Current Topics in Organic Chemistry

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Lecture notes:
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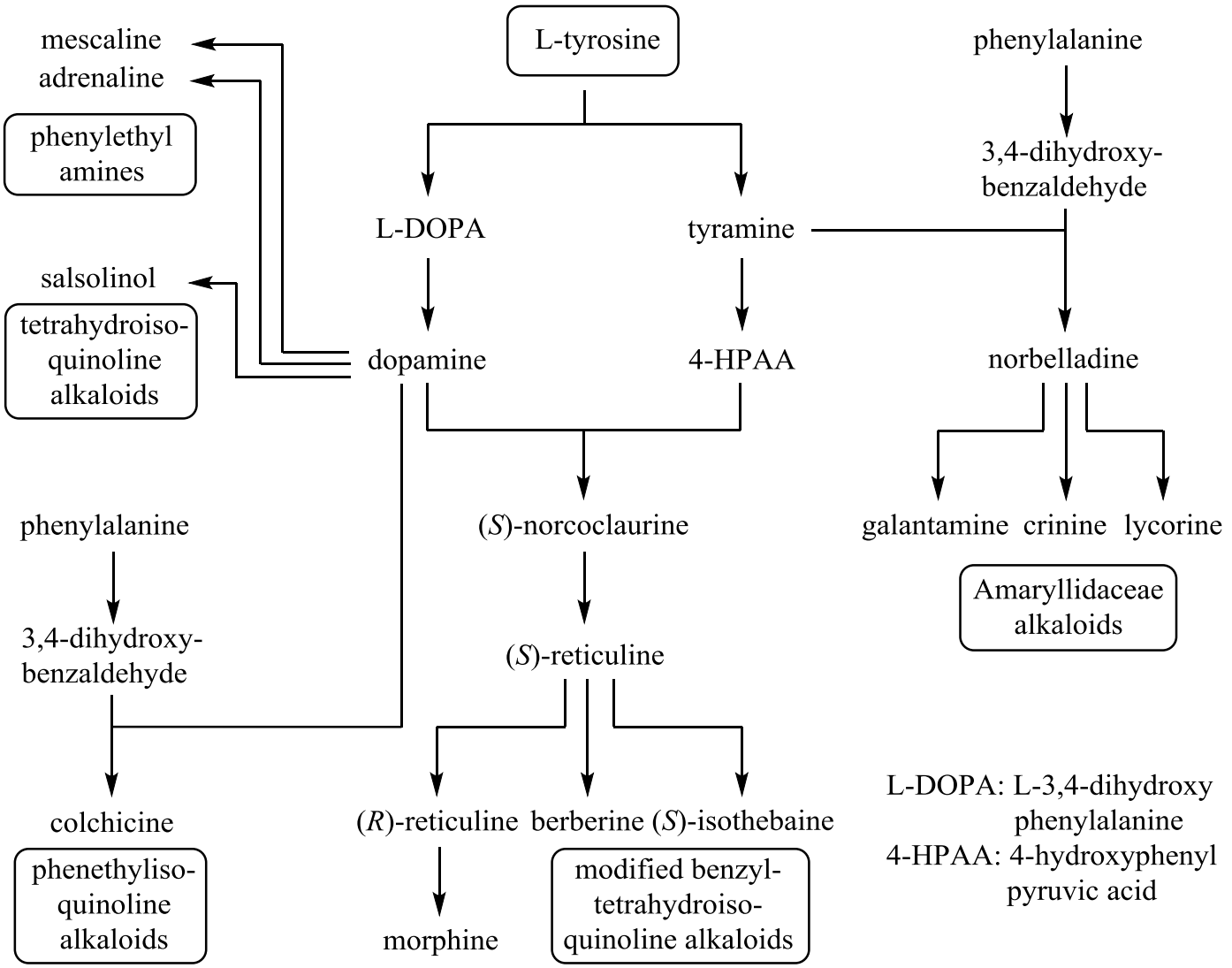
Scheduled meeting times:

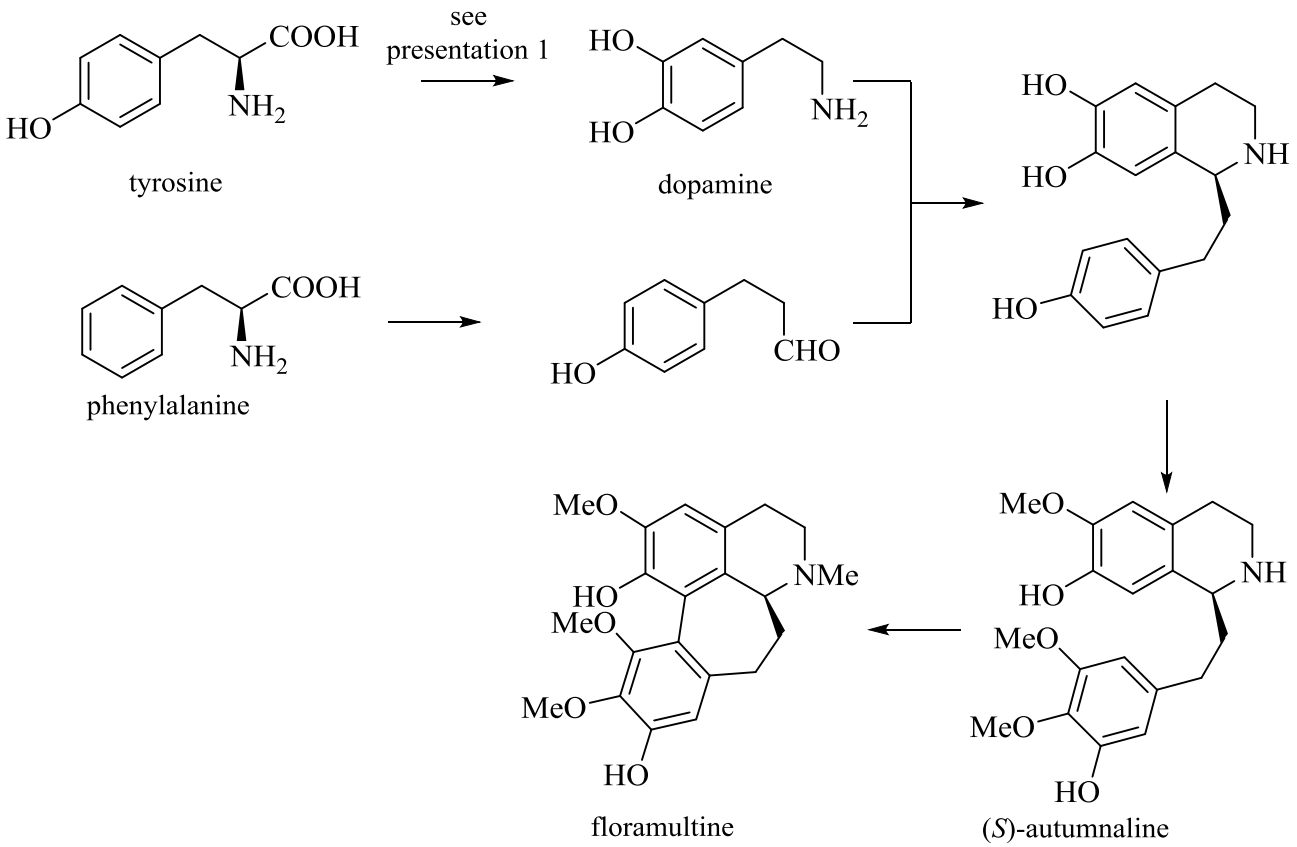
Dienstag, 10.03	10:15 – 12:45
Mittwoch, 11.03	10:15 – 12:45
Dienstag, 17.03	10:15 – 12:45
Mittwoch, 18.03	10:15 – 12:45
Dienstag, 31.03	10:15 – 12:45
Mittwoch, 01.04	10:15 – 12:45

Tyrosine is an important starting material for a variety of natural products:

