
v: a) $HO_2CCH_2P(O)(OMe)_2$, DCC; b) TFA, H_2O; c) K_2CO_3, DMF, 18-crown-6; d) H_2, Pd/C, EtOH; e) Ac_2O, py; f) $BH_3{\cdot}SMe_2$; g) NaOMe, MeOH; h) TFA, H_2O.

Notes:

18-Crown-6 is the trivial name for 1,4,7,10,13,16-hexaoxacyclooctadecane. The crown ethers complex with metallic cations, increasing thus the salts ionization in the reaction medium.

Bibliography: Austin, G.N.; Baird, P.D.; Fleet, G.W.J.; Peach, J.M.; Smith, P.W.; Watkin, D.J. *Tetrahedron* **1987**, *43*, 3095.

Exercise 44.



i: a) L-Diethyl tartrate, $Ti(O^iPr)_4$, TBHP; b) Et_2AlNBn_2, CH_2Cl_2; c) AcCl, Et_3N; d) MOMCl, $(i\text{-}Pr)_2EtN$; e) $LiAlH_4$, Et_2O; f) $Cl_2C_2O_2$, DMSO, Et_3N.

ii: 1º- AcOEt, LHMDS, THF, -80 ºC; 2º- Addition of compound **A**.

iii: a) TBAF, THF; b) 1º- TsCl (1 equiv), py; 2º- Separation of the *R* epimer; c) H_2, Pd/C, MeOH.

iv: NaH, THF.

v: a) $BH_3{\cdot}SMe_2$, THF; b) HCl (conc.), MeOH, ref..

vi: a) $LiAlH_4$, Et_2O; b) *t*-butyldimethylsilyl chloride, imidazole, DMF.

vii: a) AcOH, Ph_3P, DEAD; b) $LiAlH_4$, Et_2O.

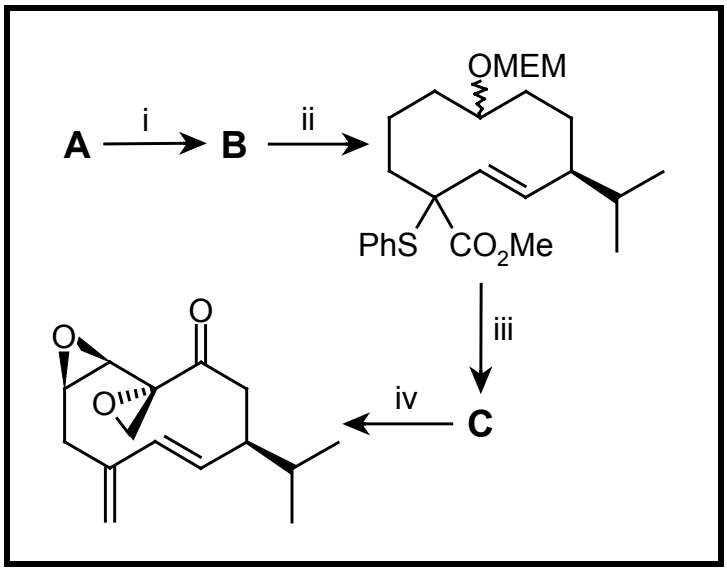
viii: a) TBAF, THF; b) TsCl, py; c) H_2, $Pd(OH)_2$, MeOH; d) Et_3N, MeOH, ref.; e) HCl (conc.), MeOH, ref..

Notes:

The conditions used on the step i b) allow the regio- and stereoselective epoxyde opening. Compound **B** is actually the mixture of the *R* and *S* epimers in 89:11 ratio.

Bibliography: Ina, Hiroji e Kibayashi, Chihiro, *J. Org. Chem.* **1993**, *58*, 52.

Exercise 45.



A: (4*R*)-4-Isopropyl-1-methyl-cyclohexene.
B: Mixture of diastereoisomers of the (3*R*)-9-Hydroxy-3-isopropyl-6-(methoxyethoxymethoxy) nonanal dimethyl acetal.
C: (8*S*)-8-Isopropyl-5-methylen-2,6-cyclodecadienone.

i: a) 1º- O_3, MeOH, -20 ºC; b) 2º- Me_2S, *p*-TsOH; b) 1º- CO_3Me_2, NaH, dioxane, ref., 24 h; 2º- Allyl bromide, ref., 2 h; c) KOH 5%, MeOH/H_2O 2:3, 90 ºC, 2 h; d) $LiAlH_4$, Et_2O; e) MEMCl, (*i*-Pr)$_2$EtN, CH_2Cl_2, 40 ºC, 20 h; f) OsO_4, $NaIO_4$, Et_2O, H_2O, t.a., 4 h; g) $LiAlH_4$, Et_2O.

