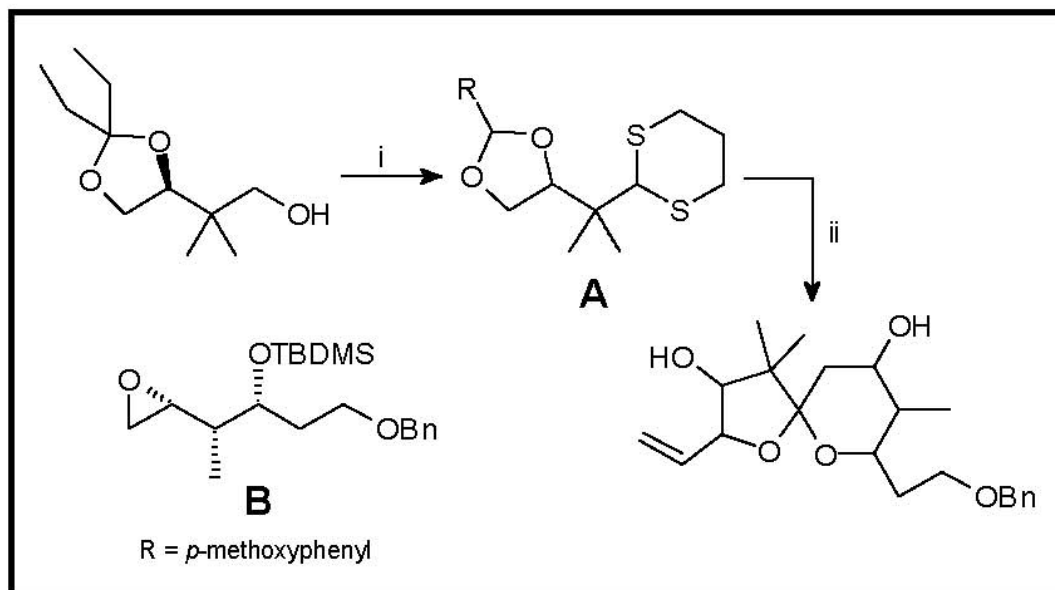




**EXERCISES
IN
ORGANIC SYNTHESIS**

Exercise 1.



i: a) $\text{Cl}_2\text{C}_2\text{O}_2$, DMSO, Et_3N , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; b) 1,3-Propanedithiol (2.5 equiv), $\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; c) *p*-methoxybenzaldehyde dimethyl acetal, *p*-TsOH, DMF, t.a..

ii: a) 1 $^\circ$ - Compound **A** (1.5 equiv), *n*-BuLi (1.5 equiv), TMEDA (6 equiv), THF, $-78 \rightarrow -20\text{ }^\circ\text{C}$; 2 $^\circ$ - DMPU (6 equiv); 3 $^\circ$ - Compound **B** (1 equiv), THF, $-20\text{ }^\circ\text{C}$; b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; c) DIBAL, CH_2Cl_2 , $-78 \rightarrow 0\text{ }^\circ\text{C}$; d) DMSO, $\text{SO}_3\cdot\text{py}$, Et_3N , CH_2Cl_2 , t.a.; e) Vinylmagnesium bromide, THF, $-78\text{ }^\circ\text{C}$; 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 bicyclic acetals using DIBAL yields the primary alcohol and an ether.

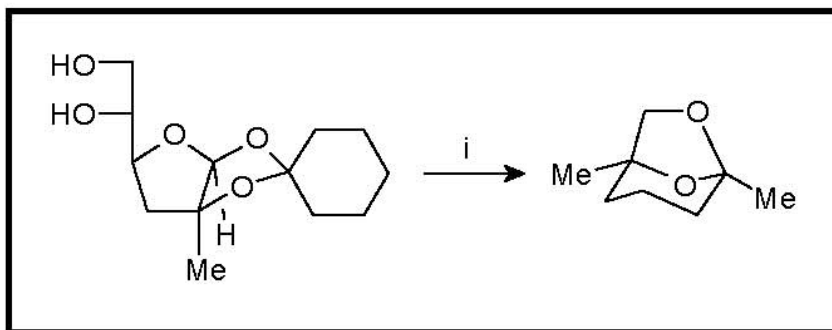
Conditions ii d) yield an aldehyde.

On the step ii e), the addition of the magnesium reagent produces mainly the *S* epimer.

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.

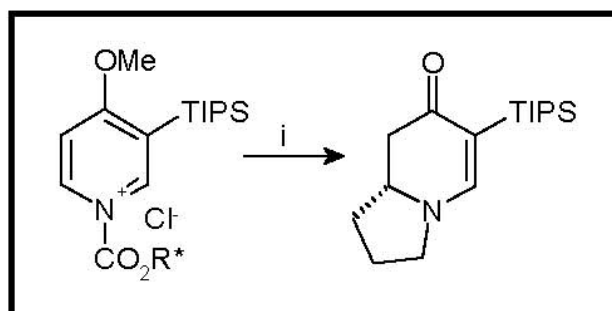
Exercise 2.



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) $\text{Ph}_3\text{P}=\text{CHCOMe}$; j) H_2 , Pd/C ; k) $p\text{-TsOH}$.

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

Exercise 3.



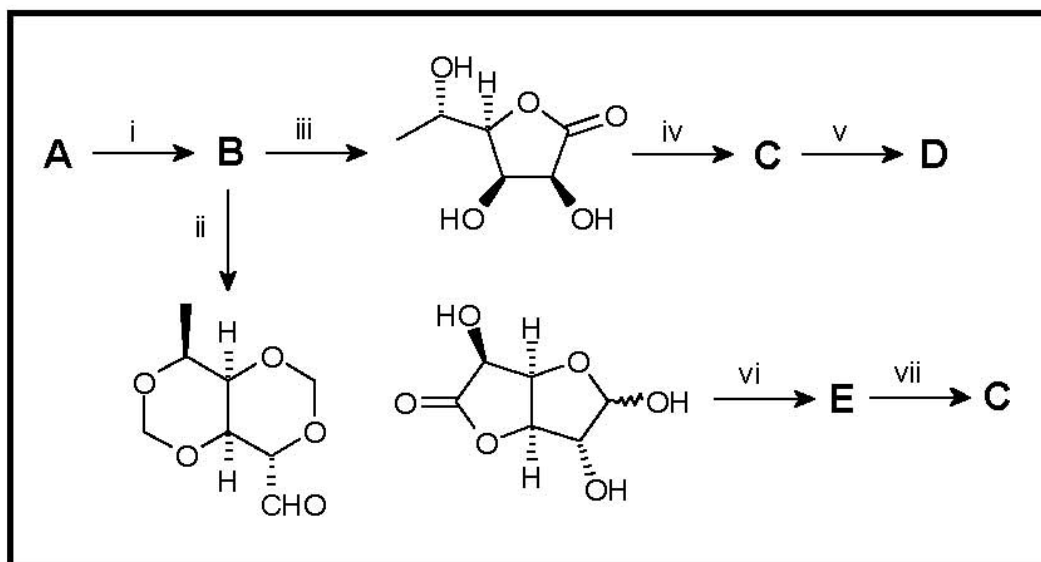
i: a) 1°- 3-butenyl magnesium bromide; 2°- H_3O^+ ; b) 1°- OsO_4 (cat.), NaIO_4 ; 2°- L-Selectride®; c) Ph_3P , NCS , CH_2Cl_2 ; d) NaOMe , MeOH .

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-Deoxy-2,3-*O*-isopropylidene-4-*O*-methyl-*L*-gulopyranose.

E: 2-*O*-(*t*-Butyldimethylsilyl)-6-deoxy-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) $\text{Na}(\text{Hg})$, H_3O^+ ; b) MeOH , H^+ .

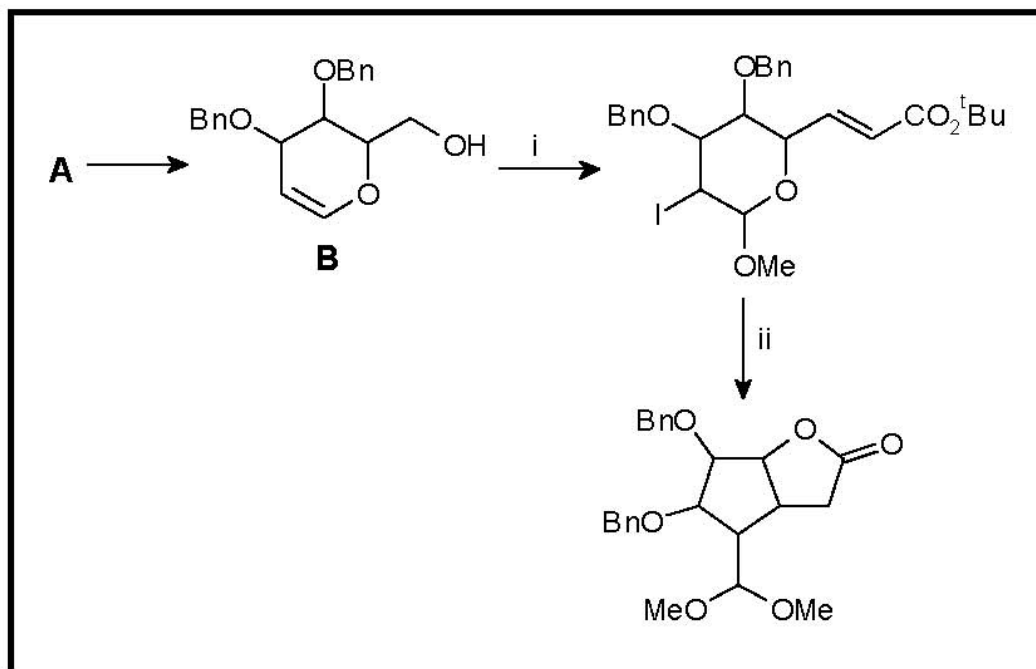
v: a) 2,2-Dimethoxypropane, acetone, H^+ ; b) KH , MeI , THF ; c) H_2O , H^+ ; d) 2,2-Dimethoxypropane, acetone, H^+ .

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) $\text{Ph}_3\text{C}-\text{CH}=\text{CO}_2^t\text{Bu}$; c) *N*-Iodosuccinimide, MeOH.

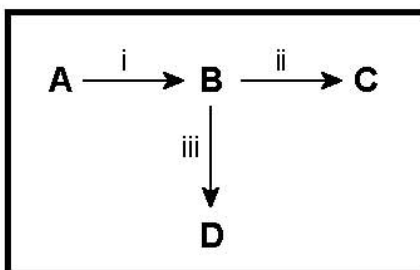
ii: a) $\text{HSn}(n\text{-Bu})_3$, AIBN; b) MeOH, H^+ .

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*)-Bicyclo[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-Acetoxyethyl-2,3-*O*-isopropyliden-4-(triphenylmethoxy methyl)cyclopentan-1,2,3-triol.

D: (1*R*, 2*R*, 3*R*, 4*R*)-1-Acetoxyethyl-2,3-*O*-isopropyliden-4-(triphenylmethoxy methyl)cyclopentan-1,2,3-triol.

i: a) 1°- H₂O₂, NaOH, H₂O, Et₂O; 2°- MeI (1.1 equiv), DMF, t.a.; 3°- Ac₂O, py, DMAP, CH₂Cl₂, t.a.; b) 1°- OsO₄, NMO, acetone, t.a.; 2°- 2,2-dimethoxypropane, *p*-TsOH, t.a.; c) LiAlH₄, Et₂O, 0 °C → t.a.; d) Br₂, Ph₃P, Et₃N, CH₂Cl₂, t.a.; e) 1°- 2-nitrophenylselenenecyanate, NaBH₄, THF, t.a.; 2°- H₂O₂, THF, t.a.; f) 1°- OsO₄, NaIO₄, H₂O, Et₂O, t.a.; 2°- NaBH₄, MeOH, t.a.; g) TrCl, py, DMAP, CH₂Cl₂, t.a.; h) PDC, CH₂Cl₂, t.a..

ii: a) 1°- Me₃S(O)⁺I⁻, NaH, DMSO, THF, t.a.; 2°- Addition of compound **B**; b) CsOAc, DMF, 80 °C.