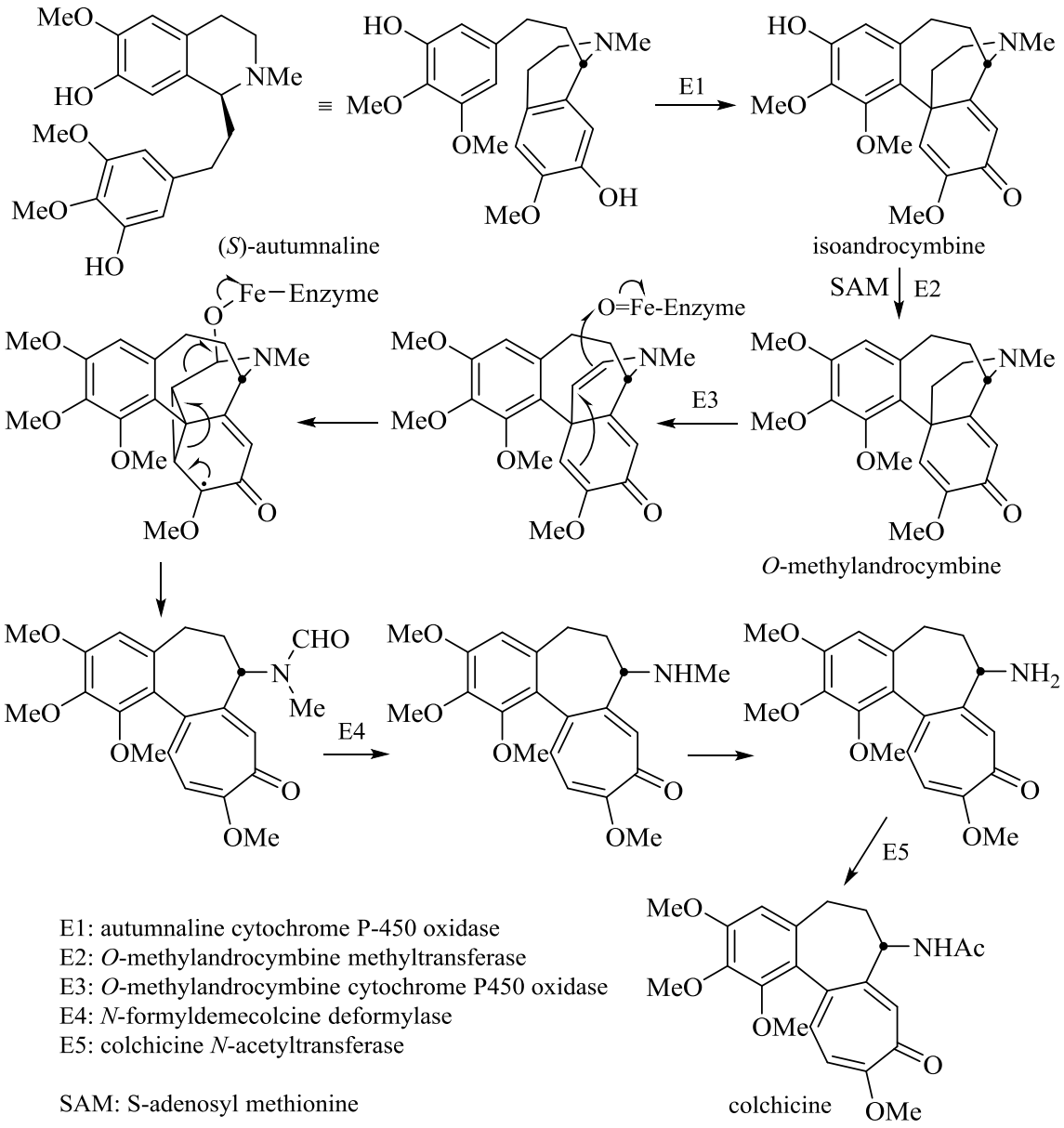


Phenethylisoquinoline alkaloids:

Phenethylisoquinoline alkaloids are biosynthesized in analogy to benzyltetrahydroisoquinoline alkaloids:



Biosynthesis of colchicine:



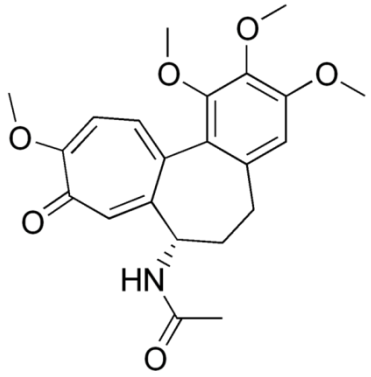
E1: autumnaline cytochrome P-450 oxidase
E2: *O*-methylandrocymbine methyltransferase
E3: *O*-methylandrocymbine cytochrome P450 oxidase
E4: *N*-formyldemecolcine deformylase
E5: colchicine *N*-acetyltransferase

SAM: S-adenosyl methionine

Colchicine:

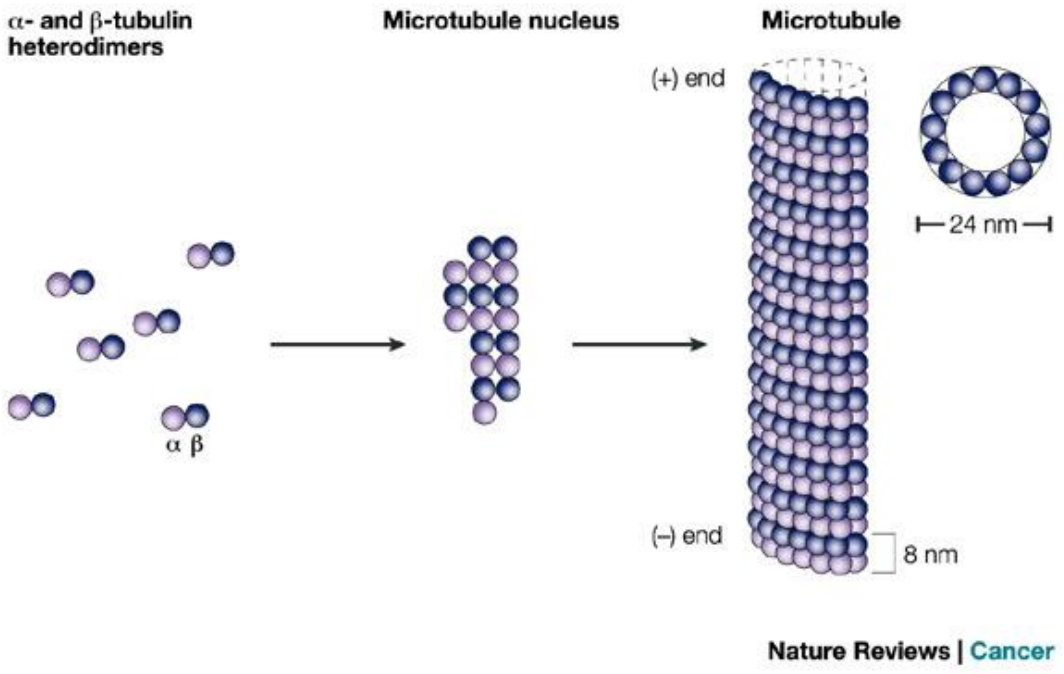
Highly toxic natural product isolated from the autumn crocus (*Colchicum autumnale*).
Traditionally used to treat gout and swellings.
Used as herbal remedies by ancient cultures (Ancient Egypt 1500 BC); first isolated in 1820 by Pelletier and Caventou

Approved to treat gout – also used in the treatment of various forms of cancer (inhibits tubulin polymerization)



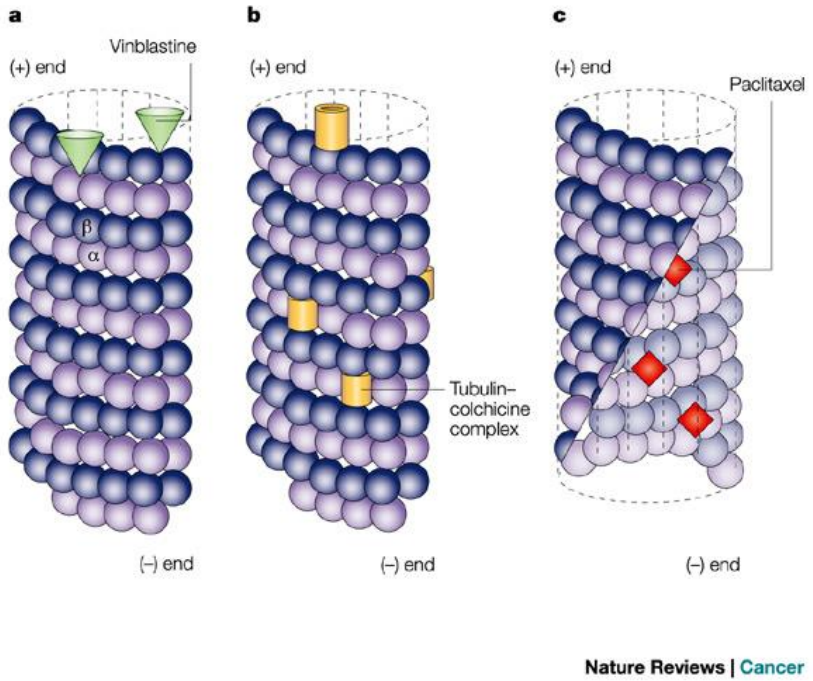
Biological Activity - microtubuli:

- long, filamentous, tube-shaped protein polymers
- essentiell in development and maintenance of cell shape, transport of vesicles, in cell signaling, cell division, mitosis
- composed of α- and β- tubulin heterodimers
- dynamic polymers



Biological Activity - microtubuli:

- importance in mitosis and cell division makes microtubules as a target for anticancer drugs
- various binding-sites for antimitotic drugs
- chemically diverse substances bind to soluble tubulin and/or directly to tubulin in the microtubules
- inhibition of cell proliferation by acting on the polymerization dynamics of spindle microtubules
- two groups of microtubule-targeted antimitotic drugs