ii: a) Ac_2O, py; b) AcOH (aq.) 75%, 40 ºC, 1 h; c) LDA, $PhSCH_2CO_2Me$, THF, -70 ºC, 10 min.; d) Ac_2O, NaOAc, 130 ºC, 30 min.; e) NaOMe cat., MeOH, t.a., 1 h; f) TsCl, py, 0-5 ºC, 7 h; g) NaHMDS, DME, ref., 50 min..

iii: a) $LiAlH_4$, Et_2O; b) BzCl, DMAP, py, THF, t.a., 24 h; c) TMSCl, NaI, CH_3CN, -8 ºC, 40 min.; d) Na-naphthalene, THF, -70 ºC, 6 min.; e) PCC, *molecular sieves* 3Å, CH_2Cl_2, t.a., 1 h; f) LHMDS, $PhSSO_2Ph$, THF, -10 ºC, 15 min.; g) $NaIO_4$, MeOH/H_2O, t.a., 20 h; h) $CaCO_3$, BHT, toluene, ref., 4 h.

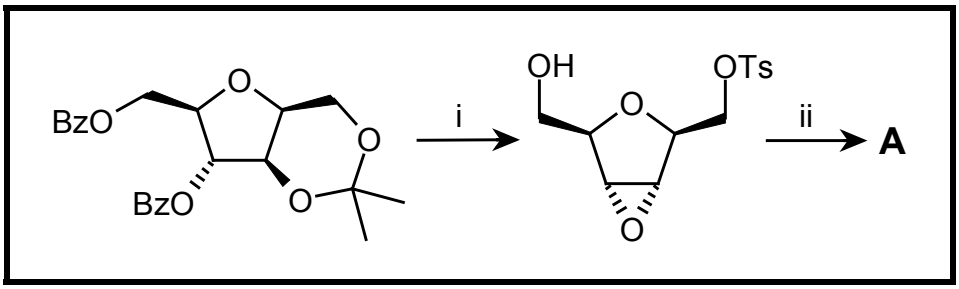
iv: a) TBHP, KH, THF, t.a., 1 h; b) 1º- LHMDS, THF, -70 ºC, 30 min.; 2º- MOPH, -22 ºC, 15 min.; c) *t*-Butyldimethylsilyl chloride, imidazole, DMF, 40 ºC, 16 h; d) $Me_3S^+I^-$, *n*-BuLi, -5 ºC, 30 min.; e) TBAF, THF, t.a., 30 min., f) PCC, *molecular sieves* 3Å, CH_2Cl_2, t.a., 1 h.

Notes:

The *molecular sieves* are zeolites which serve as catalysts in many reactions.
Conditions used on the step iii c) deprotect the MEM group.
Conditions used on the step iv a) yield selectively epoxydes of α,β-unsaturated alkenes.
The treament of enolates with MOPH yields α-hydroxycarbonyl compounds.

Bibliography: Kitahara, T.; Masataka, M.; Mori, K. *Tetrahedron* **1987**, *43*, 2689.

Exercise 46.



i: a) MeOH, H^+; b) TsCl (2 equiv), py; c) NaOMe (1.1 equiv), MeOH.

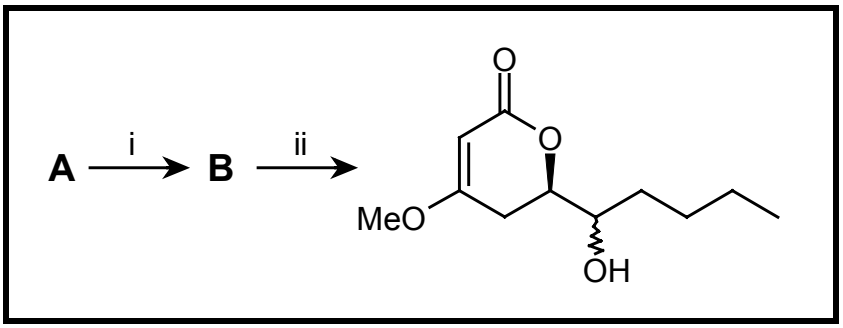
ii: a) Red-Al®, THF; b) TsCl (1 equiv), py; c) 1º- Me_3N, MeOH; 2º- HCl.

Notes:

On the step ii a), the sodium bis-(2-methoxyethoxy)aluminium hydride (Red-Al®) produces the reductive regioselective opening of the epoxyde by complexation with the hydroxy group, and the reductive elimination of the tosylate group.
On the step ii c), the treatment with HCl is an anionic exchange reaction.