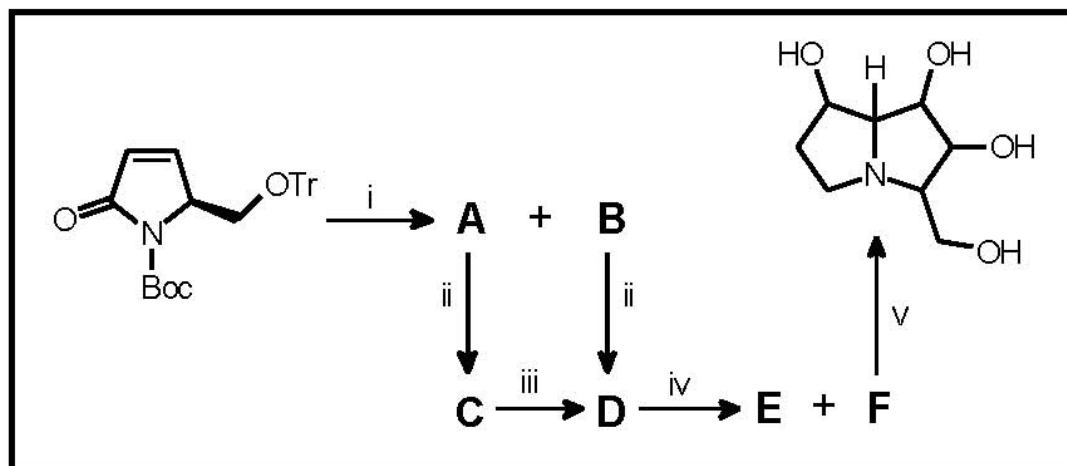
iii: a) 1°- CH₂Br₂, *n*-BuLi, THF, -80 °C → t.a.; 2°- Addition of compound **B**; b) CsOAc, DMF, 80 °C.

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) 1°- OsO₄ cat., *N*-methylmorpholine *N*-oxide, acetone-H₂O; 2°- 2,2-Dimethoxypropane, *p*-TsOH cat., acetone; b) Vinylmagnesium bromide, THF, -50 °C; c) NaBH₄, CeCl₃·7H₂O, MeOH; d) 1°- O₃, CH₂Cl₂, -78 °C; 2°- NaBH₄, EtOH.

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

iii: 1°- Cl₂C₂O₂, DMSO, Et₃N, CH₂Cl₂, -20 °C; 2°- NaBH₄, EtOH, -78 °C.

iv: a) 1°- MsCl, Et₃N, CH₂Cl₂; 2°- KO^t-Bu, THF; b) TBAF, THF; c) 1°- Cl₂C₂O₂, Et₃N, DMSO, CH₂Cl₂, -20 °C; 2°- Allylmagnesium chloride, THF.

v: a) Methoxymethyl chloride, *N,N*-diethylaniline, CH₂Cl₂; b) 1°- TBDMSOTf, 2,6-lutidine, CH₂Cl₂; 2°- TBAF, THF; 3°- BnBr, K₂CO₃, acetone; c) 1°- O₃, CH₂Cl₂, -78 °C; 2°- NaBH₄, EtOH; d) 1°- MsCl, Et₃N, CH₂Cl₂; 2°- Pd/C 10%, H₂, EtOH; e) HCl 10%, MeOH, 60 °C.

Notes:

The use of Ce³⁺ salts allows the selective reduction of the carbonyl moiety in α,β -unsaturated compounds.

Compound C possesses a hydroxy group on a carbon with *R* configuration.

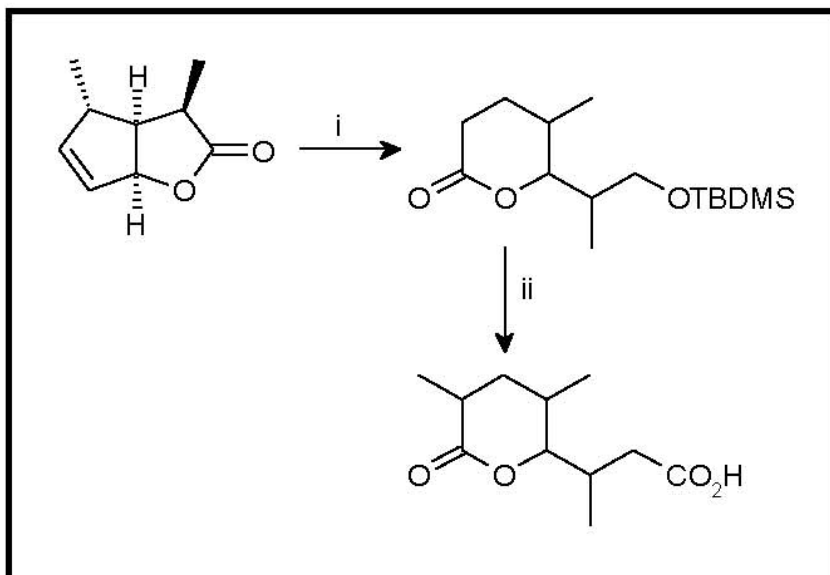
The step iii yields a mixture of the compounds C and D in a 1:18 ratio.

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.

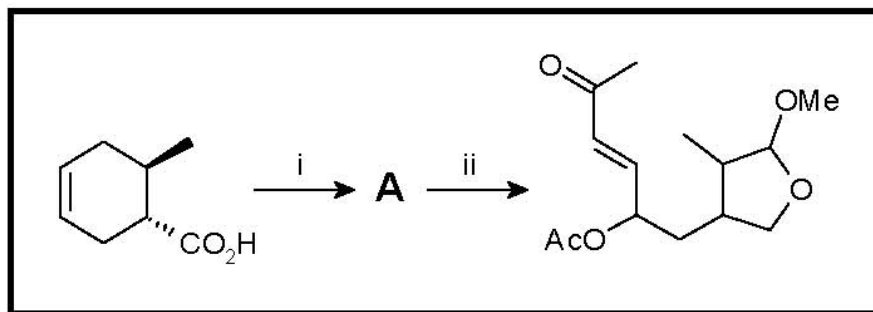
ii: a) 1°- LDA; 2°- MeI; 3°- H^+ ; b) CrO_3 .

Notes:

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

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

Exercise 9.



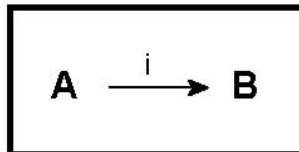
A: (2*R*)-2-Methyl-6-oxabicyclo[3.2.1]octen-3-en-7-one.

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) 1° - O_3 , MeOH, $-78^\circ C$; 2° - Me_2S ; f) $Ph_3P=CHCOMe$, $CHCl_3$; g) PPTS, MeOH, $50^\circ C$.

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

Exercise 10.



A: Methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside.

B: Uronic acid methyl ester.

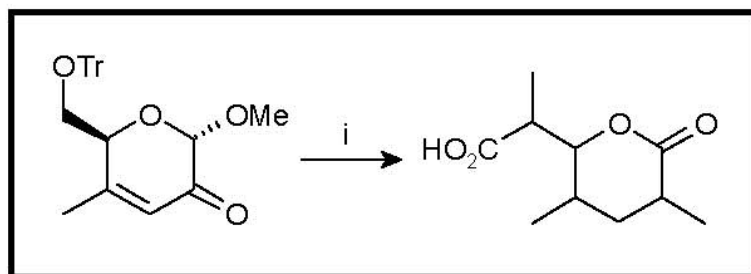
i: a) *t*-Butyldiphenylsilyl chloride, imidazole, DMF; b) Thiocarbonyldiimidazole, toluene, ref.; c) $HSn(n-Bu)_3$, AIBN, toluene, ref.; d) TBAF, THF; e) PDC, DMF; f) 1° - $Cl_2C_2O_2$, DMF cat., CH_2Cl_2 ; 2° - CH_2N_2 , Et_2O ; g) $h\nu$, MeOH.

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.



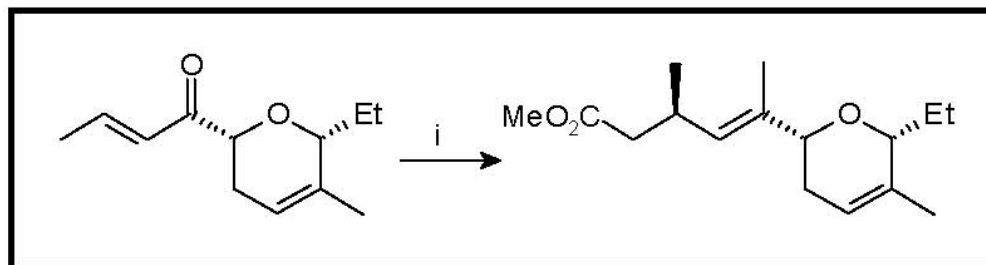
i: a) $\text{Ph}_3\text{P}=\text{CH}_2$; b) H_2 , Pd/C; c) CrO_3 , py; d) MeLi; e) CrO_3 , py; f) 1°- $\text{Ph}_3\text{P}=\text{CHOMe}$; 2°- H_3O^+ ; g) CrO_3 ; h) Separation of the epimer with the *R* configuration on the position adjacent to the carboxy moiety.

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.

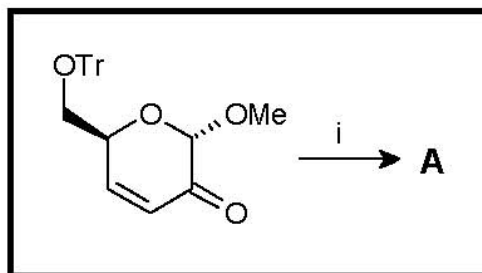
Exercise 12.



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

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

Exercise 13.



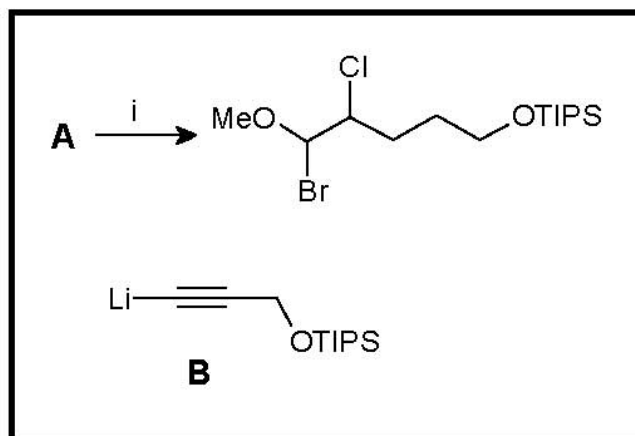
i: a) 1°- MeLi; 2°- Ac₂O; b) Me₂CuLi; c) H₂, Pt; d) Cl₂C₂O₂, DMSO, Et₃N; e) MeNO₂, KF; f) Ac₂O, DMAP.

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.

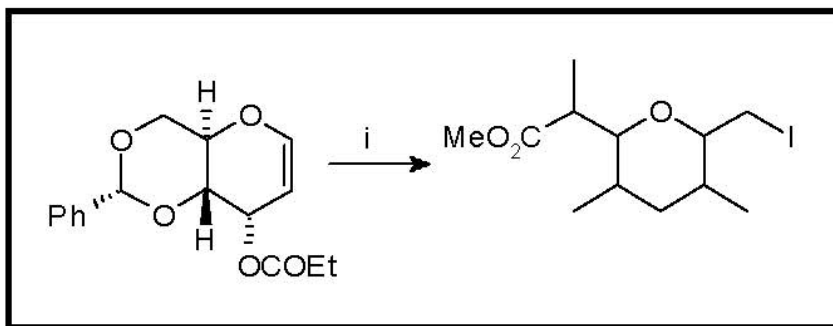
i: a) Cl₂C₂O₂, DMSO, Et₃N; b) Addition of compound **B**; c) CrO₃, H₂O, H₂SO₄, acetone; d) (R)-Binal-H; e) H₂, Pd/BaSO₄; f) Tf₂O, py; g) TBAC, CH₂Cl₂, 25 °C; h) Me₂BBr, -78 °C.

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) 1°- $\text{LiN}(\text{TMS})_2$; 2°- *t*-Butyldimethylsilyl chloride, imidazole; 3°- Δ ; b) CH_2N_2 ; c) H_3O^+ ; d) *t*-Butyldimethylsilyl chloride, imidazole; e) PDC; f) Me_2CuLi ; g) $\text{Ph}_3\text{P}=\text{CH}_2$; h) H_2 , Pt; i) TBAF; j) TsCl, py; k) NaI.

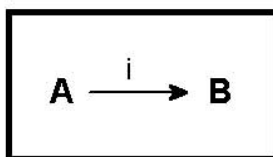
Notes:

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.



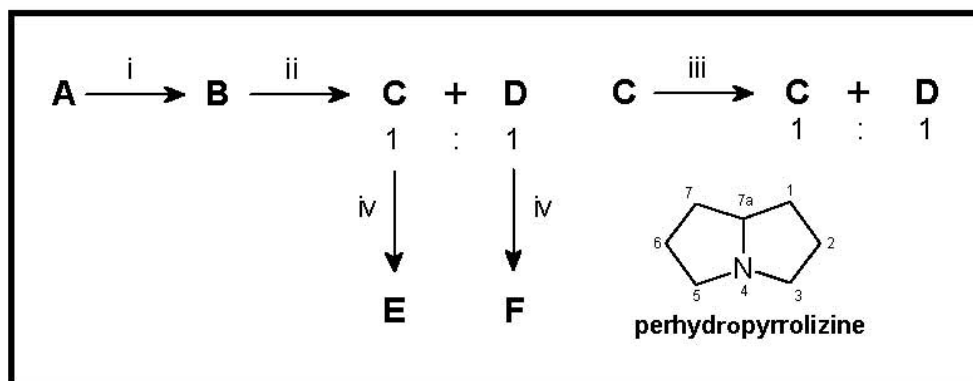
A: (*S*)-*N*-Phenylsulfonylserine.