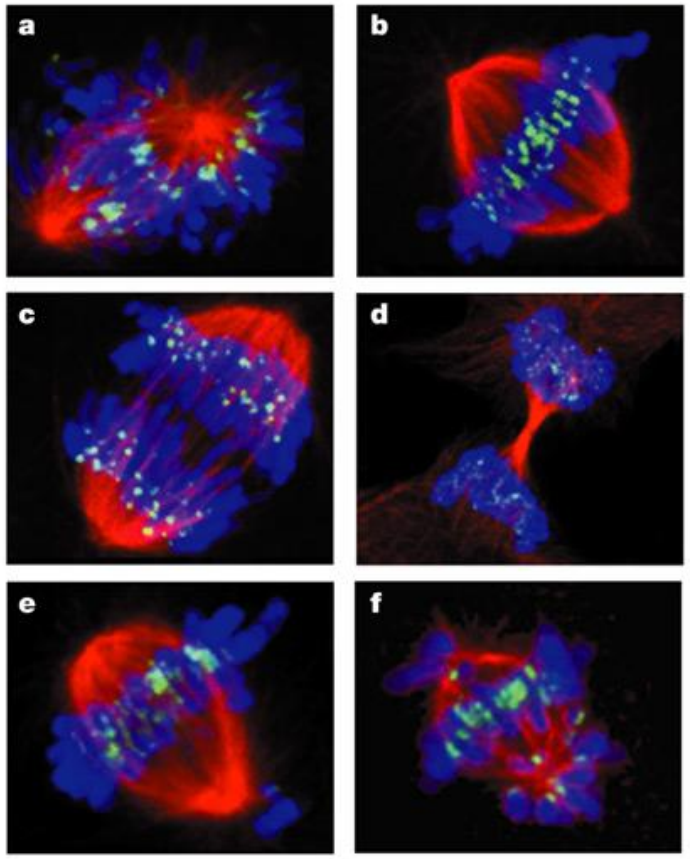
microtubule-destabilizing agents

microtubule-stabilizing agents

Biological Activity - microtubuli:

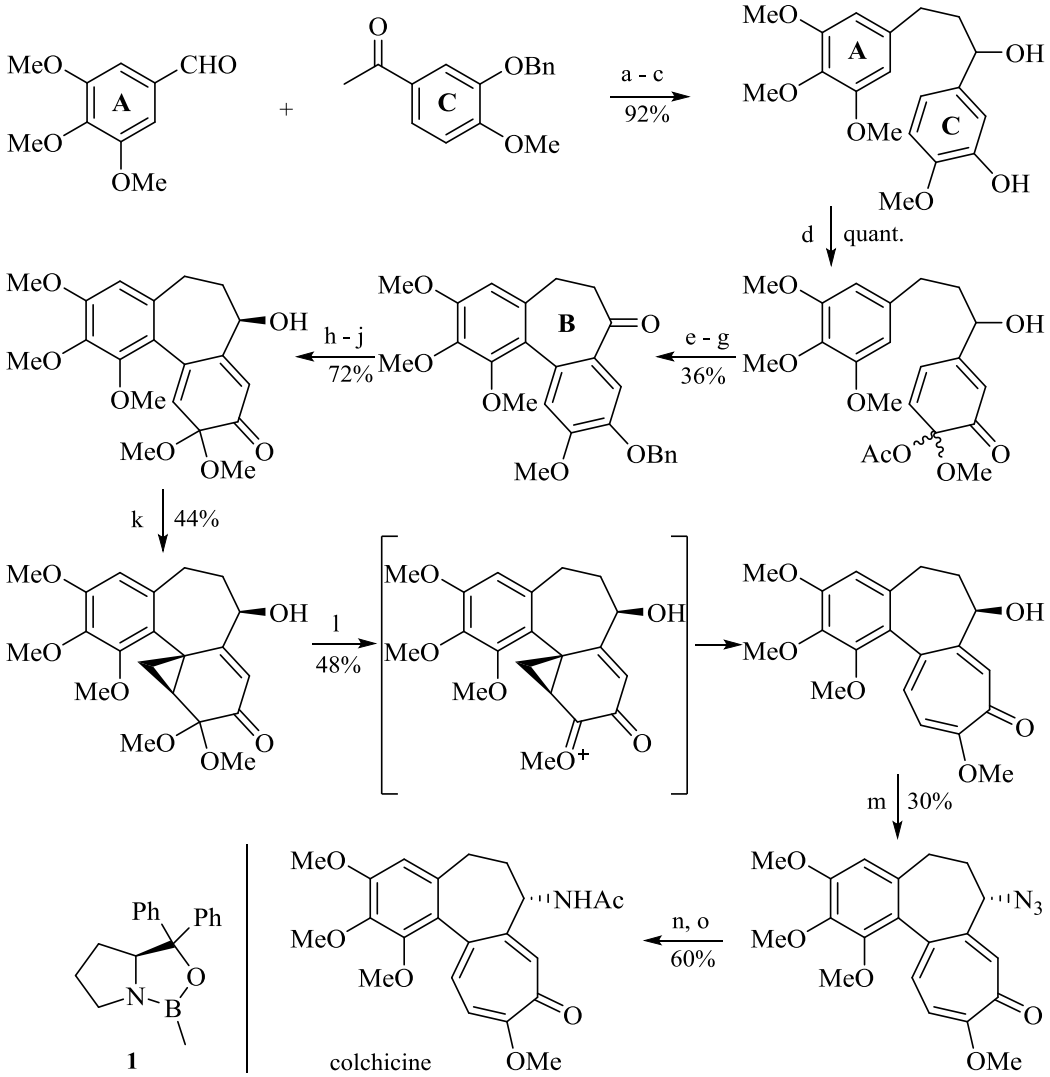
- colchicine binds to tubulin
- inhibits tubulin poymerization
- disruption of dynamic equilibrium needed in formation of microtubules from α- and β-tubulin heterodimers

Formation of abnormal mitotic spindles results in cell cycle arrests in the M-phase and apoptotic cell death



Nature Reviews | Cancer

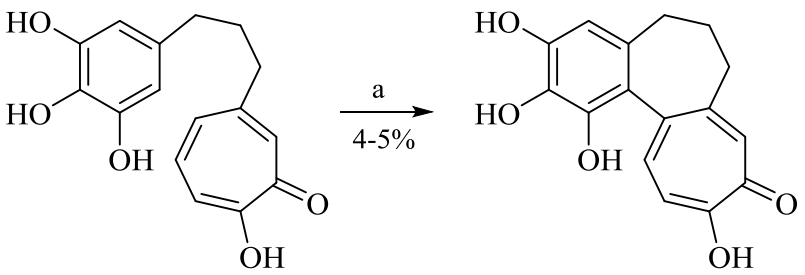
Banwell's synthesis of colchicine:



Reagents and conditions: a) NaOH, MeOH, 96%; **b)** H_2, Pd/C, EtOAc, 15 °C, 96%; **c)** $NaBH_4$, THF, MeOH, 96%; **d)** $Pb(OAc)_4$, 3Å molecular sieves, CH_2Cl_2, 15 °C, 100%; **e)** CF_3CO_2H, 3Å molecular sieves, THF, C_6H_6, 0 °C, 42%; **f)** BnBr, MeCN, 88%; **g)** NMO, TPAP, 4Å molecular sieves, CH_2Cl_2, 15 °C, 98%; **h)** **1**, BH_3, THF, 15 °C, 88%; **i)** H_2, Pd, Pd/C, EtOAc, 15 °C, 99%; **j)** $Tl(NO_3)_3$, MeOH, -20 °C, 83%; **k)** $Me_3S(O)I$, NaH, DMSO, 54%; **l)** CF_3CO_2H, CH_2Cl_2, 15 °C, 48%; **m)** DIAD, PPh_3, $Zn(N_3)_2$•2py, THF, 15 °C, 30%; **n)** PPh_3, H_2O, THF, 15 °C; **o)** Ac_2O, py, 60% (over 2 steps).

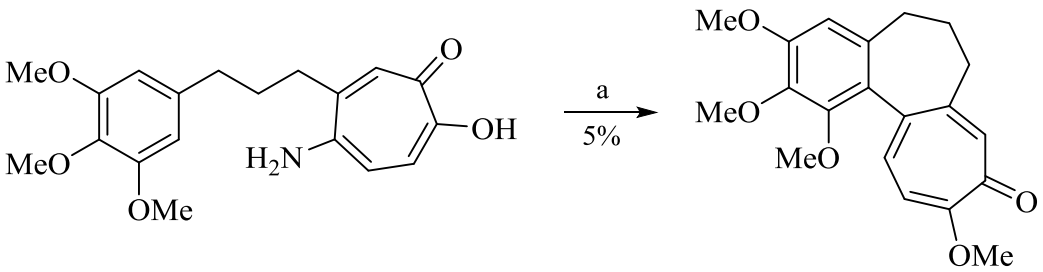
Alternative strategies towards colchicine – oxidative phenol couplings:

Desacetmidocolchiceine; Scott, 1965:



Reagents and conditions: a) $FeCl_3 \cdot 6H_2O$, H_2SO_4 (6 N), EtOH, $CHCl_3$ 4-5%.