Bibliography: Mubarak, A.M.; Brown, D.M. *Tetrahedron Lett*, **1980**, *21*, 2453.

Exercise 47.



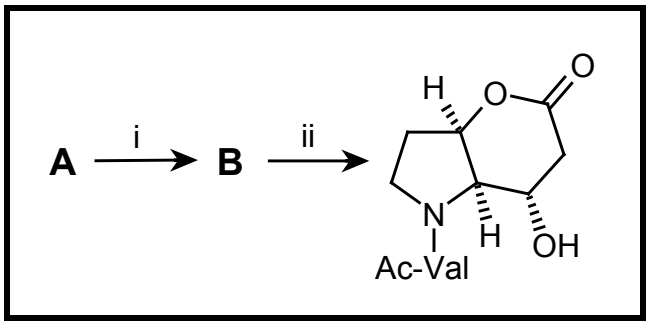
A: (*R*)-2,2-Dimethyl-4-formyl-1,3-dioxolane.
B: Mixture of epimers of the (2*R*)-2-[1-(benzyloxy)pentyl]oxirane.

i: a) *n*-BuMgBr, Et_2O; b) BnCl, NaOH, DMSO, 30-40 ºC, 2 h; c) HCl 1%, MeOH, 60 ºC, 1 h; d) TsCl (1 equiv), py, -10 ºC, 2 h; e) KOH, t.a., 30 min..

ii: a) 1º- 2-Propinoic acid, LDA (2 equiv), THF, HMPA, -45 ºC; 2º- Addition of compound **B**; b) H_2SO_4, MeOH; c) NaOMe, MeOH; d) H_2, Pd/C, EtOH.

Bibliography: Mori, K.; Oda, M. y Matsui, M. *Tetrahedron Lett.* **1976**, *17*, 3173.

Exercise 48.



A: Methyl 2-deoxy-α-D-glucopyranoside.
B: Methyl 3-*O*-benzyl-6-cyano-2,6-dideoxy-4-*O*-mesyl-α-D-alopyranoside.

i: a) PhCHO, $ZnCl_2$; b) CrO_3, py; c) $NaBH_4$; d) NaH, BnBr; e) AcOH, H_2O; f) MsCl (2 equiv), py; g) NaCN, DMSO.

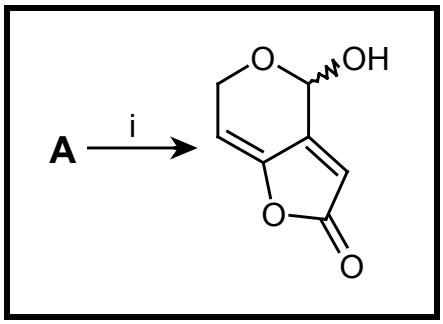
ii: a) $NaBH_4$, $CoCl_2$, MeOH; b) KOH, MeOH; c) Cbz-Val, DCC; d) HCl, H_2O; e) PCC, CH_2Cl_2; f) H_2, Pd/C; g) Ac_2O, MeOH.

Notes:

Conditions used on the step ii a) allow the conversion of cyano groups into amines.
Val stands for the aminoacid L-Valine.

Bibliography: Kakinuma, K.; Õtake, N.; Yonehara, H. *Tetrahedron Lett*, **1980**, *21*, 167.

Exercise 49.



A: L-Arabinose.

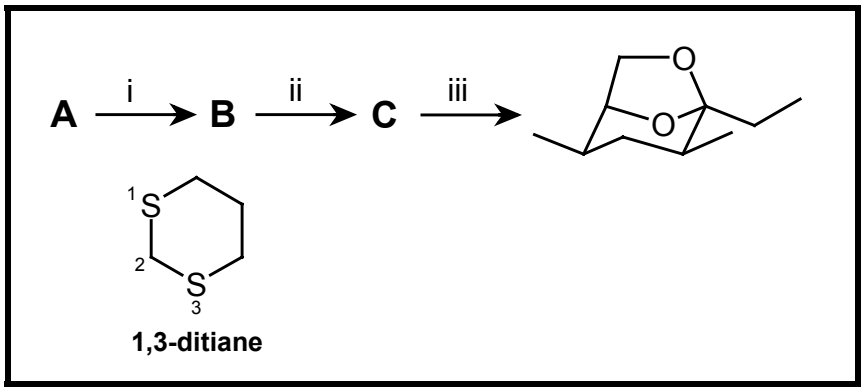
i: a) MeOH, H^+; b) Acetone, $CuSO_4$, H_2SO_4, t.a., 24 h; c) PCC, *molecular sieves*, CH_2Cl_2; d) $Ph_3P{=}CHCO_2Me$, bencene, 50 ºC; e) MeOH, HCl, ref.; f) MsCl, py, 0 ºC → t.a., 24 h; g) TFA 90%, H_2O, 50 ºC, 1 h.