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

i: a) MeLi; b) 1°- NaH; 2°- Triphenylvinylphosphonium bromide; c) *t*-Butyldimethylsilyl chloride, imidazole; d) OsO_4 cat., *N*-methylmorpholine *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-benzyloxy-2-deoxy- α -D-mannofuranoside.

C: $C_{23}H_{27}NO_4$.

E: (1*R*, 2*R*, 3*R*, 7*S*, 7*aS*)-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 °C; b) Tf_2O , py, -30 °C; c) 1°- H_2 , Pd/C 10%, AcOEt; 2°- BnBr, KOH, DMF; d) TBAF, THF; e) 1°- $Cl_2C_2O_2$, DMSO; 2°- Et_3N ; f) Vinylmagnesium bromide, THF.

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

iv: a) *t*-Butyldimethylsilyl chloride, imidazole, DMF; b) 1°- $BH_3 \cdot SMe_2$, THF; 2°- 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.

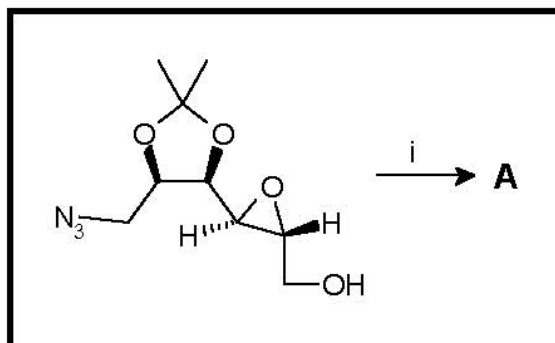
Notes:

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*, 7*aR*)perhydro-1,2,7-pyrrolizinetriol.

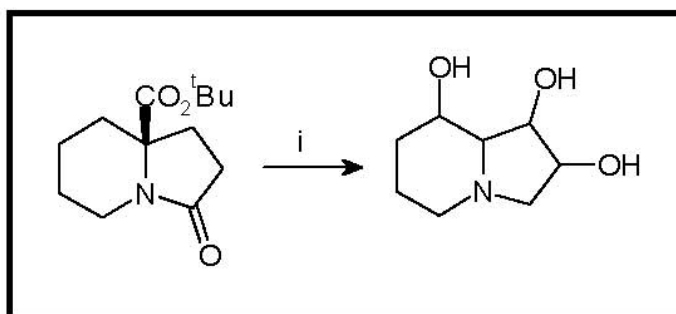
i: a) Tf_2O ; b) LiCN ; c) H_2 , Pd/C , EtOH ; d) Benzyl chloroformate; e) H_2O_2 , MeOH ; f) *t*-Butyldimethylsilyl chloride, imidazole; g) H_2 , Pd/C ; h) NaHCO_3 ; i) $\text{BH}_3\text{-SMe}_2$; j) TFA , H_2O .

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.

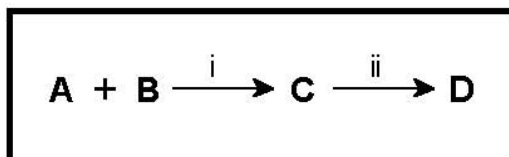
Exercise 19.



i: a) 1°- LDA ; 2°- PhSeCl ; b) H_2O_2 , AcOH ; c) OsO_4 cat., *N*-methylmorpholine *N*-oxide; d) 2,2-Dimethoxypropane, H^+ ; e) TFA , H_2O ; g) $\text{Cl}_2\text{C}_2\text{O}_2$; h) Xylene, ref.; i) 1°- B_2H_6 ; 2°- 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, H₂O; b) H₂, Pd/C, MeOH; c) Benzyl chloroformate, NaHCO₃; d) TsCl, py.

ii: a) H₂, Pd/C, MeOH; b) Benzyl chloroformate, NaHCO₃; c) Separation of epimers; d) HCl; e) NaBH₄; f) H₂, Pd/C.

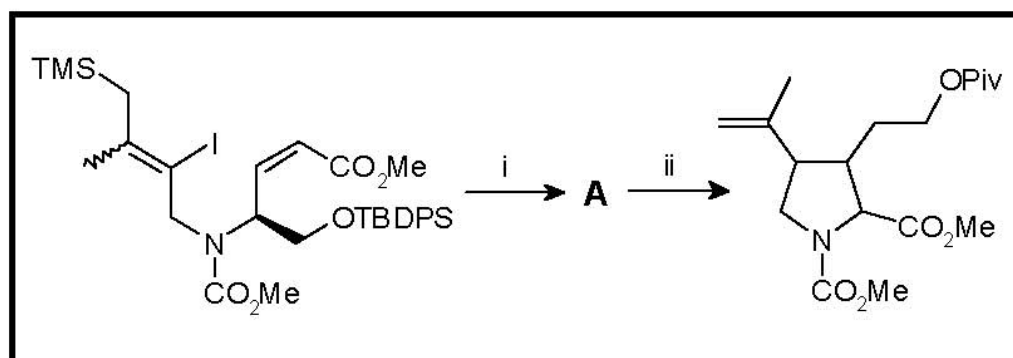
Notes:

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.; Pätzelt, M.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1295.

Exercise 21.



i: a) HSn(*n*-Bu)₃, AIBN, benzene, ref.; b) LiAlH₄; c) Pivaloyl chloride, Et₃N; d) TBAF.

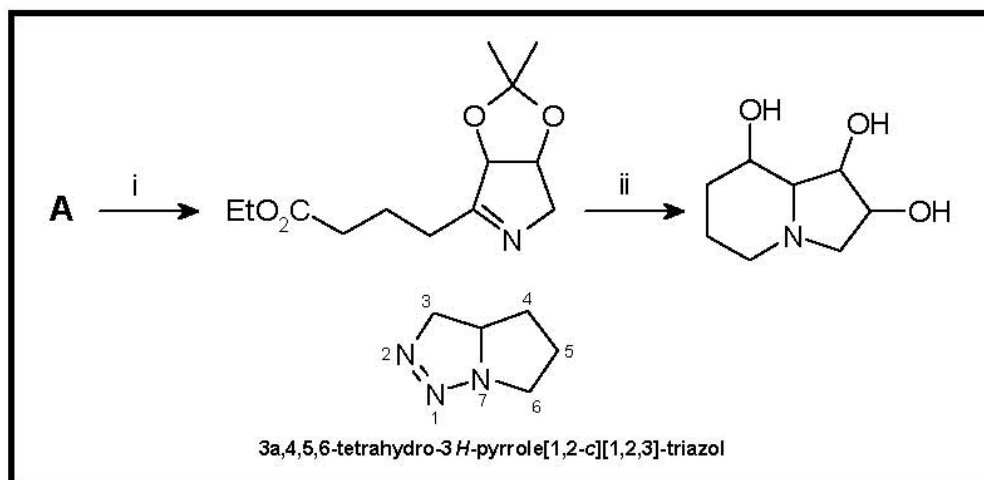
ii: a) Cl₂C₂O₂, DMSO, Et₃N; b) NaClO₂, NaH₂PO₄, 2-methyl-2-butene; c) BF₃·Et₂O; d) CH₂N₂.

Notes:

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

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

Exercise 22.



A: 2,3-O-Isopropyliden-D-erythrose.

i: a) $\text{BrPh}_3\text{P}(\text{CH}_2)_3\text{CO}_2\text{Et}$, KHMDS, THF; b) TsCl, Et_3N ; c) NaN_3 , DMF, Δ .

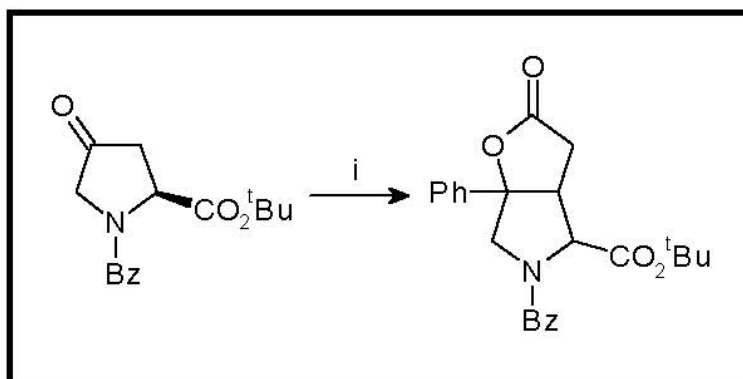
ii: a) K_2CO_3 , H_2O , MeOH; b) Toluene, ref.; c) 1°- $\text{BH}_3\cdot\text{THF}$; 2°- H_2O_2 , OH^- ; d) HCl, THF.

Notes:

On the step i c) a 3a,4,5,6-tetrahydro-3H-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.

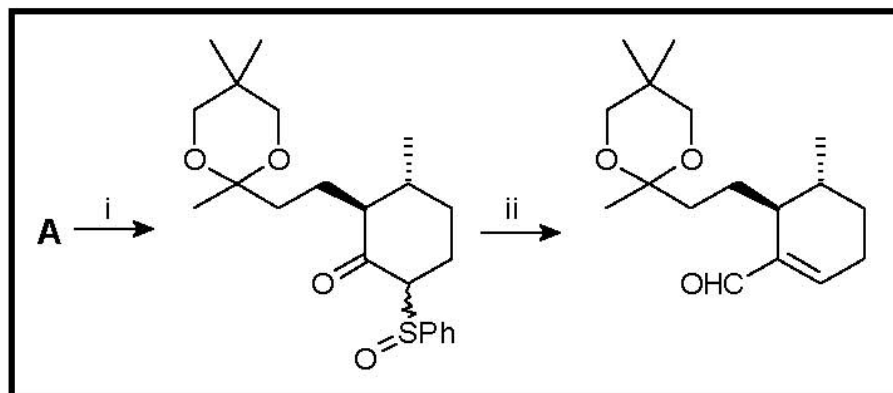
Exercise 23.



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

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

Exercise 24.



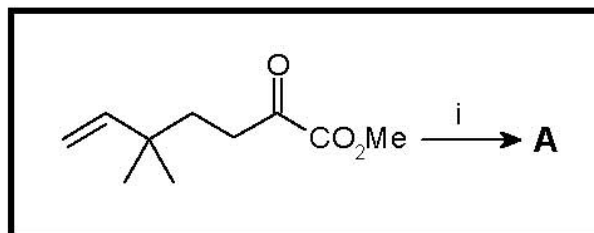
A: (5*R*)-2-Isopropylidene-5-methylcyclohexanone.

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

ii: a) Al(Hg), THF, H_2O ; b) *p*-TsNHNH₂, water distillation; c) 1°- *n*-BuLi (4 equiv), TMEDA, $0^\circ C$; 2°- DMF.

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

Exercise 25.



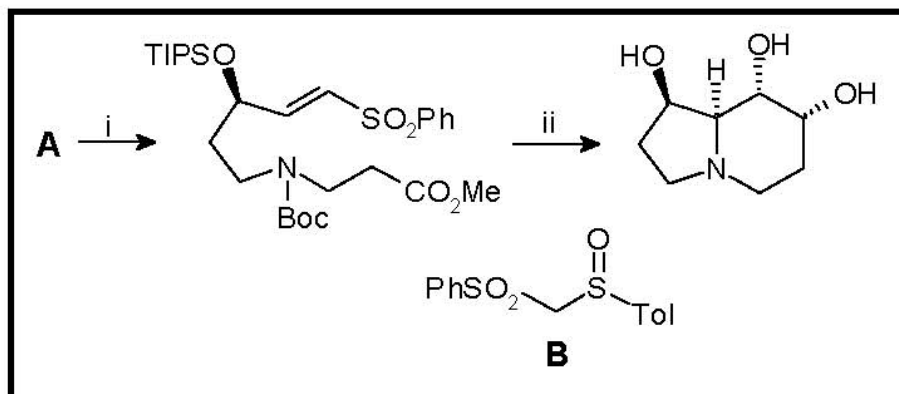
i: a) *N*-methylhydroxylamine hydrochloride, Et₃N, MeOH/toluene (6:94), 60 °C, 12 h; b) H₂, 5% Rh/C, MeOH, 5 h.

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.* **1994**, *33*, 3533.

Exercise 26.



A: 4-aminebutanol.

i: a) Methyl acrylate, EtOH, 0 °C; b) Boc₂O, CH₂Cl₂, t.a.; c) Cl₂C₂O₂, DMSO, Et₃N, CH₂Cl₂, -78 °C; d) Compound **B**, piperidine, CH₂Cl₂, 0 °C, 10 h; e) TIPSOTf, 2,6-lutidine, CH₂Cl₂.