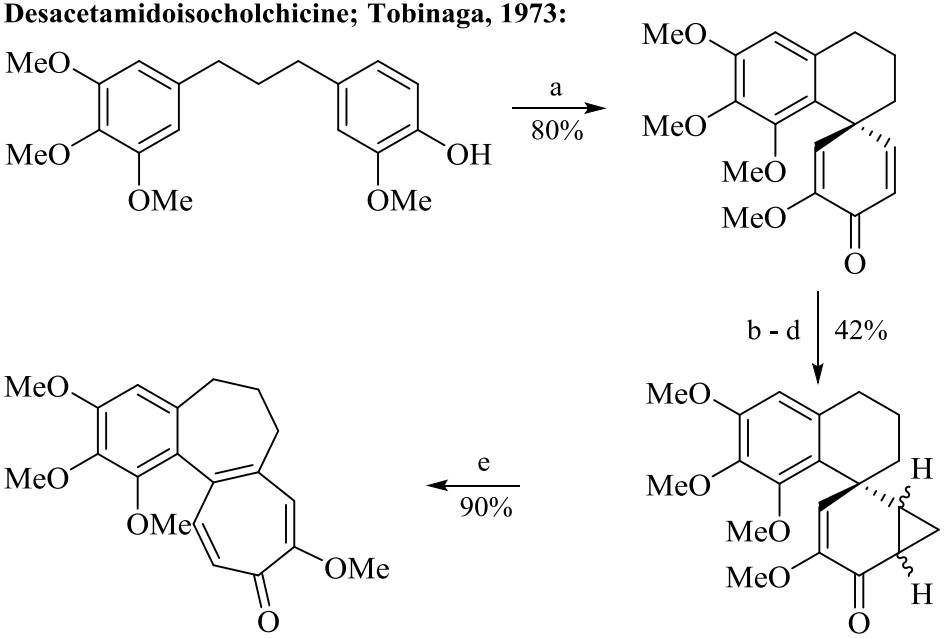
Desacetmidocolchiceine; Kaneko, 1968:



Reagents and conditions: a) isoamylnitrite, H_2SO_4 (conc), 7 - 10 °C; then Cu, dioxane, rt, 24 h, 5%.

Alternative strategies towards colchicine – oxidative phenol couplings:

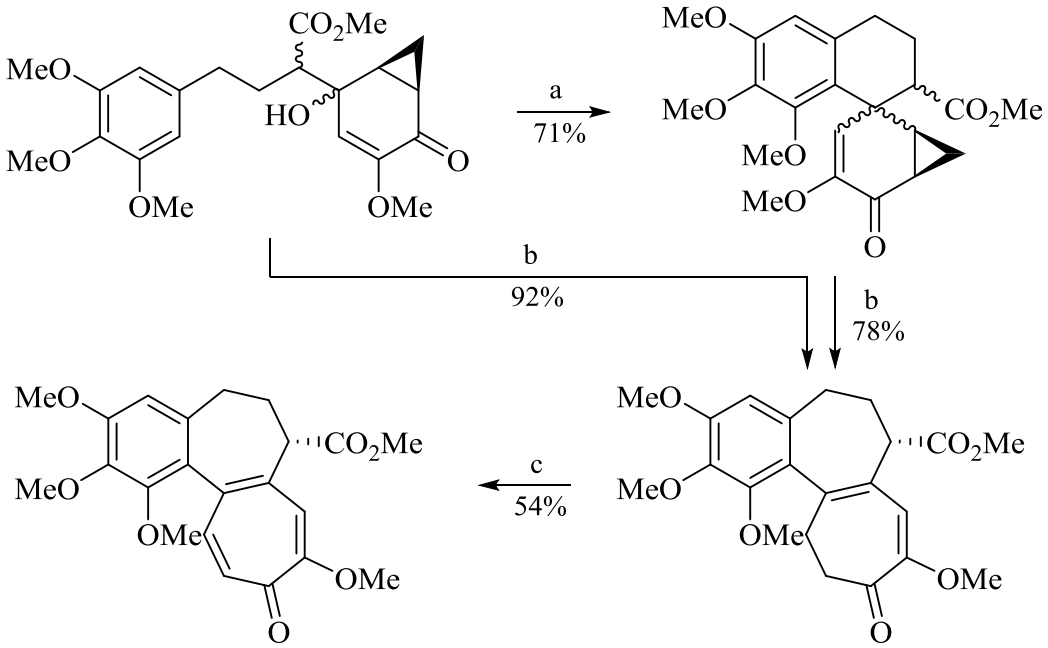
Desacetamidoisocholchicine; Tobinaga, 1973:



Reagents and conditions: a) anodic oxidation, HBF_4, MeCN, 0.92-1.00 V, 20 min, 80%; **b)** $NaBH_4$; **c)** CH_2I_2, Zn/Cu couple; **d)** Jones oxidation, 42% **e)** Ac_2O, H_2SO_4, 90%.

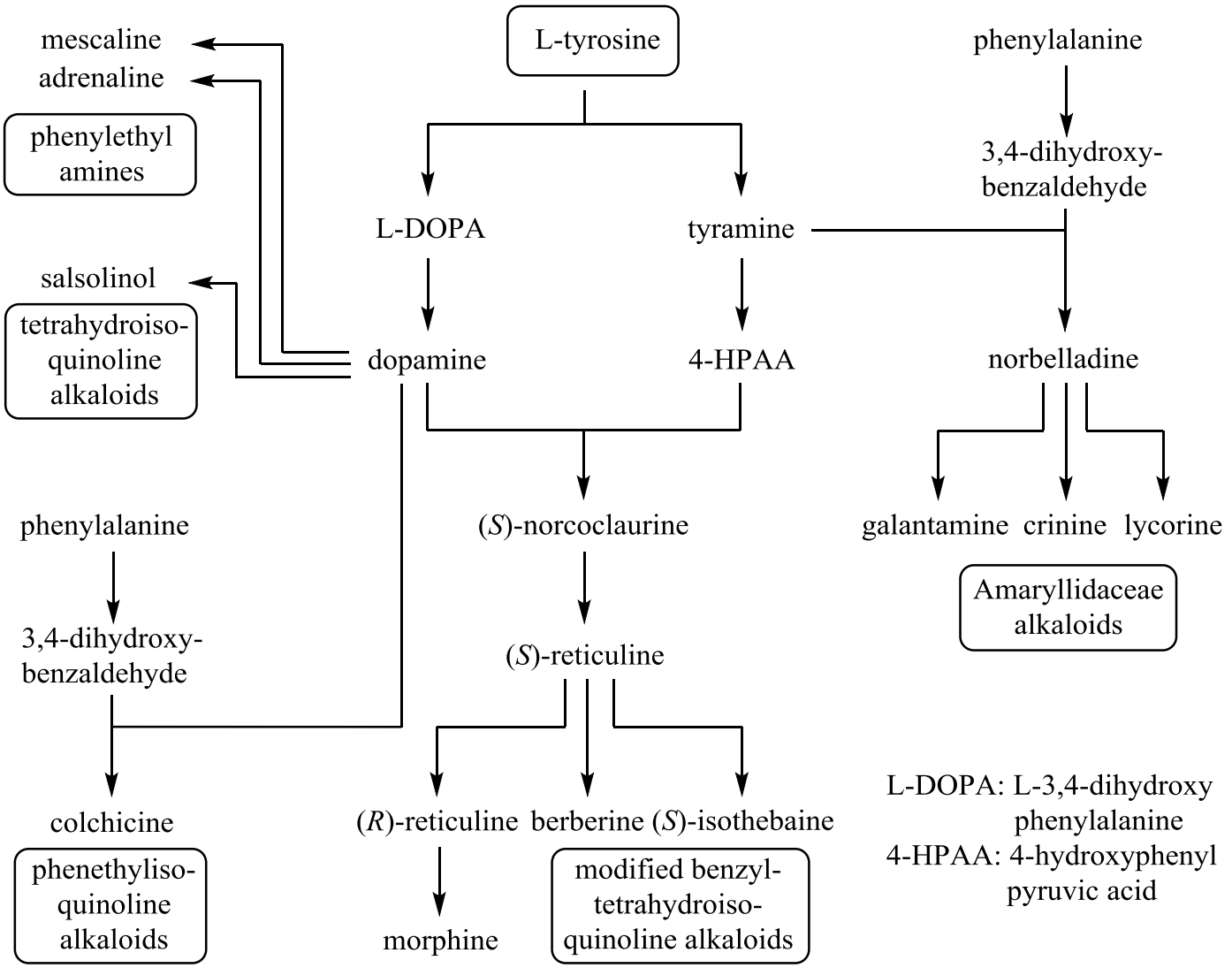
Alternative strategies towards :

Trimethylcolchicinic acid; Evans, 1978:



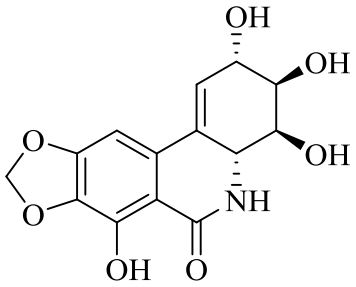
Reagents and conditions: a) CF_3CO_2H, rt, 71%; **b)** CF_3CO_2H, rf; **c)** DDQ, C_6H_6, reflux, 54%.