Notes:

Conditions used on the step i a) yield the α epimer.

Bibliography: Seijas, J.A.; Vázquez Tato, M.P.; Estévez, R.J.; Castedo, L.; Riguera, R. *Heterocycles*, **1989**, *29*, 181.

Exercise 50.



1,3-ditiane

A: D-Glucose.
B: Methyl 2,3-Anhydro-4,6-*O*-benzyliden-α-D-alopyranoside.
C: (2*S*, 3*R*, 5*S*)-5-(1,3-Ditian-2-yl)-3-methylhexane-1,2-diol.

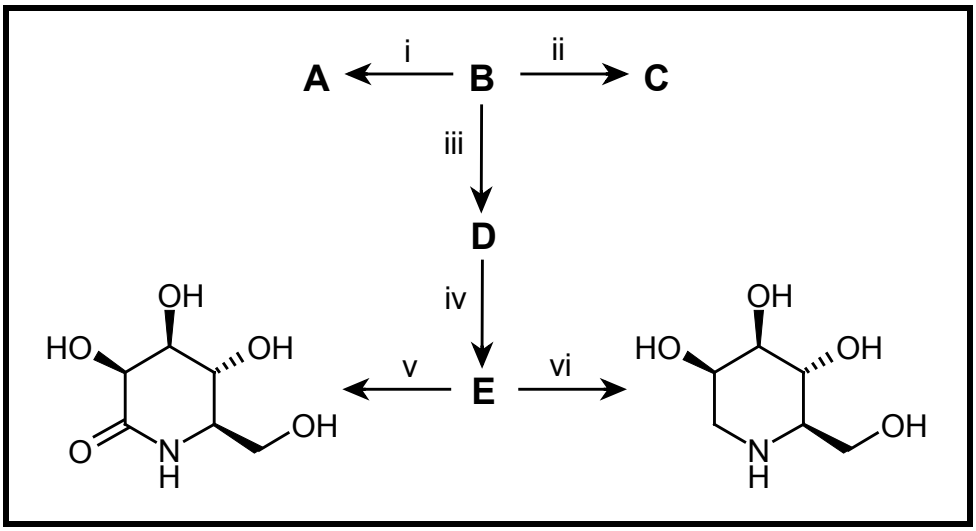
i: a) MeOH, H^+; b) PhCHO, $ZnCl_2$; c) TsCl, py, -30 ºC; d) NaOMe, MeOH.

ii: a) Me_2CuLi, Et_2O; b) 1º- NaH, CS_2; 2º- MeI, Et_2O; c) $HSn(n\text{-}Bu)_3$, AIBN, toluene; d) *p*-TsOH, MeOH; e) TrCl, py; f) $CrO_3 \cdot 2py$, CH_2Cl_2; g) $Ph_3P{=}CH_2$, Et_2O; h) H_2, $(Ph_3P)_3RhCl$, benceno; i) 1,3-Propanedithiol, $BF_3 \cdot Et_2O$, CH_2Cl_2.

iii: a) 2,2-Dimethoxypropane, *p*-TsOH, acetone; b) 1º- *t*-BuLi, hexane; 2º- EtI, HMPA; c) *p*-TsOH, MeOH; d) $HgCl_2$, HgO, CH_3CN.

Bibliography: Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1978**, *56*, 2700.

Exercise 51.



A: Benzyl 2-propinyl ether.
B: (5*S*, 6*S*)-5-Acetyl-1-benzyl-6-(benzyloxymethyl)-2-piperidinone.
C: Tetronic acid (4-hydroxy-2,5-dihydro-2-furanone).
D: (5*S*, 6*R*)-1-Benzyl-5-benzyloxy-6-(benzyloxymethyl)-2-piperidinone.
E: (3*S*, 4*S*, 5*R*, 6*R*)-1-Benzyl-5-benzyloxy-6-(benzyloxymethyl)-3,4-dihydroxy-2-piperidinone.

i: a) 1º- *n*-BuLi; 2º- $ClCO_2Et$; b) 1º- $BnNH_2$, THF, 66 ºC; 2º- Acrylic anhidride, THF, 66 ºC; c) H_2 (1 atm), Pd/C, Na_2CO_3, EtOH; d) Et_3N, MeMgBr; e) DBU.

ii: a) 1º- $BnNH_2$, bencene, 80 ºC; 2º- Acrylic anhidride, THF, 66 ºC; b) H_2 (1 atm), Pd/C, Na_2CO_3, EtOH; c) Et_3N, MeMgBr; d) KOH, BnBr.

iii: a) *m*-CPBA, TFA; b) KOH, H_2O; c) KOH, BnBr.

iv: a) 1º- LDA; 2º- PhSeCl; 3º- $NaIO_4$; b) OsO_4, NMO.

v: a) Li/NH_3.