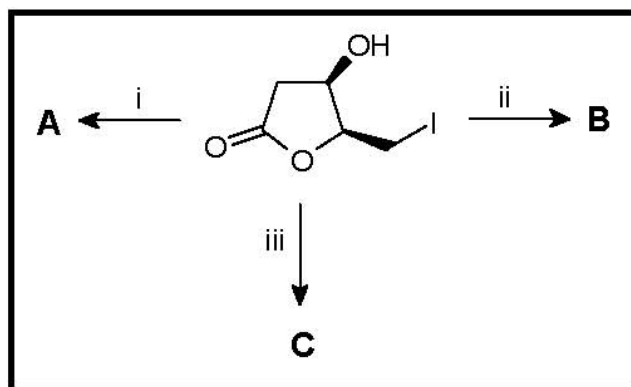
ii: a) TFA, CH₂Cl₂, t.a.; b) Et₃N, -78 °C; c) Separation of diastereoisomers; d) LHMDS, THF, 0 °C; e) NaBH₄; f) Na(Hg), MeOH; g) OsO₄, Me₃NO; h) HCl.

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-pentyltetrahydro-2-furanone [(+)-Lactone of cognac].

C: (2*R*, 3*S*, 4*S*)-4-Methyl-5-oxo-2-dodecyltetrahydro-3-furancarboxylic acid.

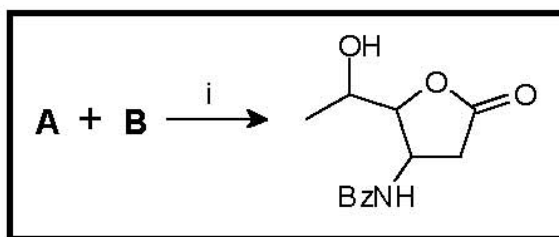
i: a) Propylmagnesium bromide, CuBr·Me₂S; b) Benzoyl chloride, py; c) NH₃, MeOH; d) Me₂CuLi, THF.

ii: a) Butylmagnesium bromide, CuBr·Me₂S; b) Benzoyl chloride, py; c) NH₃, MeOH; d) Me₂CuLi, THF.

iii: a) C₁₁H₂₃MgBr, CuBr·Me₂S; b) Benzoyl chloride, py; c) NH₃, MeOH; d) 1°- (PhS)₃CLi; 2°- MeI; e) HgO, BF₃·Et₂O, THF, H₂O.

Bibliography: Takahata, H.; Lichida, 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 .

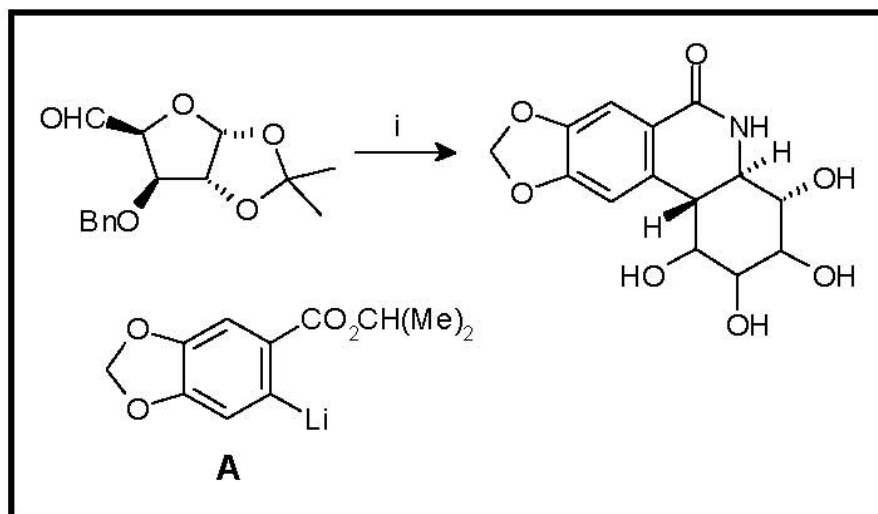
Notes:

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.



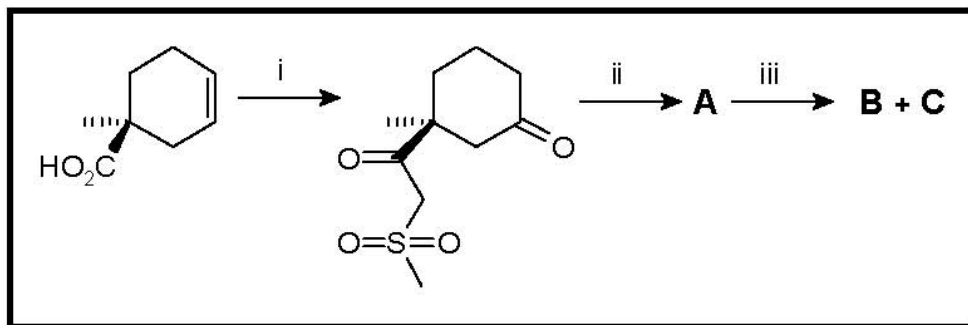
i: a) MeNO_2 , KF; b) Ac_2O , *p*-TsOH; c) NaHCO_3 , benzene, 80 °C; d) Compound A, THF, -110 °C; e) AcOH (50%), ref.; f) NaHCO_3 (2.25%), MeOH ; g) H_2 (1 atm), Pd/C 10%; h) K_2CO_3 , MeOH .

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-methylbicyclo[3.2.1]octan-6-one.

B: C₁₃H₁₆O₂.

i: a) I_2 , NaHCO₃, H₂O, THF; b) HSn(*n*-Bu)₃, AIBN, benzene, ref.; c) 1°- LiCH₂SO₂CH₃, DME; 2°- H₂CrO₄.

ii: a) NaOH, H₂O, THF; b) Na(Hg), K₂HPO₄, MeOH.

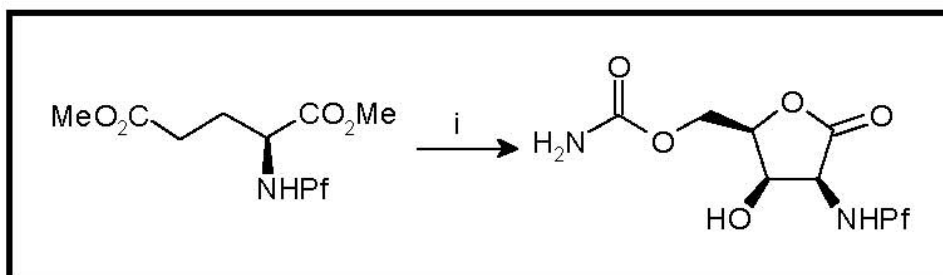
iii: a) MsCl, py; b) Et₃N, furane, ref..

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.

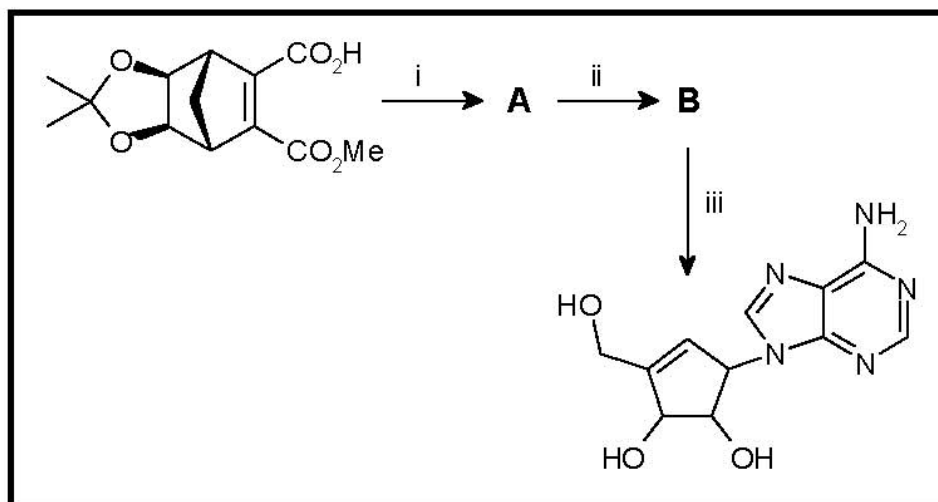
Exercise 31.



i: a) 1°- KHMDs; 2°- PhSeCl; b) *m*-CPBA; c) DIBAL (2 equiv); d) *p*-NO₂-PhOCOCl; e) NH₃; f) OsO₄; g) Et₃N.

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-oxabicyclo[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, $-78\text{ }^\circ\text{C}$; b) $NaBH_4$; c) $NaIO_4$, HCl 2 N; d) $NaBH_4$; e) Ac_2O , py.

ii: a) $NaSePh$, DMF; b) 1 $^\circ$ - $ClCO_2Et$, Et_3N ; 2 $^\circ$ - NaN_3 ; 3 $^\circ$ - Δ , benzene; 4 $^\circ$ - MeOH, c) 1 $^\circ$ - O_3 , CH_2Cl_2 ; 2 $^\circ$ - py (cat.); d) *m*-CPBA, CH_2Cl_2 ; e) 1 $^\circ$ - TMSOTf, 2,6-lutidine, toluene; 2 $^\circ$ - DBU; 3 $^\circ$ - K_2CO_3 ; f) MOMCl, (*i*-Pr) $_2$ EtN, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; g) KOH, H_2O .

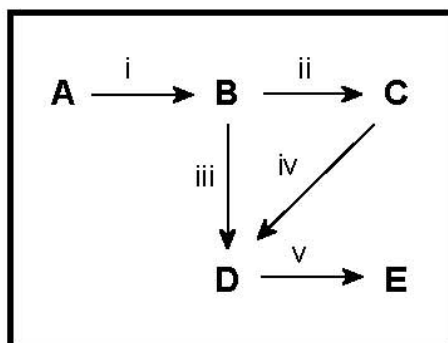
iii: a) 5-Amino-4,6-dichloropyrimidine, Et_3N ; b) 1 $^\circ$ - Triethoxymethyl, Ac_2O ; 2 $^\circ$ - NH_3 ; c) HCl 2 M.

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**, *f05*, 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 , 0°C ; f) Zn , AcOH , NaOAc , H_2O .

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

v: a) $\text{BF}_3\cdot\text{Et}_2\text{O}$, MeOH , CH_2Cl_2 .

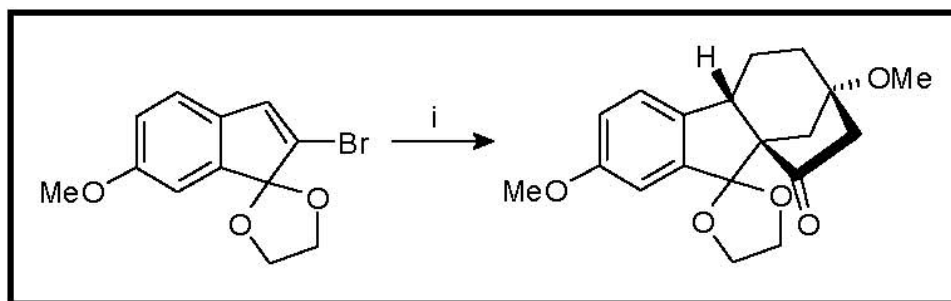
Notes:

On the step iii b) the α epimer is obtained selectively.

Conditions on the step iii f) yield an alkene through 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.

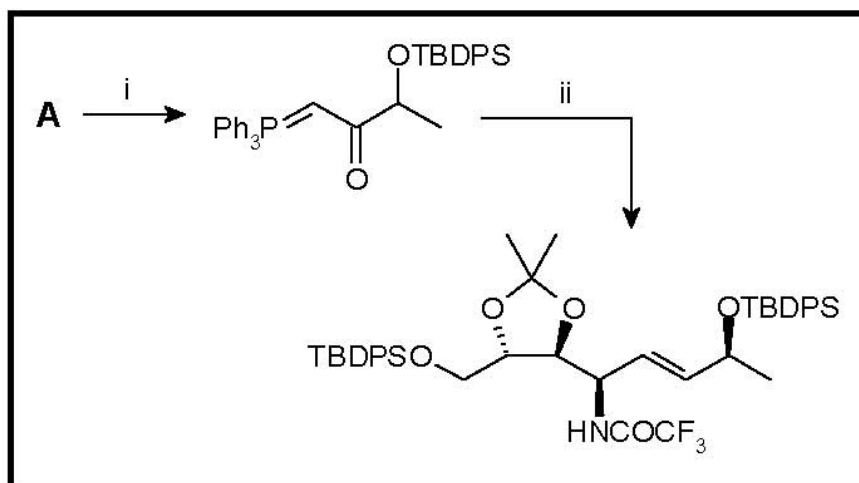
Exercise 34.



i: a) 1°- *n*-BuLi, Me₂O, hexane; 2°- CO₂; 3°- H₂O; b) CH₂N₂; c) 1,3-Butadiene, 130-140 °C; d) NaOH 4 M, MeOH; e) 1°- I₂, NaHCO₃, H₂O, THF; 2°- HSn(*n*-Bu)₃, AIBN, benzene, ref.; f) 1°- LiCH₂P(O)(OMe)₂, DME, -78 °C; 2°- H₂O; g) H₂CrO₄; h) Na₂CO₃, 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-[(*tert*-butyldiphenylsilyloxy)methyl]-1,3-dioxolane.

i: a) *t*-Butyldiphenylsilyl chloride, imidazole; b) KOH, MeOH; c) 2-Pyridinethiol, DCC; d) Ph₃P=CH₂.