Tyrosine is an important starting material for a variety of natural products:

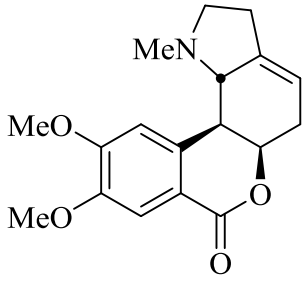


Amaryllidaceae alkaloids:

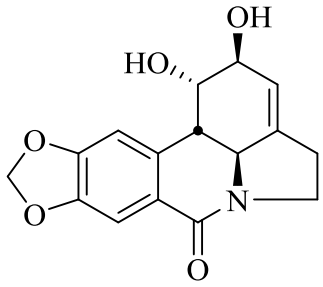
The great variety of Amaryllidaceae alkaloids can be explained by different coupling protocols of the key intermediate.



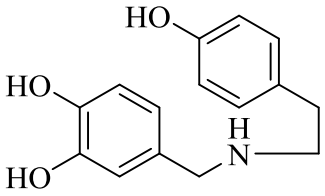
narciclasine



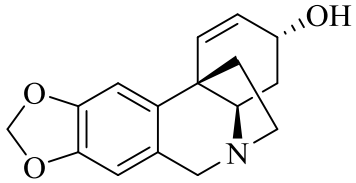
homolycorine



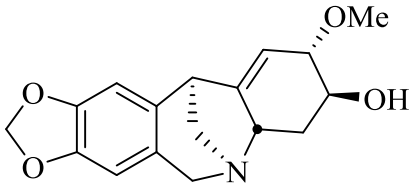
lycorine



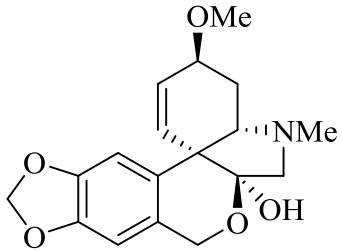
norbelladine



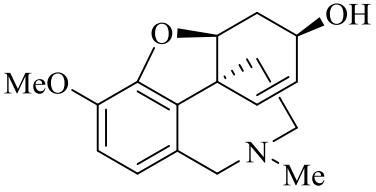
crinine



montanine



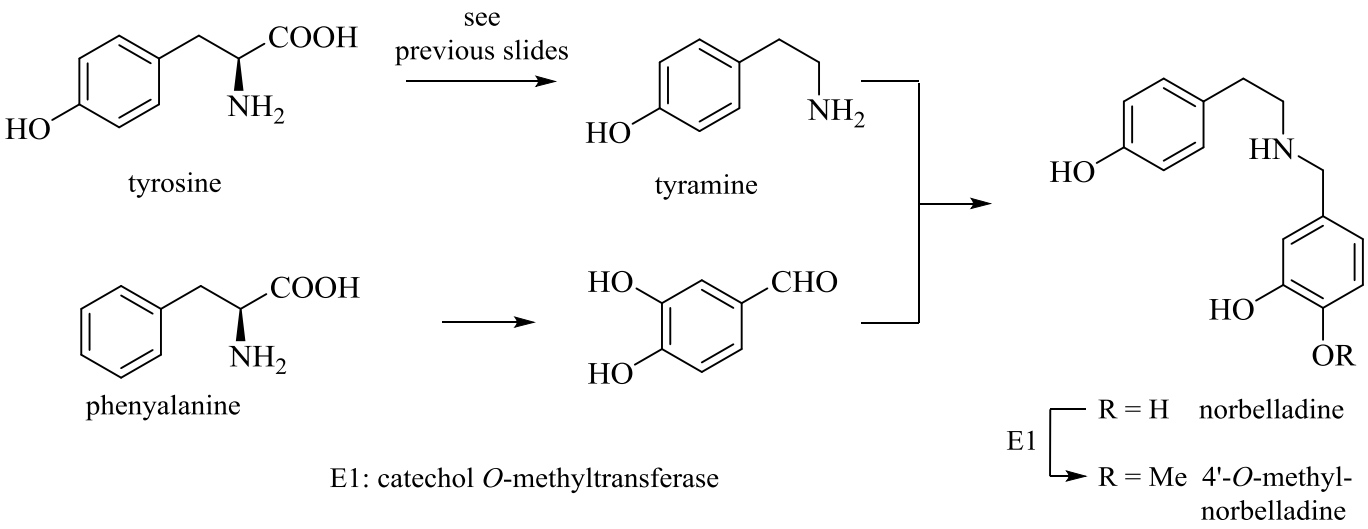
tazettine



galantamine

Amaryllidaceae alkaloids:

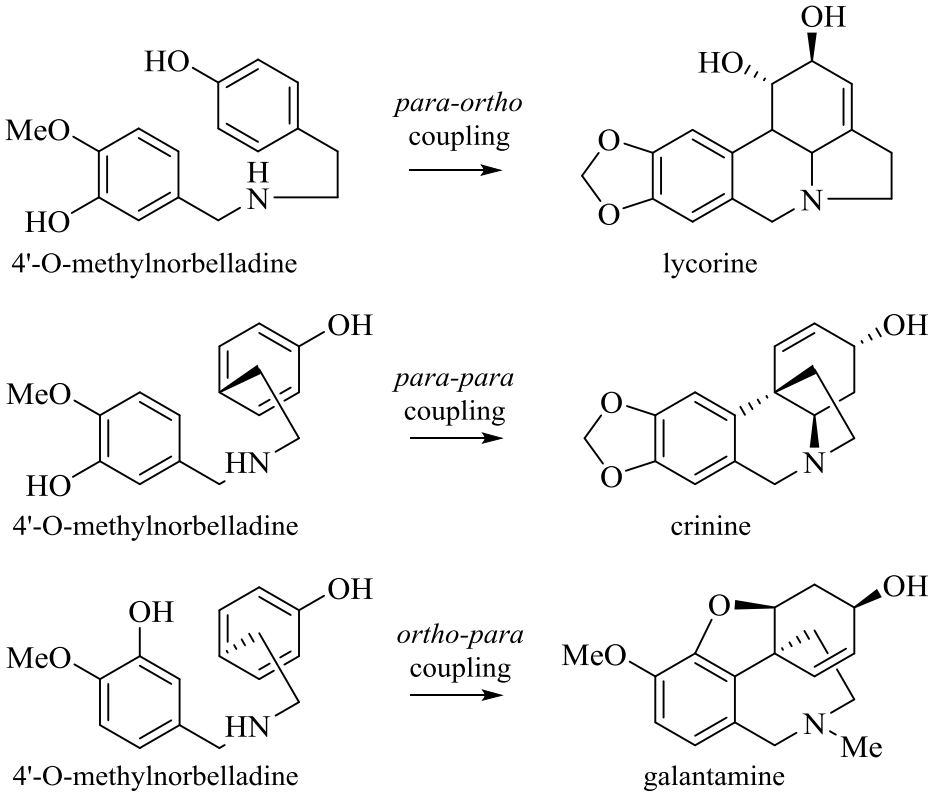
The biosynthesis of Amaryllidaceae alkaloids starts with the formation of 4‘-O-methylnorbelladine from tyrosine and phenylalanine.



Amaryllidaceae alkaloids:

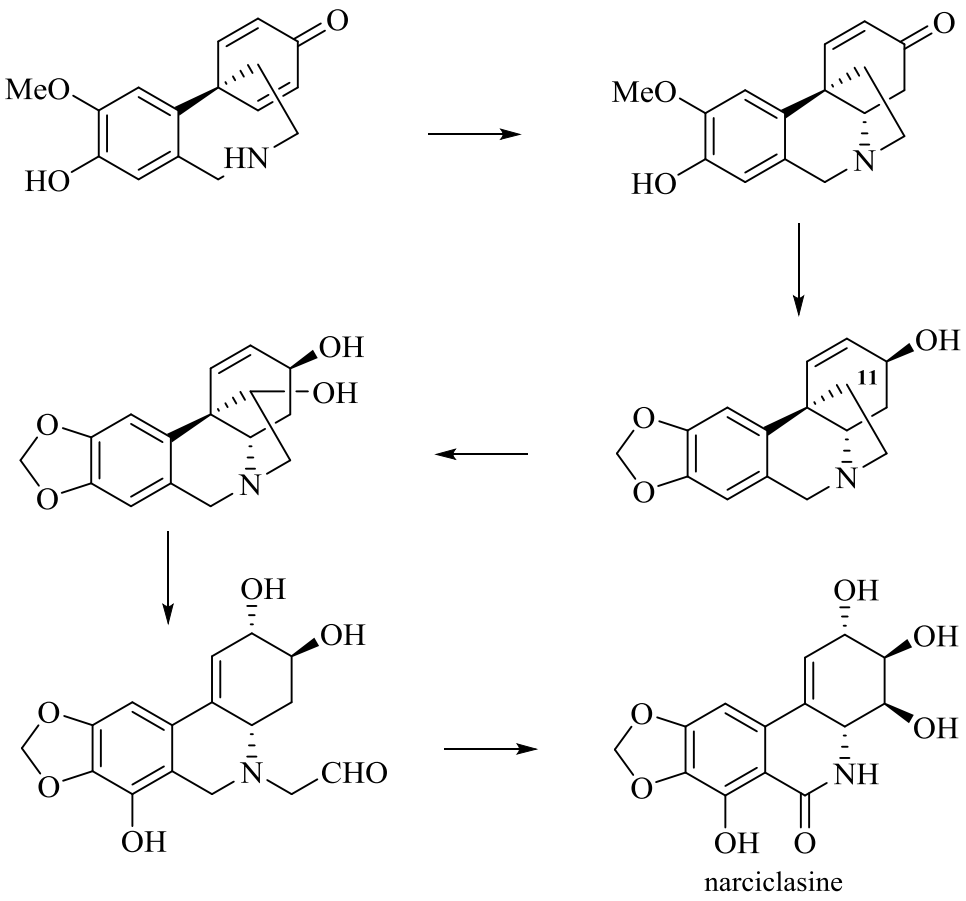
Only few enzymes have been identified which are responsible for the elaboration of the characteristic carbon frameworks.