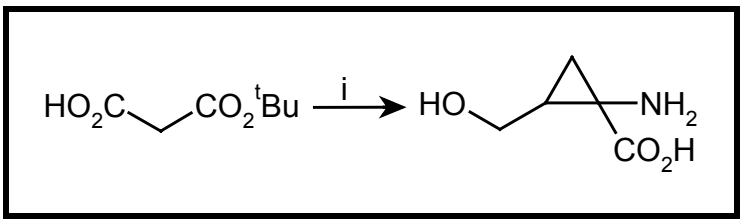
vi: a) 1º- $LiAlH_4$; 2º- NaOH, H_2O; b) H_2 (1 atm), Pd/C, MeOH.

Notes:

The benzyl group can be deprotected by treatment with Li in NH_3.

Bibliography: Cook, G.R.; Beholz, L.G.; Stille, J.R. *J. Org. Chem.* **1994**, *59*, 3575.

Exercise 52.



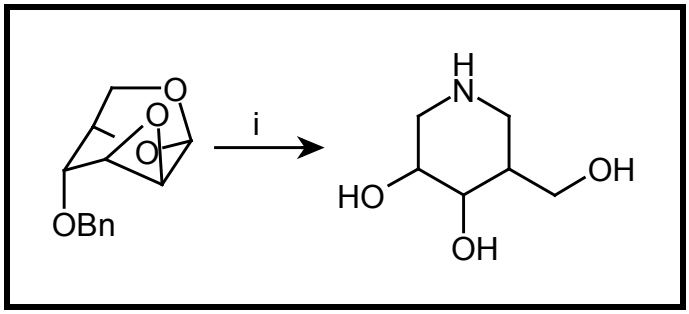
i: a) 2-Propenol, DCC, DMAP; b) *p*-TsN_3, K_2CO_3, CH_3CN; c) $CuI{\cdot}P(OEt)_3$, bencene, ref.; d) TFA, CH_2Cl_2, 0 ºC → t.a.; e) DPPA, Et_3N, *t*-BuOH, ref.; f) HCl, dioxano; g) 1º- NaOH, H_2O; 2º- Amberlite IR-120.

Notes:

The use of $(MeO)_2CH_2/P_2O_5$ is equivalent to the introduction of ClMOM and base.
The treatment of 5,6-didehydropyranosides with Hg(II) salts yields cyclohexanones.
The product obtained is a mixture of the two enantiomers. Suggest one method to carry out an enantioselective synthesis.

Bibliography: Koskinen, A.M.P. e Muñoz, L. *J. Org. Chem.* **1993**, *58*, 879.

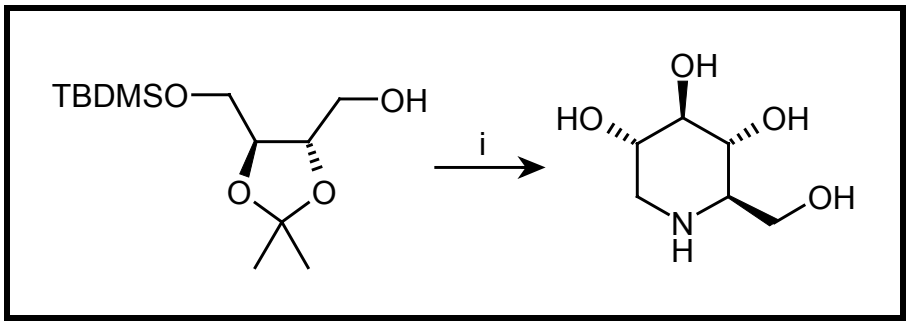
Exercise 53.



i: a) Vinylmagnesium bromide, THF, ref.; b) 1º- O_3, EtOH, 0 ºC; 2º- $NaBH_4$, $EtOH/H_2O$; c) H_2SO_4 1 M, ref.; d) $NaIO_4$, H_2O/MeOH, 45 ºC; e) NH_3, H_2 (35 atm), Pd/C, EtOH, 20 ºC; f) $HCl_{(ac)}$, H_2 (1 atm), Pd/C.

Bibliography: Jespersen, T.M.; Bols, M.; Sierks, M.R.; Skrydstrup, T. *Tetrahedron* **1994**, *50*, 13449.