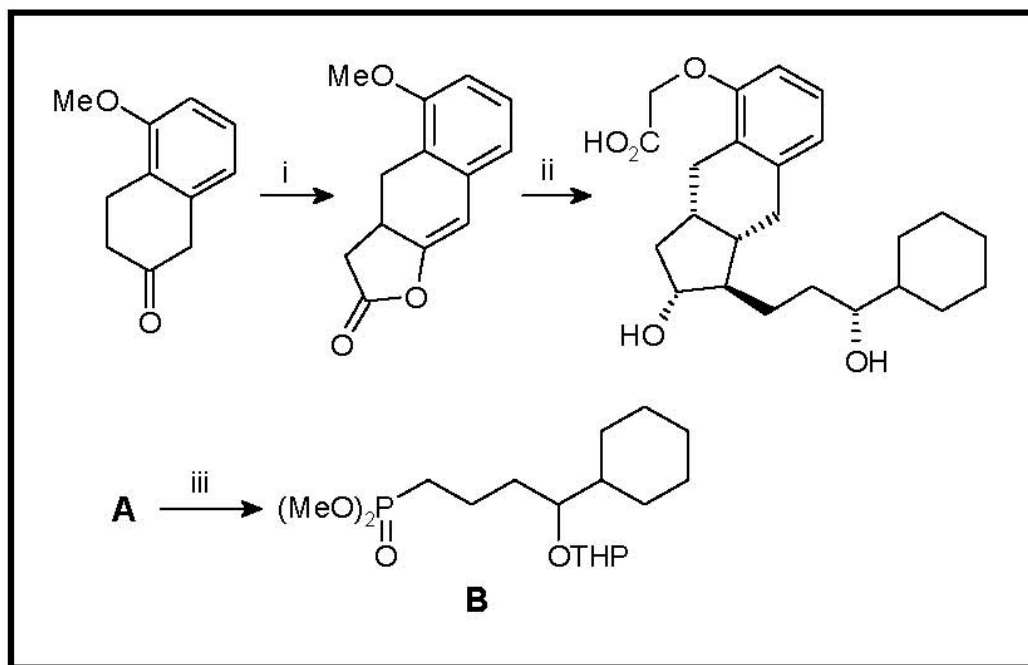
ii: a) Compound **B**, benzene, ref.; b) L-Selectride; c) 1°- *n*-BuLi; 2°- CF₃CN; d) Xilene, ref..

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, CO₃Me₂, 70 °C; b) 1°- LDA, THF, -78 °C; 2°- Allyl bromide; c) LiCl, H₂O, DMSO, 150 °C; d) Ethylen glycol, (EtO)₃CH, *p*-TsOH, CH₂Cl₂, 25 °C; e) 1°- NaIO₄, KMnO₄, H₂O, 25 °C; 2°- HCl 3 M, acetone, 60 °C; f) Ac₂O, HClO₄ (cat.), AcOEt.

ii: a) 1°- Compound **B** (2 equiv), *n*-BuLi (2 equiv), THF, -78 °C → -10 °C; 2°- AcOH; b) H₂ (3 atm), Pd/C 10%, EtOH; c) NaBH₄, NaOH, H₂O, EtOH, -10 °C; d) 1°- AcOH, H₂O, THF, 45 °C; 2°- Separation of diastereoisomers; e) LiPh₂, THF, 75 °C; f) K₂CO₃, ClCH₂CN, acetone, 60 °C; g) KOH, H₂O, MeOH, 90 °C.

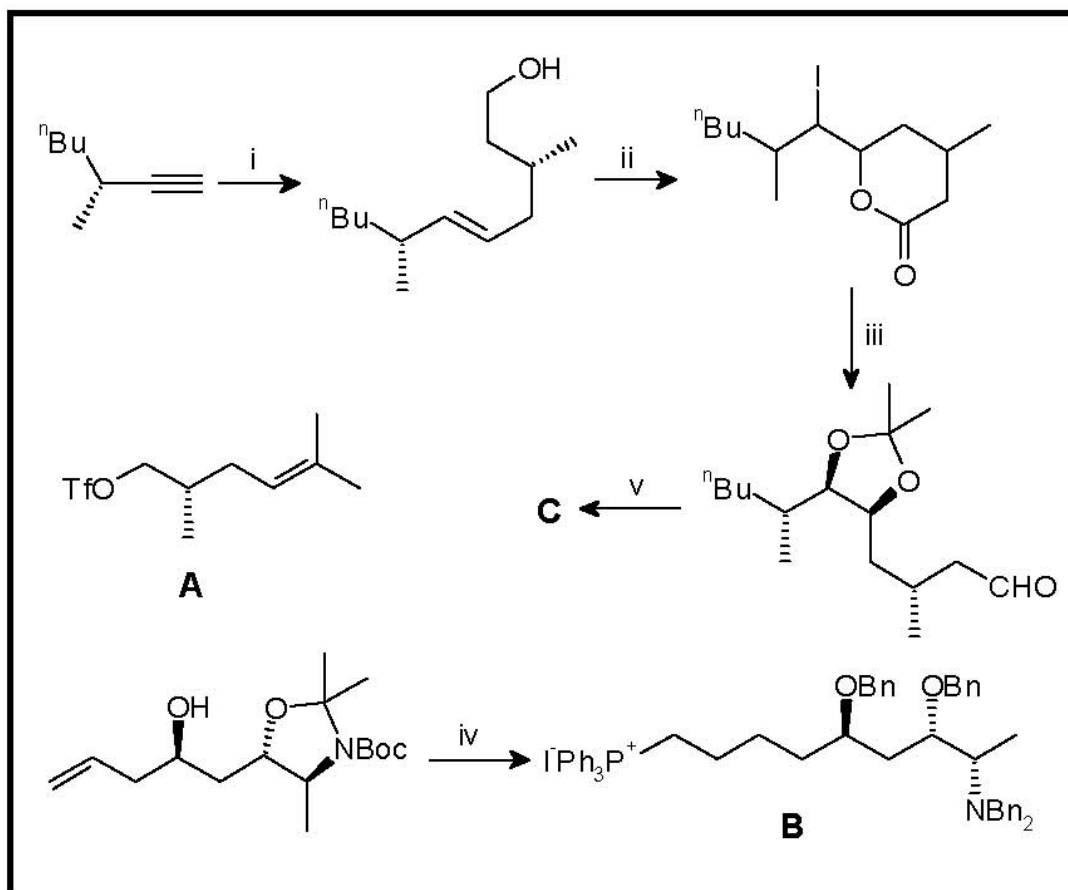
iii: a) Vinylmagnesium bromide, THF, 0 °C; b) Separation of *R* enantiomer; c) DHP, H⁺, CH₂Cl₂; d) 1°- 9-BBN, THF; 2°- H₂O₂, KOH; e) *p*-TsCl, py, 0 °C; f) NaI, (*i*-Pr)₂EtN, acetone; g) (MeO)₂P(O)CH₂Li, THF, -78 °C → -10 °C.

Notes:

LiPh₂ 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: C₅₀H₆₉NO₄.

i: a) 1°- *n*-BuLi; 2°- Addition of compound **A**; b) K₂O₈O₄·2H₂O; c) Pb(OAc)₄; d) NaBH₄; e) Na, liquid NH₃.

ii: a) Cl₂C₂O₂, DMSO, Et₃N; b) NaClO₂; c) I₂, CH₃CN, -30 °C.

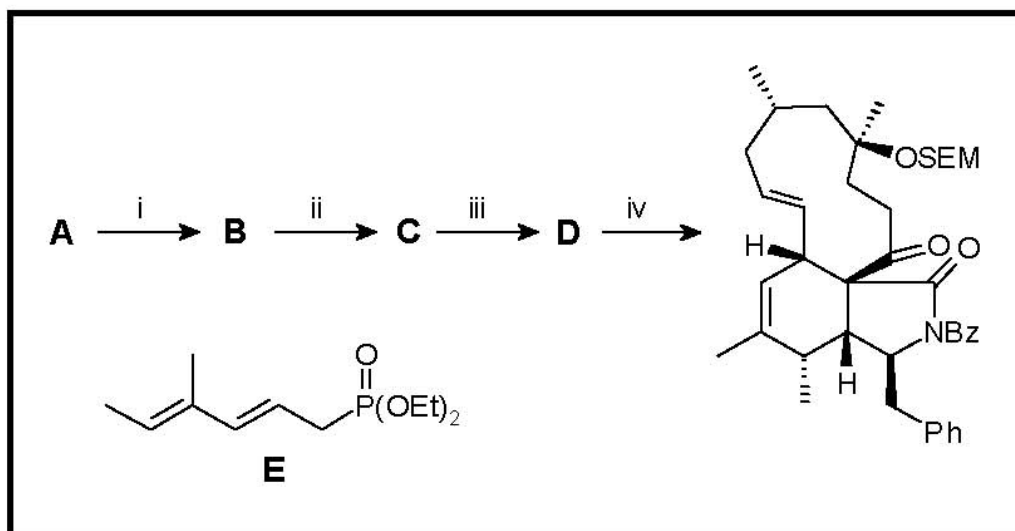
iii: a) NaOBn; b) H₂, Pd/C, *p*-TsOH cat.; c) LiAlH₄; d) *p*-TsOH cat., acetone; e) Cl₂C₂O₂, DMSO, Et₃N.

iv: a) *p*-TsOH cat., MeOH; b) NaH, BnBr (excess), TBAI; c) 1°- O₃; 2°- Me₂S; d) (MeO)₂P(O)CH₂CO₂Me, NaH; e) H₂, cat. Lindlar; f) TFA, CH₂Cl₂; g) BnBr (1 equiv), K₂CO₃; h) DIBAL; i) I₂, PPh₃, imidazole; j) PPh₃, CH₃CN, ref..

v: a) 1°- *n*-BuLi; 2°- Addition of compound **B**; b) TFA, H₂O.

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) Cl₂C₂O₂, DMSO, Et₃N; d) Ph₃P=C(Me)CO₂Et; e) DIBAL; f) *m*-CPBA; g) LiAlH₄.

ii: a) NCS, Me₂S; b) Ph₃P=CHCO₂Me; c) SEMCl, imidazole; d) Dowex 50W-X8, MeOH; e) H₂, Pd/C.

iii: a) Cl₂C₂O₂, DMSO, Et₃N; b) Ph₃P=CH₂; c) 1°- 9-BBN; 2°- H₂O₂, OH⁻; d) Cl₂C₂O₂, DMSO, Et₃N; e) Compound **E**, base; f) KOH; g) C(O)I₂.

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

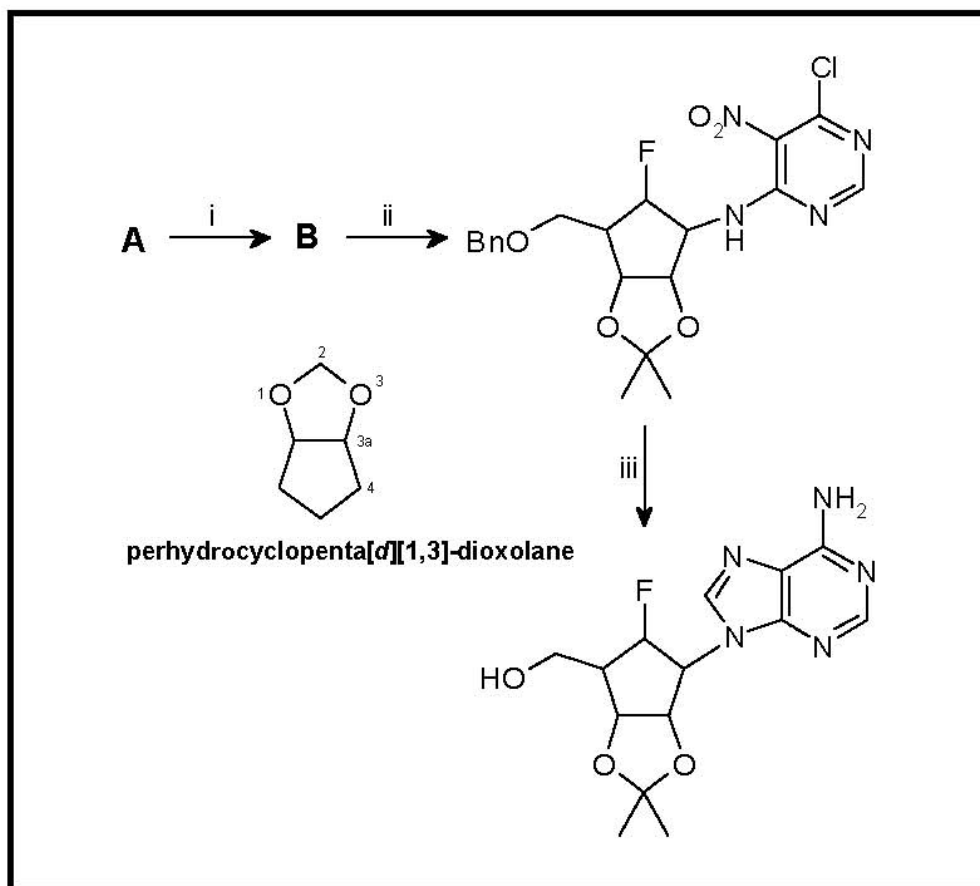
Notes:

The NCS-SMe₂ system is used as selective oxidating agent for primary hydroxy groups.