The carbon frameworks are generated by different phenolic coupling reactions of methylnorbelladine.

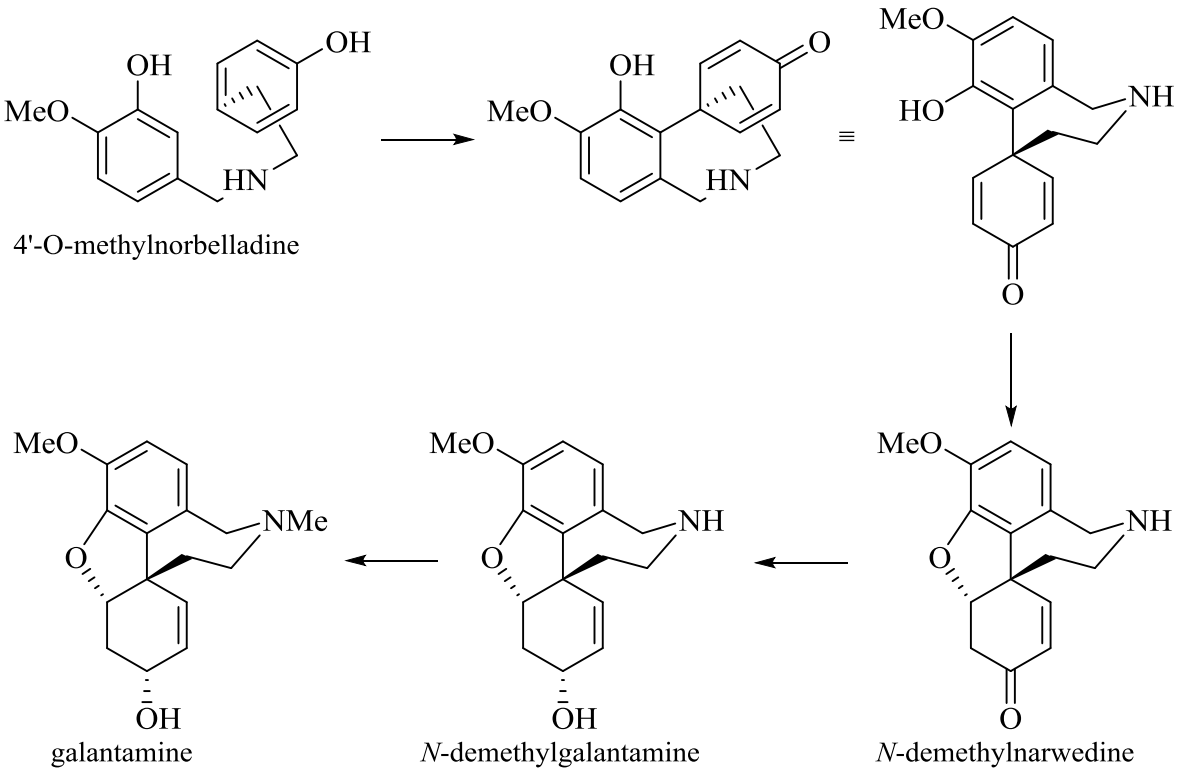


Amaryllidaceae alkaloids – proposed biosynthesis of narciclasine:

No enzymes have been identified. The proposed route has been developed after extenive studies with 13C and 14C labeled tyrosine.

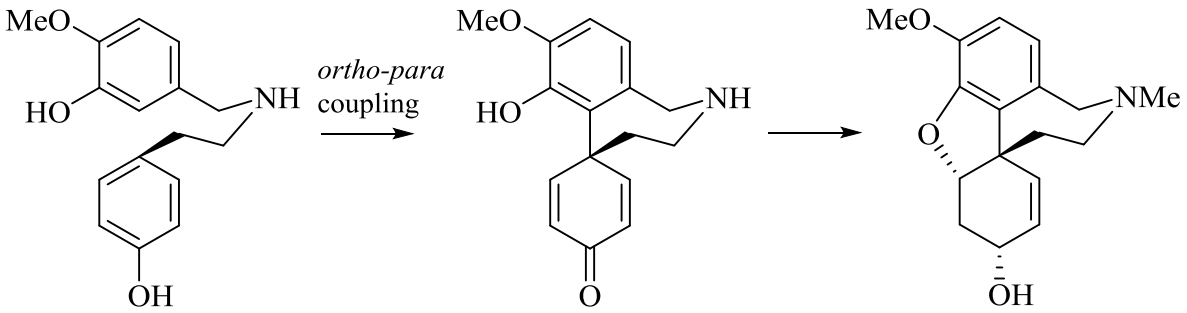


Amaryllidaceae alkaloids – proposed biosynthesis of galantamine:



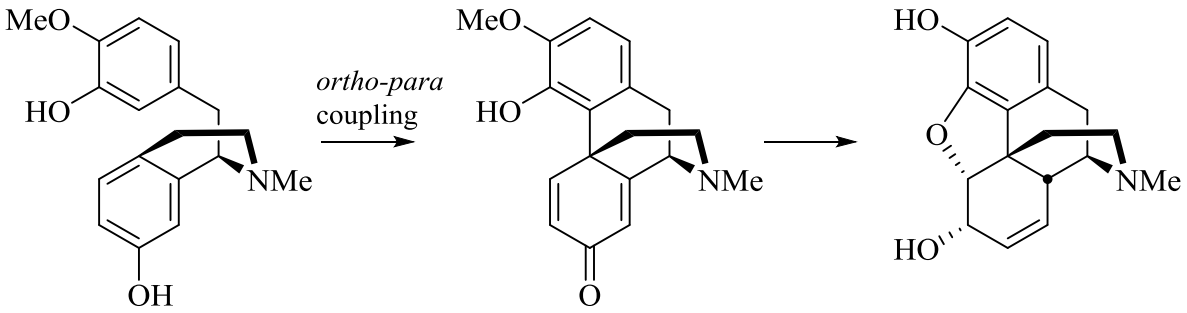
Comparison biosynthesis morphine and galantamine:

biosynthesis of galantamine:



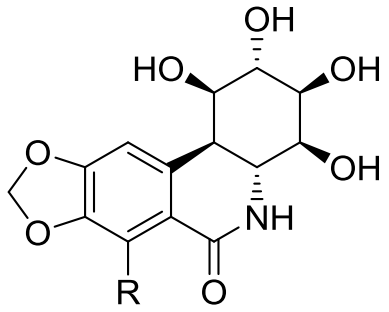
4'-O-methylnorbelladine galantamine

biosynthesis of morphine:



(*R*)-reticuline morphine

Amaryllidaceae alkaloids – biological activity:



Pancratistatin R = OH
7-Deoxypancratistatin R = H

Plants of the Amaryllidaceae family have been used extensively by ancient cultures worldwide. Over 30 plants have been reported effective in the primitive treatment of cancer.