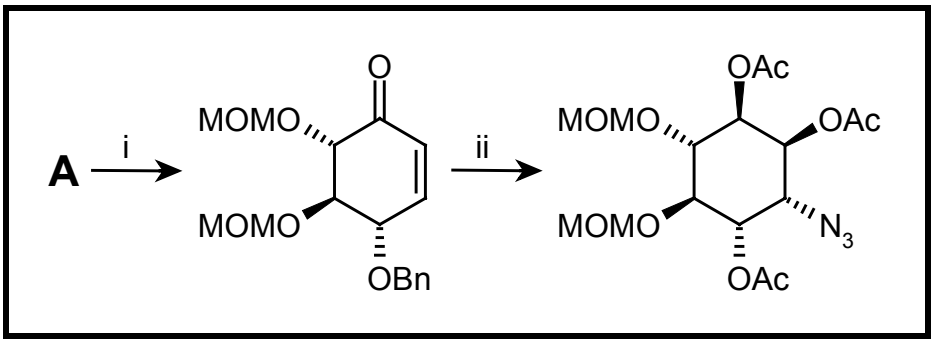
Exercise 54.



i: a) $Cl_2C_2O_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC; b) 1º- $(MeO)_2P(O)CH_2CO_2Me$, NaH, bencene, 0 ºC; 2º- Addition of the substrate; c) DIBAL (2 equiv), toluene, t.a.; d) L-Diethyl tartrate, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 ºC; e) NaN_3, NH_4Cl, DME, ref.; f) MOMCl, $(i\text{-}Pr)_2EtN$, Cl_3CH, ref.; g) TBAF, THF, t.a.; h) MsCl, Et_3N, CH_2Cl_2, 0 ºC; i) 1º- H_2 (1 atm), Pd/C 10%, MeOH, t.a.; 2º- Et_3N, ref.; j) HCl, H_2O.

Bibliography: Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

Exercise 55.



A: Methyl α-D-glucopyranoside.

i: a) TsCl (1 equiv), py; b) $(MeO)_2CH_2$, P_2O_5; c) NaI, TBAI, DBU; d) NaOMe, MeOH; e) NaH, BnBr; f) 1º- $Hg(OTf)_2$ (cat.), H_2O, acetone; 2º- Ac_2O, py.

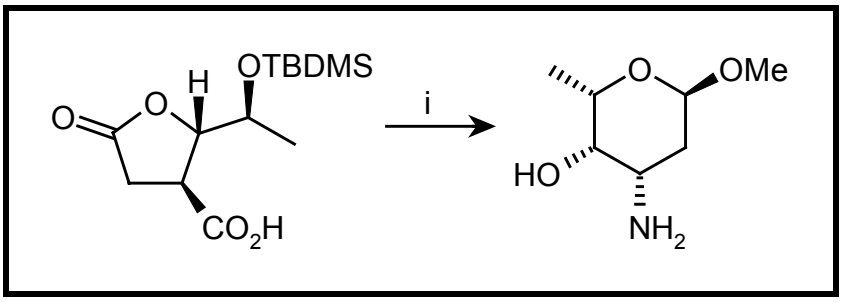
ii: a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; b) *m*-CPBA; c) H_2, $Pd(OH)_2/C$; d) NaN_3, NH_4Cl; e) Ac_2O, py.

Notes:

The use of $(MeO)_2CH_2/P_2O_5$ is equivalent to the introduction of ClMOM and base.
The treatment of 5,6-didehydropyranosides with Hg(II) salts yields cyclohexanones.

Bibliography: Miyazaki, H.; Kobayashi, Y.; Shiozaki, M.; Ando, O.; Nakajima, M.; Hanzawa, H.; Haruyama, H. *J. Org. Chem.* **1995**, *60*, 6103.

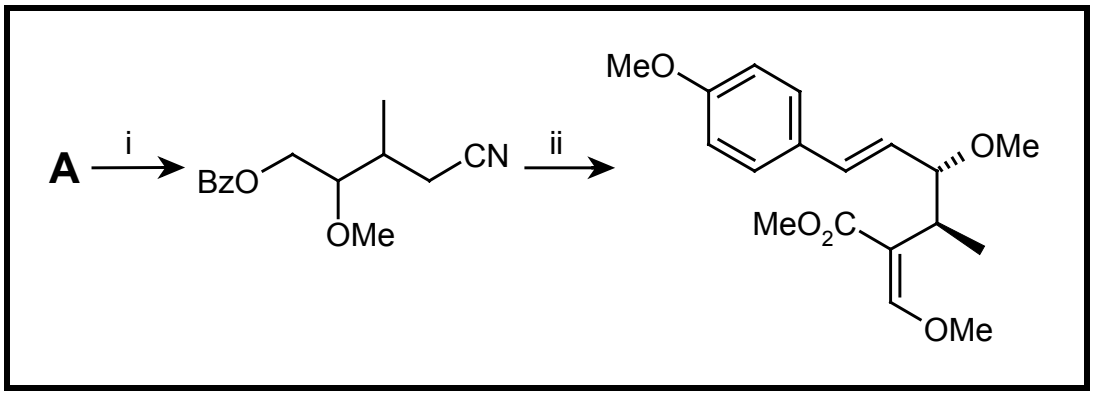
Exercise 56.