The Dowex 50W-X8 is an ion exchange resin. Use handbooks of fine chemicals to find out if this resin 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: (3*aS*, 4*R*, 5*S*, 6*S*, 6*aR*)-4-Azido-6-(benzyloxymethyl)-5-[(methoxyethoxy)methoxy]-2,2-dimethylperhydrocyclopenta[d][1,3]-dioxolane.

i: a) *m*-CPBA, CH₂Cl₂, 0 °C, 24 h; b) MEMCl, (*i*-Pr)₂EtN, CH₂Cl₂, t.a., 48 h; c) K₂CO₃, MeOH, t.a., 2 h; d) 1°- NaN₃, NH₄Cl, EtOH/H₂O (4:1), ref., 3 días; 2°- 2,2-dimethoxypropane, *p*-TsOH cat., 2 h.

ii: a) Me₂BBr, CH₂Cl₂/Et₂O (10:1), -78 °C, 2 h; b) Tf₂O, py, CH₂Cl₂, 0 °C, 30 min.; c) LiOBz, DMF, t.a., 30 min.; d) K₂CO₃, MeOH, t.a., 2 h; e) DAST, CH₂Cl₂, 0° C, 2 h; f) H₂, cat. Lindlar, EtOH, t.a., 3 h; g) 4,6-Dichloro-5-nitropyrimidine, Et₃N, CH₂Cl₂, t.a., 3 h.

iii: a) H₂, Ni Raney, EtOH, t.a., 30 min.; b) (EtO)₃CH, ref., 5 h; c) NH₃ liq., 24 h; d) H₂, Pd(OH)₂, cyclohexane/EtOH (1:2), ref., 12 h.

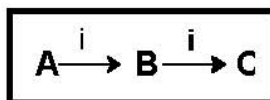
Notes:

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: (3*aR*, 4*R*, 6*R*, 7*aR*)-4-Chloro-6-isopropenyl-3*a*-methylperhydrobenzo[*b*]furan-2-one.

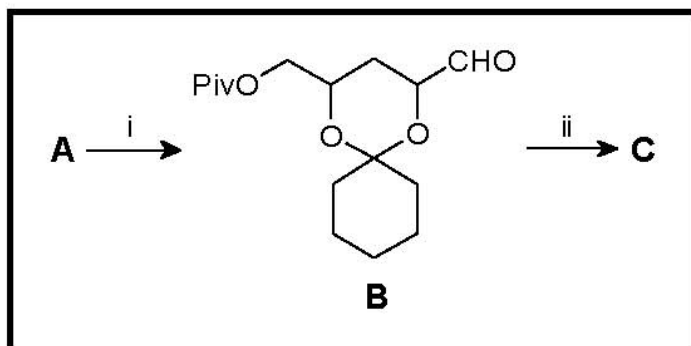
C: (1*R*, 2*R*, 3*R*, 5*R*)-2-[(1*R*)-1-Bromo-2-hydroxyethyl]-3-chloro-5-isopropenyl-2-methylcyclohexan-1-ol.

i: a) 1°- MeO₂CCH₂COCl, Et₃N, CH₂Cl₂, -30 °C; 2°- *p*-AcNHC₆H₄SO₂N₃, DBU, CH₃CN, 23 °C; b) Cu(II)bis(salicylidene-*t*-butylamine), CH₂Cl₂, 70 °C, 8 h; c) LiCl, CSA, DMF, 140 °C.

ii: a) 1°- LDA, -78 °C, THF; 2°- CBr₄, -78 °C → 23 °C; b) 1°- DIBAL, -78 °C, CH₂Cl₂; 2°- NaBH₄, EtOH, 23 °C.

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

Exercise 41.



A: D-(+)-Xilose.

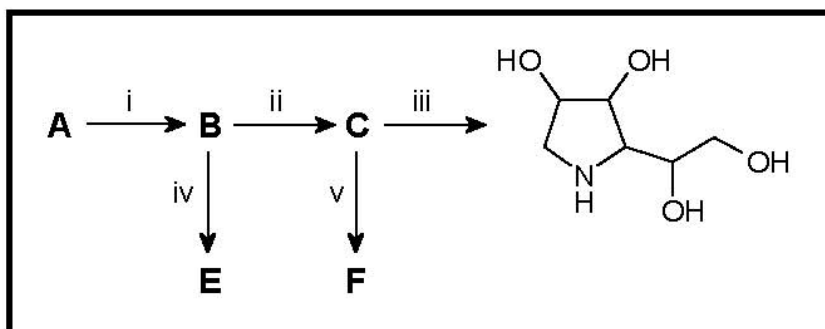
C: C₂₀H₃₄O₅.

i: a) Acetone, CuSO₄, H₂SO₄; b) HCl 0.2%; c) Me₃COCl, py, 0 °C → t.a.; d) 1°- NaH, CS₂, THF; 2°- MeI, 0 °C → t.a.; e) HSn(*n*-Bu)₃, AIBN, toluene, 80 °C; f) EtSH (10 equiv), HCl 6*N*; g) Cyclohexanone dimethyl acetal, *p*-TsOH, 16 h, t.a.; h) HgCl₂, CaCO₃, CH₃CN/H₂O (4:1), 0 °C → t.a..

ii: 1°- [(2*S*)-3-Hydroxy-2-methylpropyl]triphenylfosfonium bromide (2 equiv), *n*-BuLi (4 equiv), THF, -78 °C → t.a., 2 h; 2°- TMSCl (2 equiv), 0 °C → t.a., 30 min.; 3°- Addition of compound **B**, THF, -78 °C → t.a.; 4°- NH₄F, THF/H₂O (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*-isopropylidene-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) NaBH₄; f) Tf₂O; g) NaN₃; h) TBAF.

ii: a) H₂, Pd/C, MeOH; b) H₂, Pd/C, AcOH.

iii: TFA, H₂O.

iv: a) MsCl, Et₃N; b) NaN₃; c) H₂, Pd/C, MeOH; d) H₂, Pd/C, AcOH; e) H⁺, MeOH.

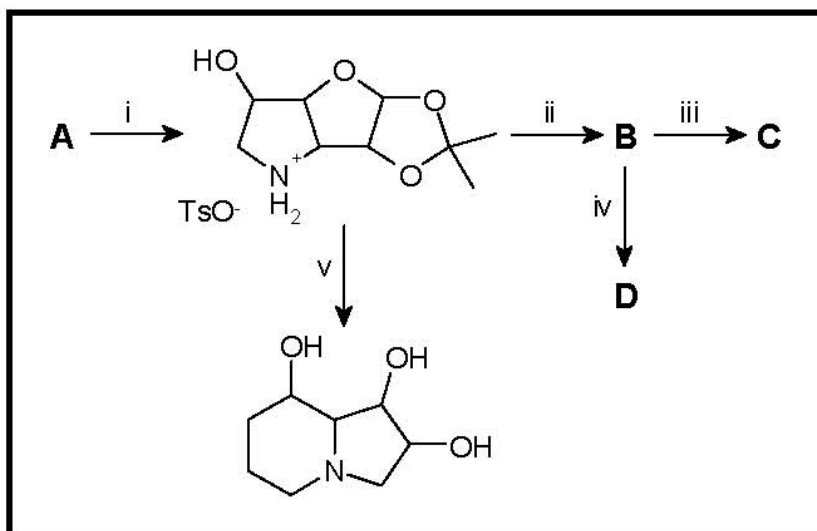
v: a) (Boc)₂O, py; b) NaIO₄, EtOH; c) NaBH₄; d) TFA, H₂O.

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-isopropylidene- α -D-glucopyranose.

B: (2*S*, 3*S*, 4*R*)-4-Benzyloxy-*N*-benzyloxycarbonyl-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) H₂, Pd/C.

ii: a) CbzCl; b) NaH, BnBr, TBAI; c) TFA, H₂O; d) NaIO₄, EtOH, H₂O.

iii: a) NaBH₄; b) H₂, Pd/C, AcOH.

iv: a) NaClO₂, KH₂PO₄, H₂O; b) H₂, Pd/C, AcOH.

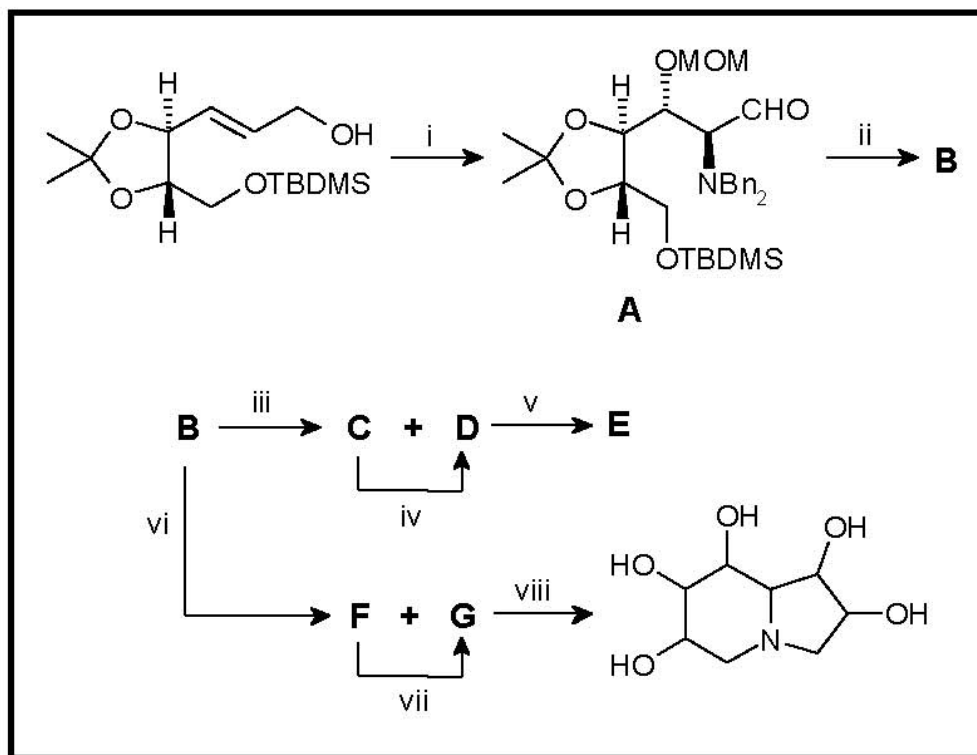
v: a) HO₂CCH₂P(O)(OMe)₂, DCC; b) TFA, H₂O; c) K₂CO₃, DMF, 18-crown-6; d) H₂, Pd/C, EtOH; e) Ac₂O, py; f) BH₃-SMe₂; g) NaOMe, MeOH; h) TFA, H₂O.

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, $\text{Ti}(\text{O}^i\text{Pr})_4$, TBHP; b) $\text{Et}_2\text{AlNBn}_2$, CH_2Cl_2 ; c) AcCl , Et_3N ; d) MOMCl , $(i\text{-Pr})_2\text{EtN}$; e) LiAlH_4 , Et_2O ; f) $\text{Cl}_2\text{C}_2\text{O}_2$, DMSO , Et_3N .

ii: 1°- AcOEt , LHMDS , THF , $-80\text{ }^\circ\text{C}$; 2°- Addition of compound **A**.

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

iv: NaH , THF .

v: a) BH_3SMe_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 .