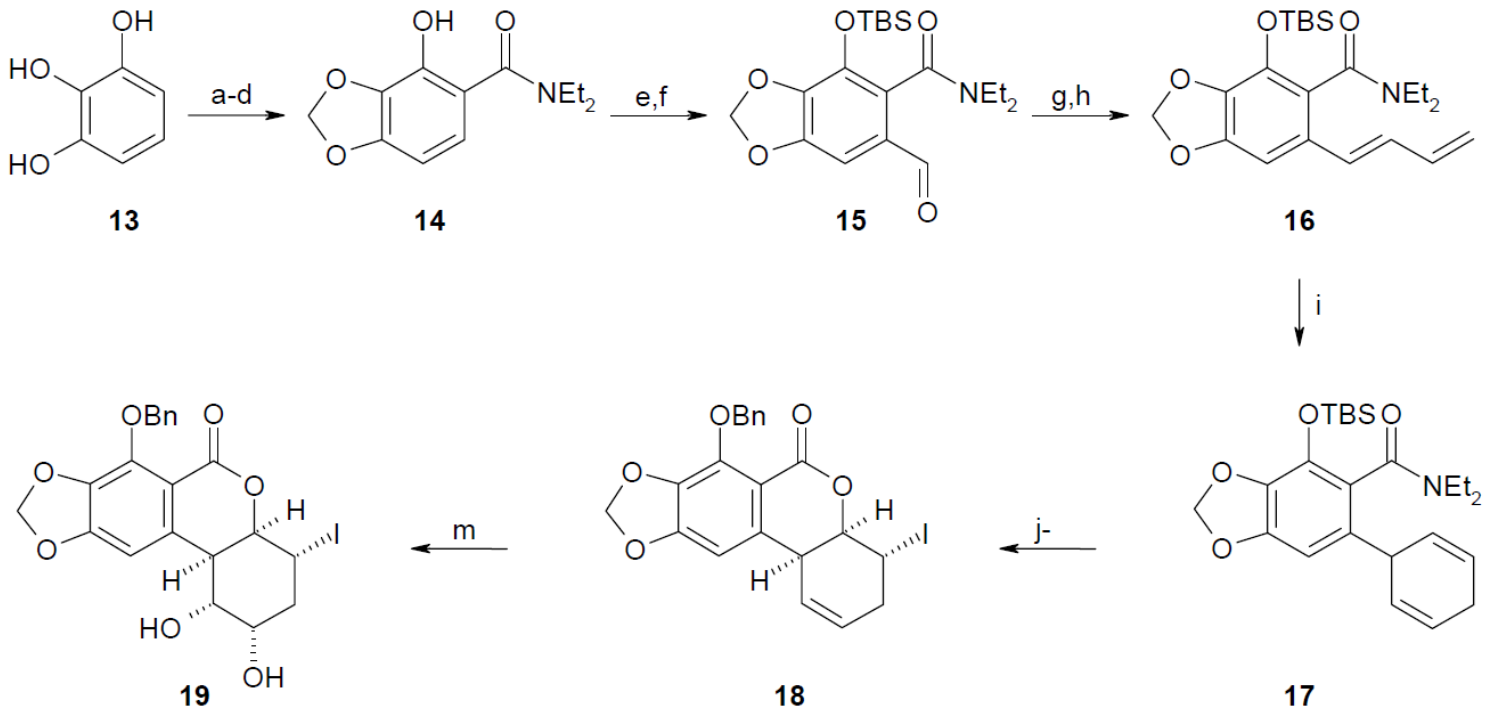
The chemical investigation of Amaryllidaceae alkaloids began with the isolation of lycorine from *Narcissus pseudonarcissus* in 1877.

Isolated in 1984 from *Pancratium littorale*, pancratistatin was identified to be highly active against several human cancer cell lines.

Derivatives of pancratistatin are currently used in clinical trials.

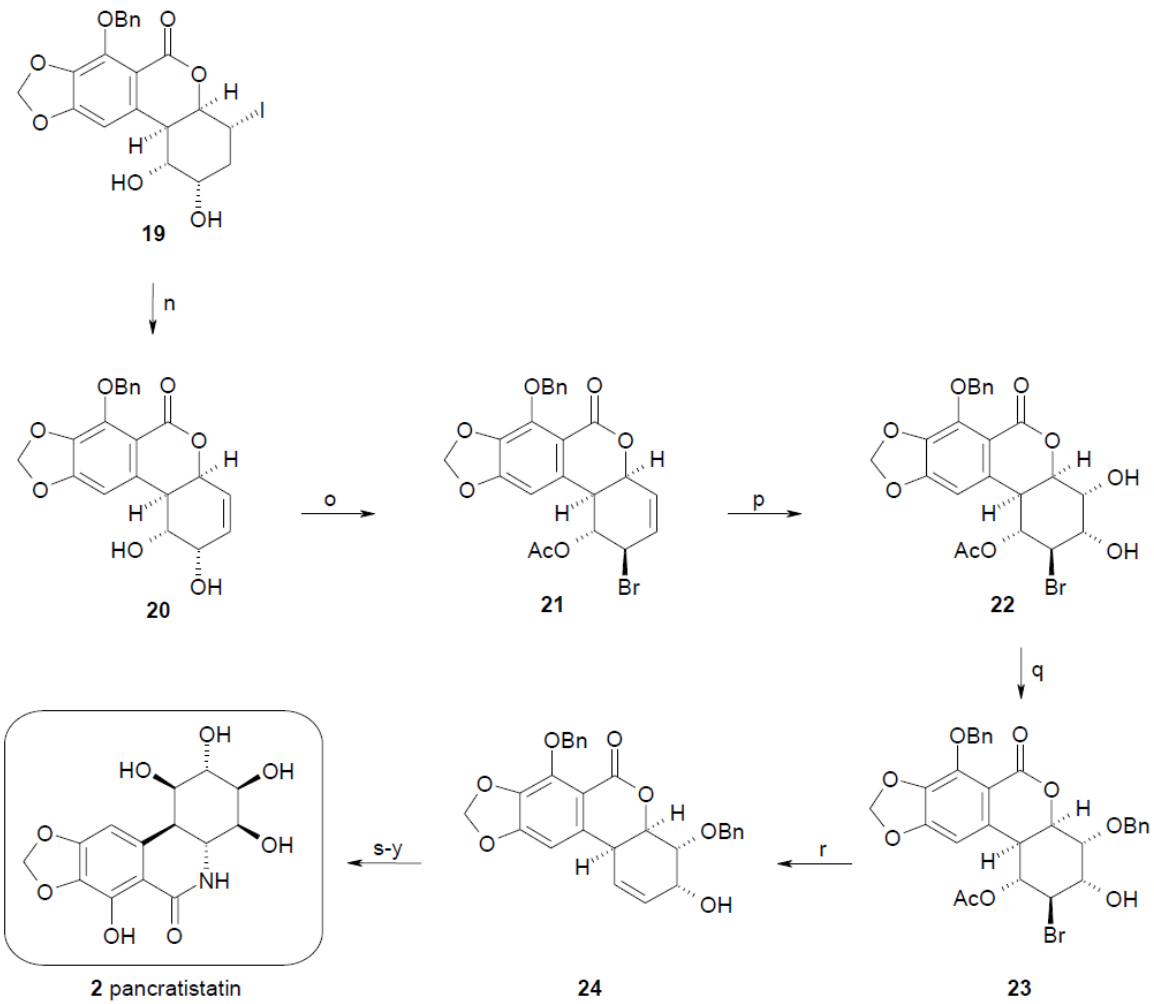
Hartwell, J. L. *Lloydia* **1967**, *30*, 379.
Gerrard, A. W. *Pharm. J*. **1877**, *40*, 221.

Danishefsky‘s synthesis of pancratistatin:



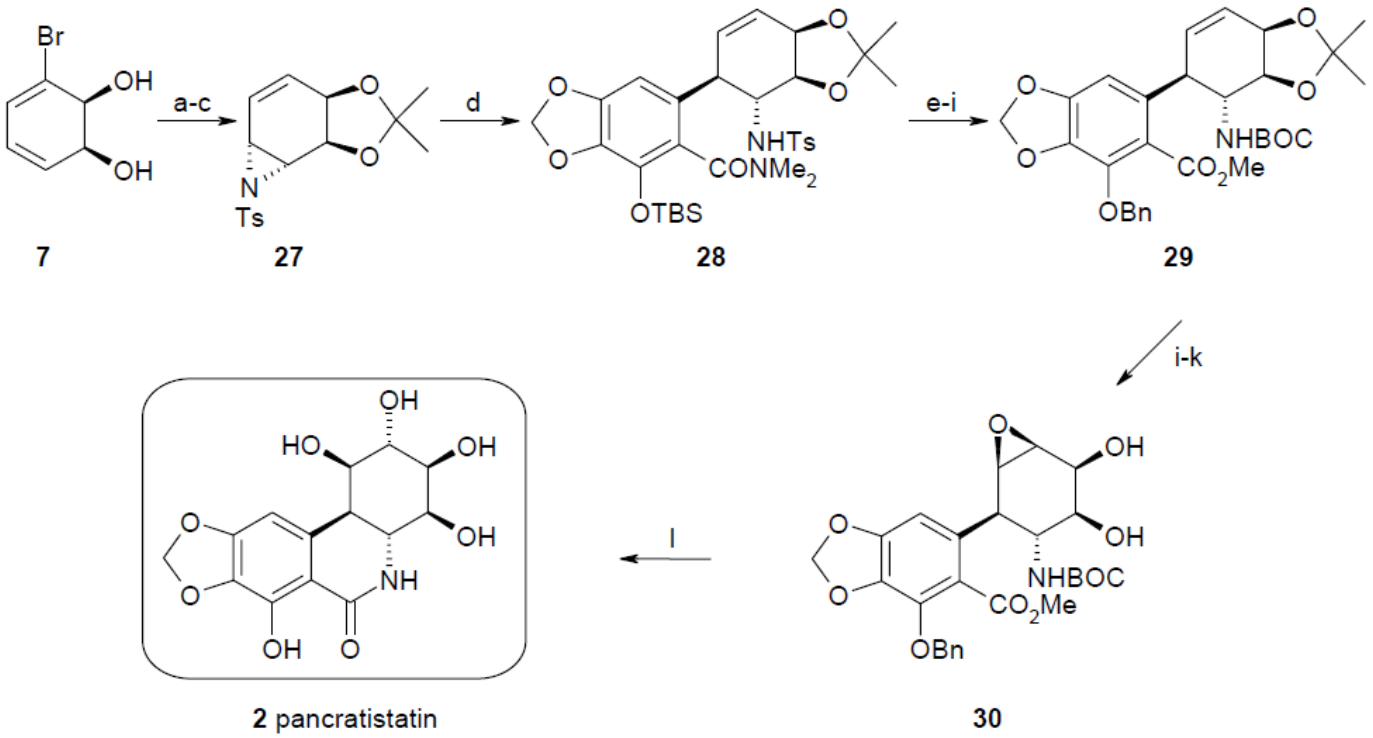
Reaction conditions: (a) $HC(OEt)_3$, Amberlyst-15, C_6H_6, 86%; (b) NaH, Et_2NCOCl, THF, 86%; (c) K_2CO_3, CH_2Br_2, CuO, DMF, 70%; (d) *s*-BuLi, TMEDA, THF, 58%; (e) TBSCl, imidazole, CH_2Cl_2, 86%; (f) *s*-BuLi, TMEDA, THF, 70%; (g) allylmagnesium bromide, Et_2O, 92%; (h) (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (ii) DBU, 54%; (i) 1-(benzene-sulfonyl)-2-nitroethene, $CHCl_3$, 96%; Bu_3SnH, AIBN, $PhCH_3$, 72%; (j) TBAF, THF, 79%; (k) (i) $(Bu_3Sn)O$, $C_6H_5CH_3$, (ii) I_2, THF, 67%; (l) BnBr, Ag_2O, DMF, 85%; (m) OsO_4, NMO, CH_2Cl_2, THF, H_2O, 90%;