i: a) 1º- DPPA, Et_3N, Δ; 2º- *t*-BuOH; b) TBAF, THF, t.a.; c) DIBAL, THF, -78 ºC; d) MeOH, HCl.

Bibliography: Sibi, M.P.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864.

Exercise 57.



A: (1*R*, 2*R*, 3*S*, 4*S*, 5*R*)-1,2-di-*O*-isopropyliden-5-methylen-6-methoxy-1,2,3,4-cyclohexanetetrol.

i: a) H_2, Ni-Raney, EtOH; b) 1º- $NaIO_4$, $NaHCO_3$, acetone/H_2O, 0 ºC; 2º- $NaBH_4$, MeOH, 0 ºC; c) BzCl (excess), py, 0 ºC; d) AcOH 80%, 70 ºC; e) 1º- $NaIO_4$, $NaHCO_3$, acetone/H_2O, 0 ºC; 2º- $NaBH_4$, MeOH, 0 ºC; f) MsCl, py; g) NaCN, DMF, 50 ºC, 6 h.

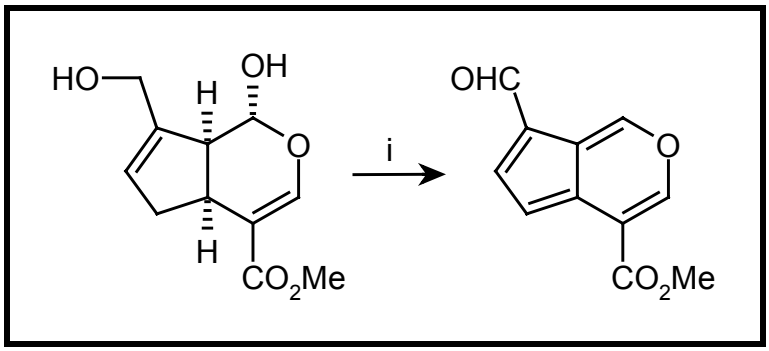
ii: a) NaOMe, MeOH; b) PCC, CH_2Cl_2; c) 1º- $Ph_3P^+CH_2C_6H_4$(*p*-OMe)Cl^-, *n*-BuLi, THF, 0 ºC; 2º- PhSH, AIBN, bencene, ref.; d) 1º- DIBAL, CH_2Cl_2, 0 ºC, 2 h; 2º- $NaClO_2$, NH_2SO_3H, NaH_2PO_4, *t*-BuOH/H_2O, t.a.; 3º- CH_2N_2, Et_2O/CH_2Cl_2; e) 1º- LHMDS, THF, -78 ºC $\rightarrow$ -40 ºC, 1 h; 2º- HCO_2Me, -78 ºC $\rightarrow$ 0 ºC; 3º- SO_4Me_2, K_2CO_3, acetone, t.a..

Notes:

The conditions used on the step ii c) yield the *E* alkene.

Bibliography: Chida, N.; Yamada, K.; Ogawa, S. *Chem. Lett.* **1992**, 687.

Exercise 58.



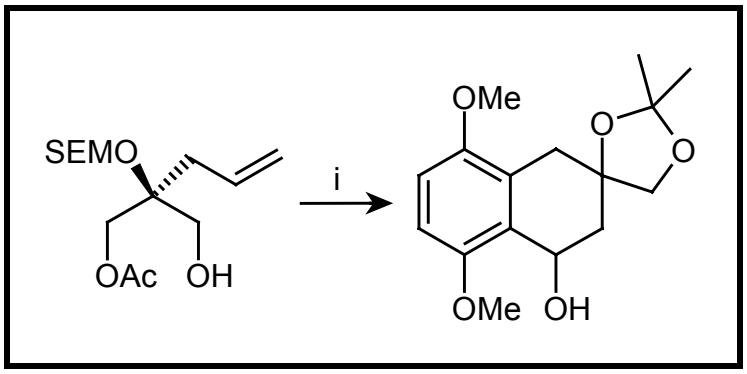
i: a) *t*-Butyldimethylsilyl chloride, (excess), $AgNO_3$, DMF; b) PPTS cat., EtOH, t.a.; c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, t.a., 3.5 h; d) TBAF, AcOH, THF, 0 ºC → t.a., 3.5 h; e) Thiocarbonyldiimidazole, bencene, t.a.; f) bencene, ref., 4 h; g) DDQ, bencene, ref..