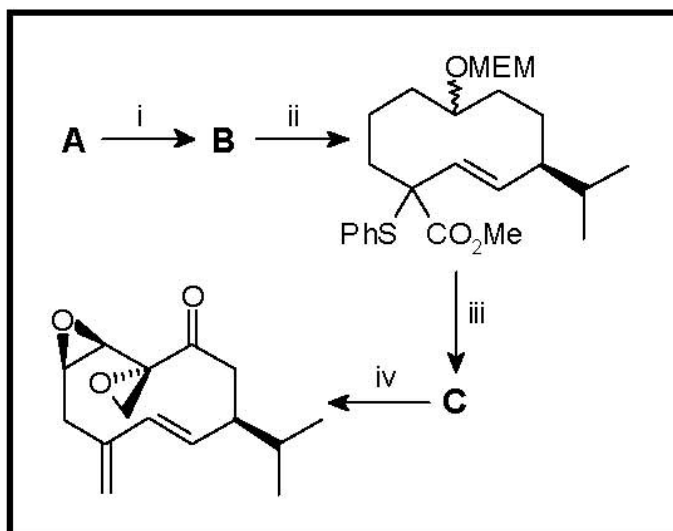
viii: a) TBAF , THF ; b) TsCl , py ; c) H_2 , $\text{Pd}(\text{OH})_2$, MeOH ; d) Et_3N , MeOH , ref.; e) HCl (conc.), MeOH , ref..

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) 1°- O_3 , MeOH, $-20\text{ }^\circ\text{C}$; b) 2°- Me_2S , *p*-TsOH; b) 1°- CO_2Me_2 , NaH, dioxane, ref., 24 h; 2°- Allyl bromide, ref., 2 h; c) KOH 5%, MeOH/ H_2O 2:3, $90\text{ }^\circ\text{C}$, 2 h; d) $LiAlH_4$, Et_2O ; e) MEMCl, (*i*-Pr) $_2$ EtN, CH_2Cl_2 , $40\text{ }^\circ\text{C}$, 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%, $40\text{ }^\circ\text{C}$, 1 h; c) LDA, PhSCH $_2$ CO $_2$ Me, THF, $-70\text{ }^\circ\text{C}$, 10 min.; d) Ac_2O , NaOAc, $130\text{ }^\circ\text{C}$, 30 min.; e) NaOMe cat., MeOH, t.a., 1 h; f) TsCl, py, $0-5\text{ }^\circ\text{C}$, 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 , $-8\text{ }^\circ\text{C}$, 40 min.; d) Na-naphthalene, THF, $-70\text{ }^\circ\text{C}$, 6 min.; e) PCC, *molecular sieves* 3Å, CH_2Cl_2 , t.a., 1 h; f) LHMDS, PhSSO $_2$ Ph, THF, $-10\text{ }^\circ\text{C}$, 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) 1°- LHMDS, THF, $-70\text{ }^\circ\text{C}$, 30 min.; 2°- MOPH, $-22\text{ }^\circ\text{C}$, 15 min.; c) *t*-Butyldimethylsilyl chloride, imidazole, DMF, $40\text{ }^\circ\text{C}$, 16 h; d) $Me_3S^+I^-$, *n*-BuLi, $-5\text{ }^\circ\text{C}$, 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.

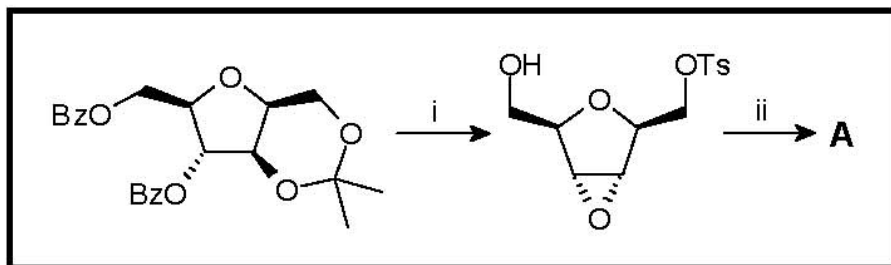
Conditions used on the step iii c) deprotect the MEM group.

Conditions used on the step iv a) yield selectively epoxydes of α,β -unsaturated alkenes.

The treatment 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) 1^o- Me₃N, MeOH; 2^o- HCl.

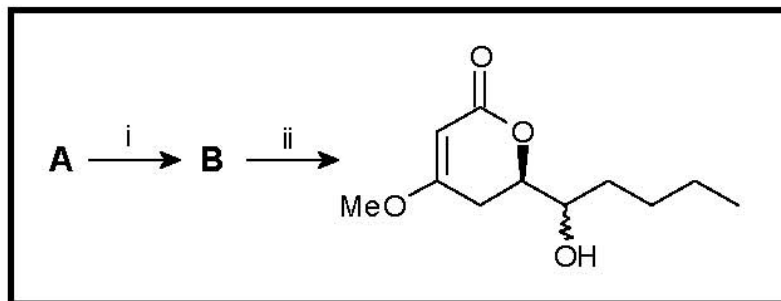
Notes:

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**, 2f, 2453.

Exercise 47.



A: (*R*)-2,2-Dimethyl-4-formyl-1,3-dioxolane.

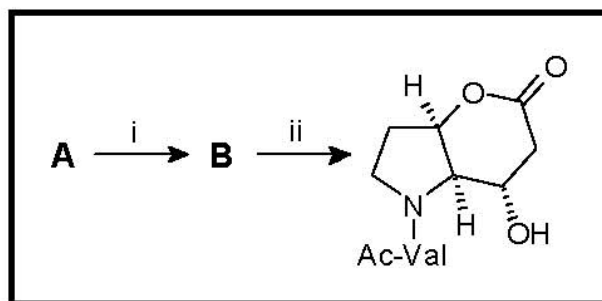
B: Mixture of epimers of the (2*R*)-2-[1-(benzyloxy)pentyl]oxirane.

i: a) *n*-BuMgBr, Et₂O; b) BnCl, NaOH, DMSO, 30-40 °C, 2 h; c) HCl 1%, MeOH, 60 °C, 1 h; d) TsCl (1 equiv), py, -10 °C, 2 h; e) KOH, t.a., 30 min..

ii: a) 1^o- 2-Propinoic acid, LDA (2 equiv), THF, HMPA, -45 °C; 2^o- Addition of compound **B**; b) H₂SO₄, MeOH; c) NaOMe, MeOH; d) H₂, Pd/C, EtOH.

Bibliography: Mori, K.; Oda, M. y Matsui, M. *Tetrahedron Lett*. **1976**, f7, 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, ZnCl₂; b) CrO₃, py; c) NaBH₄; d) NaH, BnBr; e) AcOH, H₂O; f) MsCl (2 equiv), py; g) NaCN, DMSO.

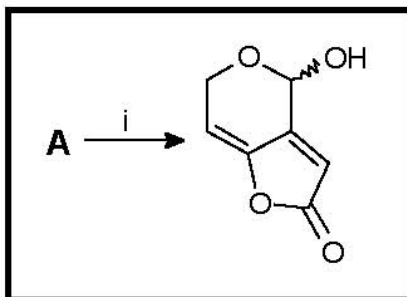
ii: a) NaBH₄, CoCl₂, MeOH; b) KOH, MeOH; c) Cbz-Val, DCC; d) HCl, H₂O; e) PCC, CH₂Cl₂; f) H₂, Pd/C; g) Ac₂O, MeOH.

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.; Ôtake, N.; Yonehara, H. *Tetrahedron Lett*, **1980**, 21, 167.

Exercise 49.



A: L-Arabinose.

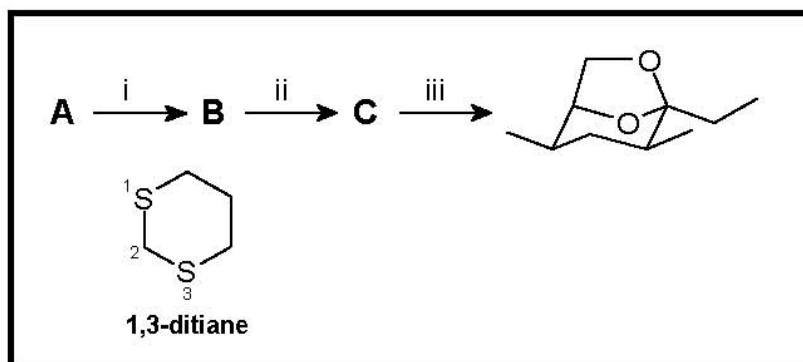
i: a) MeOH, H⁺; b) Acetone, CuSO₄, H₂SO₄, t.a., 24 h; c) PCC, *molecular sieves*, CH₂Cl₂; d) Ph₃P=CHCO₂Me, benzene, 50 °C; e) MeOH, HCl, ref.; f) MsCl, py, 0 °C → t.a., 24 h; g) TFA 90%, H₂O, 50 °C, 1 h.

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.



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.

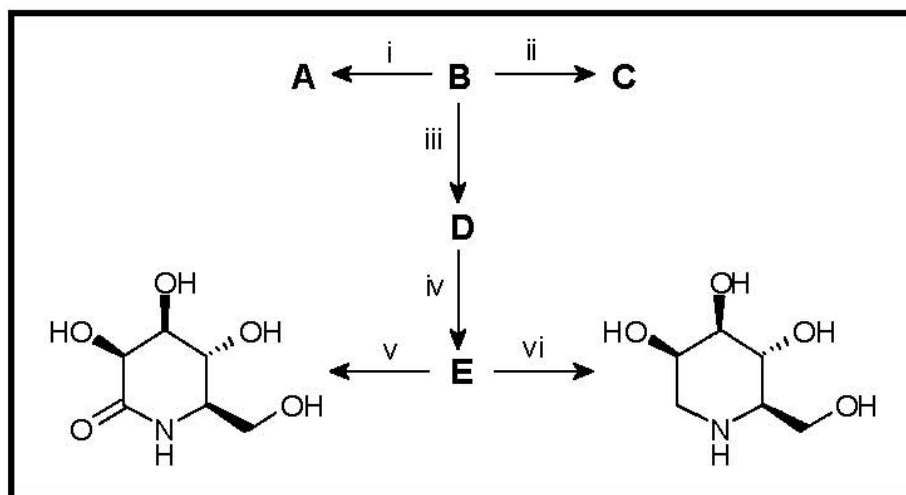
i: a) MeOH, H⁺; b) PhCHO, ZnCl₂; c) TsCl, py, -30 °C; d) NaOMe, MeOH.

ii: a) Me₂CuLi, Et₂O; b) 1°- NaH, CS₂; 2°- MeI, Et₂O; c) HSn(*n*-Bu)₃, AIBN, toluene; d) *p*-TsOH, MeOH; e) TrCl, py; f) CrO₃·2py, CH₂Cl₂; g) Ph₃P=CH₂, Et₂O; h) H₂, (Ph₃P)₃RhCl, benzene; i) 1,3-Propanedithiol, BF₃·Et₂O, CH₂Cl₂.

iii: a) 2,2-Dimethoxypropane, *p*-TsOH, acetone; b) 1°- *t*-BuLi, hexane; 2°- EtI, HMPA; c) *p*-TsOH, MeOH; d) HgCl₂, HgO, CH₃CN.

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

Exercise 51.



A: Benzyl 2-propynyl 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) 1°- *n*-BuLi; 2°- ClCO₂Et; b) 1°- BnNH₂, THF, 66 °C; 2°- Acrylic anhydride, THF, 66 °C; c) H₂ (1 atm), Pd/C, Na₂CO₃, EtOH; d) Et₃N, MeMgBr; e) DBLi.

ii: a) 1°- BnNH₂, benzene, 80 °C; 2°- Acrylic anhydride, THF, 66 °C; b) H₂ (1 atm), Pd/C, Na₂CO₃, EtOH; c) Et₃N, MeMgBr; d) KOH, BnBr.

iii: a) *m*-CPBA, TFA; b) KOH, H₂O; c) KOH, BnBr.

iv: a) 1°- LDA; 2°- PhSeCl; 3°- NaIO₄; b) OsO₄, NMO.

v: a) Li/NH₃.

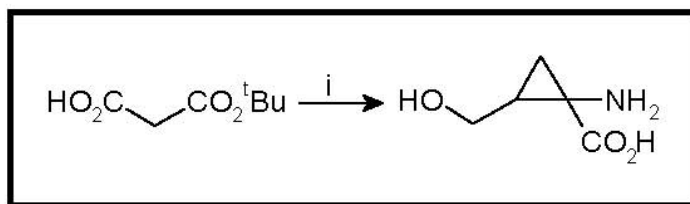
vi: a) 1°- LiAlH₄; 2°- NaOH, H₂O; b) H₂ (1 atm), Pd/C, MeOH.

Notes:

The benzyl group can be deprotected by treatment with Li in NH₃.

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*-TsN₃, K₂CO₃, CH₃CN; c) CuI·P(OEt)₃, benzene, ref.; d) TFA, CH₂Cl₂, 0 °C → t.a.; e) DPPA, Et₃N, *t*-BuOH, ref.; f) HCl, dioxano; g) 1°- NaOH, H₂O; 2°- Amberlite IR-120.

Notes:

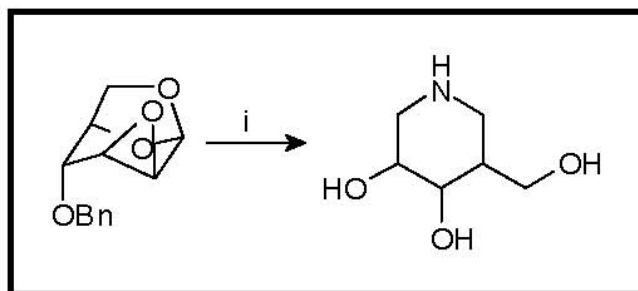
The use of (MeO)₂CH₂/P₂O₅ is equivalent to the introduction of CIMOM and base.

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.

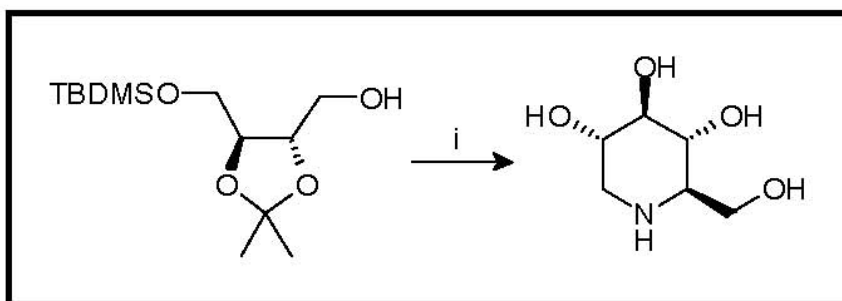
Exercise 53.



i: a) Vinylmagnesium bromide, THF, ref.; b) 1°- O₃, EtOH, 0 °C; 2°- NaBH₄, EtOH/H₂O; c) H₂SO₄ 1 M, ref.; d) NaIO₄, H₂O/MeOH, 45 °C; e) NH₃, H₂ (35 atm), Pd/C, EtOH, 20 °C; f) HCl_(ac), H₂ (1 atm), Pd/C.

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

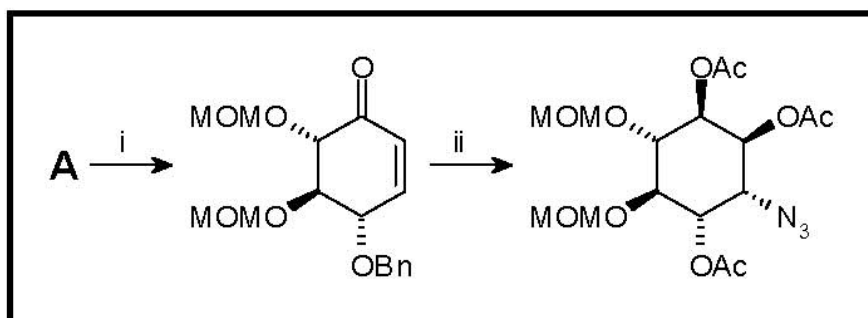
Exercise 54.



i: a) $\text{Cl}_2\text{C}_2\text{O}_2$, DMSO, Et_3N , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; b) $1^\circ\text{-}(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, NaH, benzene, $0\text{ }^\circ\text{C}$; 2°- Addition of the substrate; c) DIBAL (2 equiv), toluene, t.a.; d) L -Diethyl tartrate, $\text{Ti}(\text{O}^i\text{Pr})_4$, TBHP, CH_2Cl_2 , $-20\text{ }^\circ\text{C}$; e) NaN_3 , NH_4Cl , DME, ref.; f) MOMCl, $(i\text{-Pr})_2\text{EtN}$, Cl_3CH , ref.; g) TBAF, THF, t.a.; h) MsCl, Et_3N , CH_2Cl_2 , $0\text{ }^\circ\text{C}$; i) 1°-H_2 (1 atm), Pd/C 10%, MeOH, t.a.; 2°- 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) $(\text{MeO})_2\text{CH}_2$, P_2O_5 ; c) NaI, TBAI, DBLi; d) NaOMe, MeOH; e) NaH, BnBr; f) $1^\circ\text{-Hg}(\text{OTf})_2$ (cat.), H_2O , acetone; $2^\circ\text{-Ac}_2\text{O}$, py.

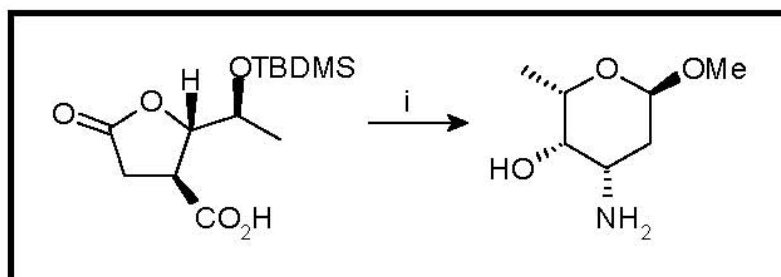
ii: a) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$; b) *m*-CPBA; c) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$; d) NaN_3 , NH_4Cl ; e) Ac_2O , py.

Notes:

The use of $(\text{MeO})_2\text{CH}_2/\text{P}_2\text{O}_5$ is equivalent to the introduction of CIMOM 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.

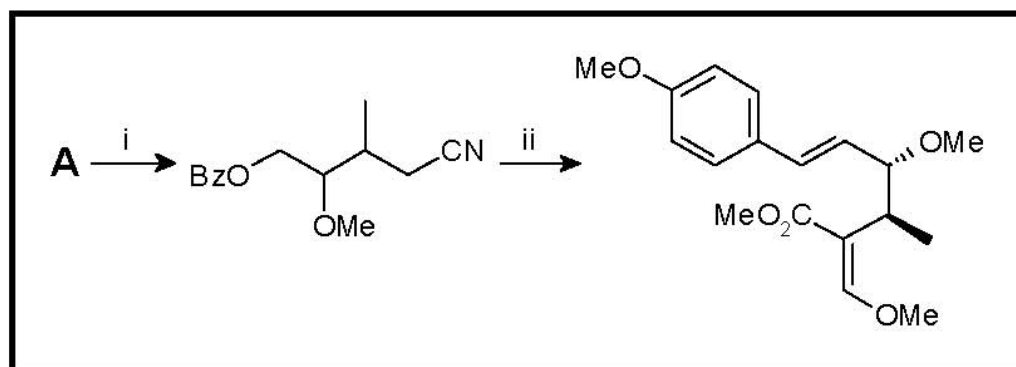
Exercise 56.



i: a) 1°- DPPA, Et₃N, Δ; 2°- *t*-BuOH; b) TBAF, THF, t.a.; c) DIBAL, THF, -78 °C; 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) H₂, Ni-Raney, EtOH; b) 1°- NaIO₄, NaHCO₃, acetone/H₂O, 0 °C; 2°- NaBH₄, MeOH, 0 °C; c) BzCl (excess), py, 0 °C; d) AcOH 80%, 70 °C; e) 1°- NaIO₄, NaHCO₃, acetone/H₂O, 0 °C; 2°- NaBH₄, MeOH, 0 °C; f) MsCl, py; g) NaCN, DMF, 50 °C, 6 h.

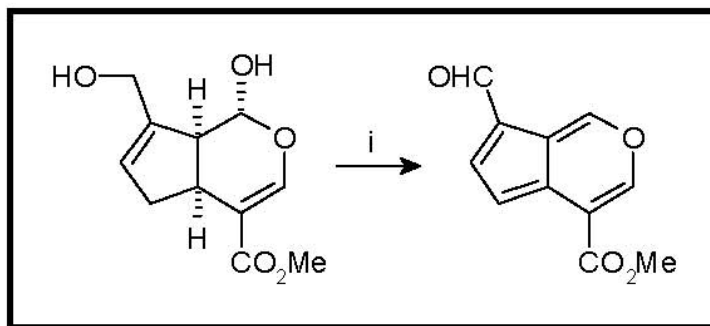
ii: a) NaOMe, MeOH; b) PCC, CH₂Cl₂; c) 1°- Ph₃P⁺CH₂C₆H₄(*p*-OMe)Cl⁻, *n*-BuLi, THF, 0 °C; 2°- PhSH, AIBN, benzene, ref.; d) 1°- DIBAL, CH₂Cl₂, 0 °C, 2 h; 2°- NaClO₂, NH₂SO₃H, NaH₂PO₄, *t*-BuOH/H₂O, t.a.; 3°- CH₂N₂, Et₂O/CH₂Cl₂; e) 1°- LHMDS, THF, -78 °C → -40 °C, 1 h; 2°- HCO₂Me, -78 °C → 0 °C; 3°- SO₄Me₂, K₂CO₃, 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.



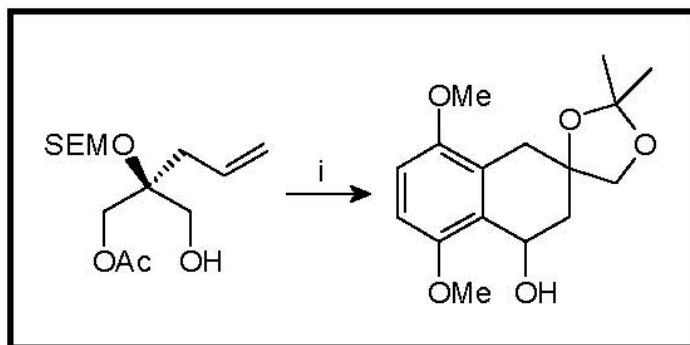
i: a) *t*-Butyldimethylsilyl chloride, (excess), AgNO₃, DMF; b) PPTS cat., EtOH, t.a.; c) Ac₂O, DMAP, Et₃N, CH₂Cl₂, t.a., 3.5 h; d) TBAF, AcOH, THF, 0 °C → t.a., 3.5 h; e) Thiocarbonyldiimidazole, benzene, t.a.; f) benzene, ref., 4 h; g) DDQ, benzene, ref.

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) K₂CO₃, MeOH; c) PDC, *molecular sieves* 3Å, CH₂Cl₂; d) 1,4-dimethoxy-2-phenyllithium, THF, -78 °C; e) 1°- NaH; 2°- CS₂; 3°- MeI, THF; f) HSn(*n*-Bu)₃, AIBN, toluene; g) TBAF, *molecular sieves* 4Å, DMPU; h) 2,2-dimethoxypropane, *p*-TsOH, acetone; i) OsO₄ cat., NaIO₄, dioxane/H₂O (1:1); j) SnCl₄, CH₂Cl₂, -78 °C.

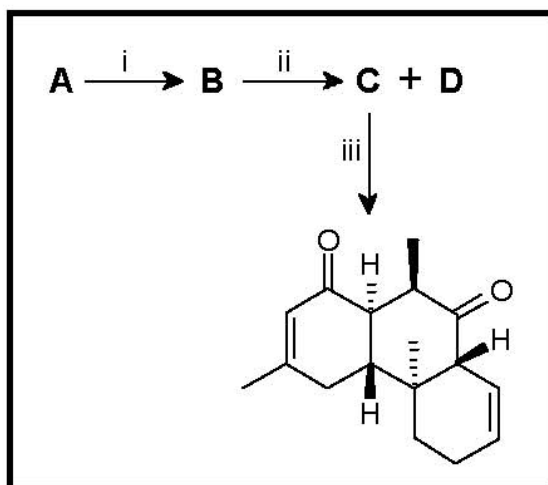
Notes:

The starting product with both hydroxymethyl groups 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-Isopropenyl-1-cyclohexenyl]methanol.

B: (1*R*, 4*R*, 6*S*)-4-Isopropenyl-6-methyl-2-cyclohexenol.

C: (3*aS*, 4*R*, 7*aR*)-4-Isopropenyl-6-methyl-2,3,3*a*,4,5,7*a*-hexahydrobenzo[*b*]furan-2-one.

D: (1*S*, 4*aR*, 7*S*, 8*aR*)-1-(iodomethyl)-1,7-dimethyl-3,4,4*a*,7,8,8*a*-hexahydro-1*H*-3-isocromanone.

i: a) (-)-Diethyl tartrate, Ti(O^{*i*}Pr)₄, TBHP, *molecular sieves* 4Å, CH₂Cl₂; b) *t*-Butyldimethylsilyl chloride, DMAP, Et₃N, CH₂Cl₂; c) Me₂CuLi, Et₂O; d) HCl, MeOH; e) Pb(OAc)₄, benzene; f) 1°-LDA, THF; 2°-PhSeBr; 3°-H₂O₂, py; g) LiAlH₄, Et₂O.

ii: a) CH₃C(OEt)₃, 2,4-dinitrophenol cat., toluene, 120 °C; b) LiOH, THF, H₂O; c) I₂, DBU, CH₃CN, 70 °C.

iii: a) LDA, MeI, THF; b) (*E*)-1-Lithium-1,3-butadiene, THF, -78 °C; c) MnO₂, CH₂Cl₂, t.a.; d) Δ, toluene.

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.