Notes:

Conditions used on the step b) deprotect the most reactive silyl ether.

Bibliography: Ge, Y.; Isoe, S. *Chem. Lett.* **1992**, 139.

Exercise 59.



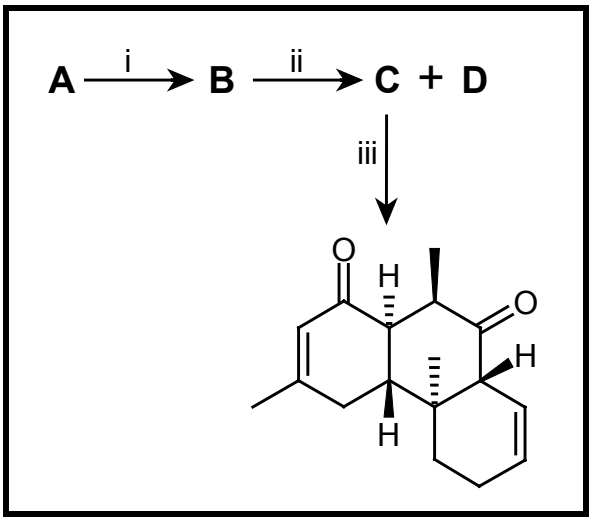
i: a) *t*-Butyldimethylsilyl chloride, imidazole, DMF; b) K_2CO_3, MeOH; c) PDC, *molecular sieves* 3Å, CH_2Cl_2; d) 1,4-dimethoxy-2-phenyllithium, THF, -78 ºC; e) 1º- NaH; 2º- CS_2; 3º- MeI, THF; f) HSn(*n*-Bu)$_3$, AIBN, toluene; g) TBAF, *molecular sieves* 4Å, DMPU; h) 2,2-dimethoxypropane, *p*-TsOH, acetone; i) OsO_4 cat., $NaIO_4$, dioxane/H_2O (1:1); j) $SnCl_4$, CH_2Cl_2, -78 ºC.

Notes:

The starting product with both hydroxymethylgroups acetylated is not chiral. Suggest a method for the preparation of the monoprotected product.
On the step j), the new stereogenic center has the *S* configuration.

Bibliography: Watanabe, N.; Ohta, H. *Chem. Lett.* **1992**, 661.

Exercise 60.



A: [(4*S*)-4-Isopropenyil-1-cyclohexenyl)]methanol.
B: (1*R*, 4*R*, 6*S*)-4-Isopropenyl-6-methyl-2-cyclohexenol.
C: (3a*S*, 4*R*, 7a*R*)-4-Isopropenyl-6-methyl-2,3,3a,4,5,7a-hexahydrobenzo[*b*]furan-2-one.
D: (1*S*, 4a*R*, 7*S*, 8a*R*)-1-(Iodomethyl)-1,7-dimethyl-3,4,4a,7,8,8a-hexahydro-1*H*-3-isocromanone.

i: a) (-)-Diethyl tartrate, $Ti(O^iPr)_4$, TBHP, *molecular sieves* 4Å, CH_2Cl_2; b) *t*-Butyldimethylsilyl chloride, DMAP, Et_3N, CH_2Cl_2; c) Me_2CuLi, Et_2O; d) HCl, MeOH; e) $Pb(OAc)_4$, bencene; f) 1º- LDA, THF; 2º- PhSeBr; 3º- H_2O_2, py; g) $LiAlH_4$, Et_2O.

ii: a) $CH_3C(OEt)_3$, 2,4-dinitrophenol cat., toluene, 120 ºC; b) LiOH, THF, H_2O; c) I_2, DBU, CH_3CN, 70 ºC.

iii: a) LDA, MeI, THF; b) (*E*)-1-Lithium-1,3-butadiene, THF, -78 ºC; c) MnO2, CH_2Cl_2, t.a.; d) Δ, tolueno.

Notes:

The Sharpless epoxidation yields the oxirane in the face opposite to the isopropenyl group.
The reaction on the step ii a) is similar to a Claisen rearrangement.
The product obtained on the step iii b) is a lactol.

Bibliography: Tanner, D.; Andersson, P.G.; Tedenborg, L.; Somfai, P. *Tetrahedron* **1994**, *50*, 9135.