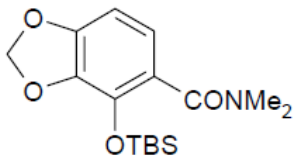
Danishefsky's synthesis of pancratistatin:



(n) DBU, C_6H_6, 88%; (o) 2-acetoxyisobutyryl bromide, CH_3CN, 88%; (p) OsO_4, NMO, CH_2Cl_2, THF, H_2O, 88%; (q) Bu_2SnO, $C_6H_5CH_3$, 4-methoxybenzyl bromide, *n*-Bu_4NI, (r) BnBr, Ag_2O, DMF, 95%; (s) DDQ, CH_2Cl_2, H_2O, 75%; (t) Zn, AcOH, H_2O, CH_2Cl_2, 81%; (u) NaH, CCl_3CN, THF, 74%; (v) 100-105 °C, 0.05-0.1mm Hg, 56%; (w) OsO_4, NMO, THF, H_2O, 75%; (x) K_2CO_3, MeOH, CH_2Cl_2, DCC, 82%; (y) H_2, $Pd(OH)_2$, EtOAc, 90%.

Hudlicky´s synthesis of pancratistatin:

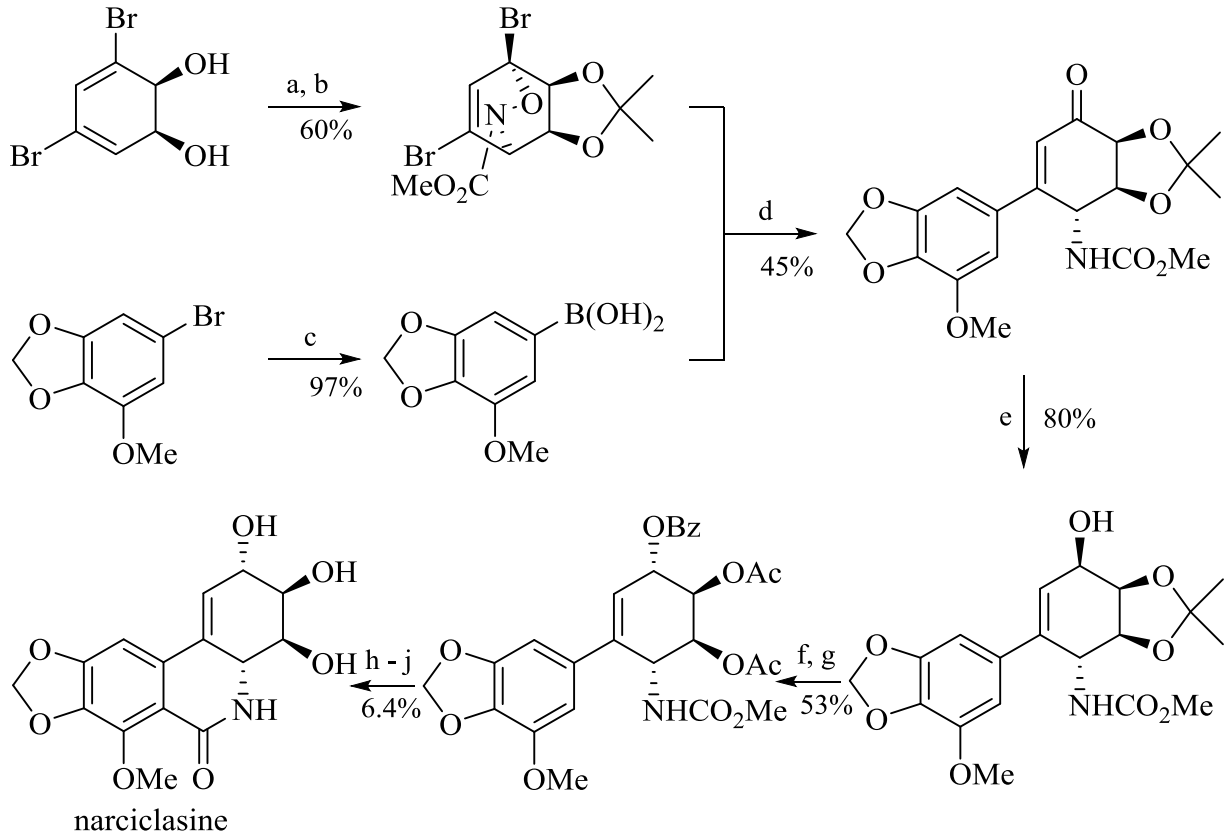




31

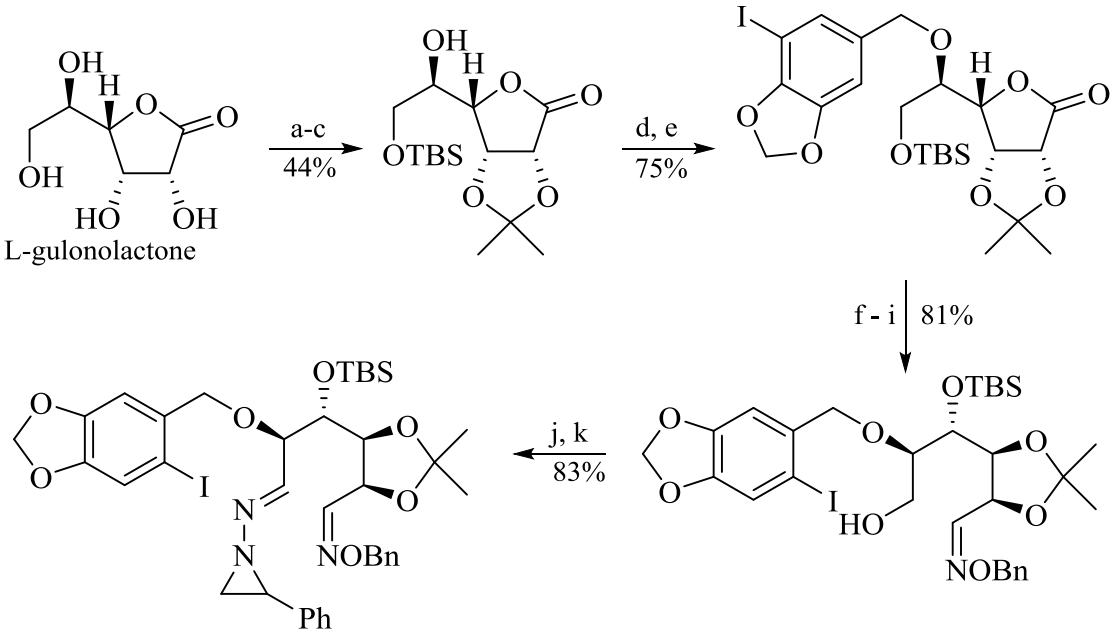
Reaction conditions: (a) DMP, *p*-TsOH, acetone; (b) PhINTs, $Cu(acac)_2$, CH_3CN, 27% (over 2 steps), (c) Bu_3SnH, AIBN, THF, reflux, 78%; (d) (i) **31**, *s*-BuLi, TMEDA, THF, (ii) CuCN, (iii) **27**, $BF_3.Et_2O$, 49%; (e) *s*-BuLi, $(BOC)_2O$, THF, 68%; (f) Na / anthracene, DME, 62%; (g) morpholine-SMEAH, THF, 72%; (h) BnBr, K_2CO_3, DMF, 83%; (i) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, CH_2N_2, 98%; (j) HOAc, THF, H_2O, 73%; (k) *t*-BuOOH, $VO(acac)_2$, C_6H_6, 53%; (l) C_6H_5COONa, H_2O, 100 °C, 51%.

Hudlicky's synthesis of narciclasine:



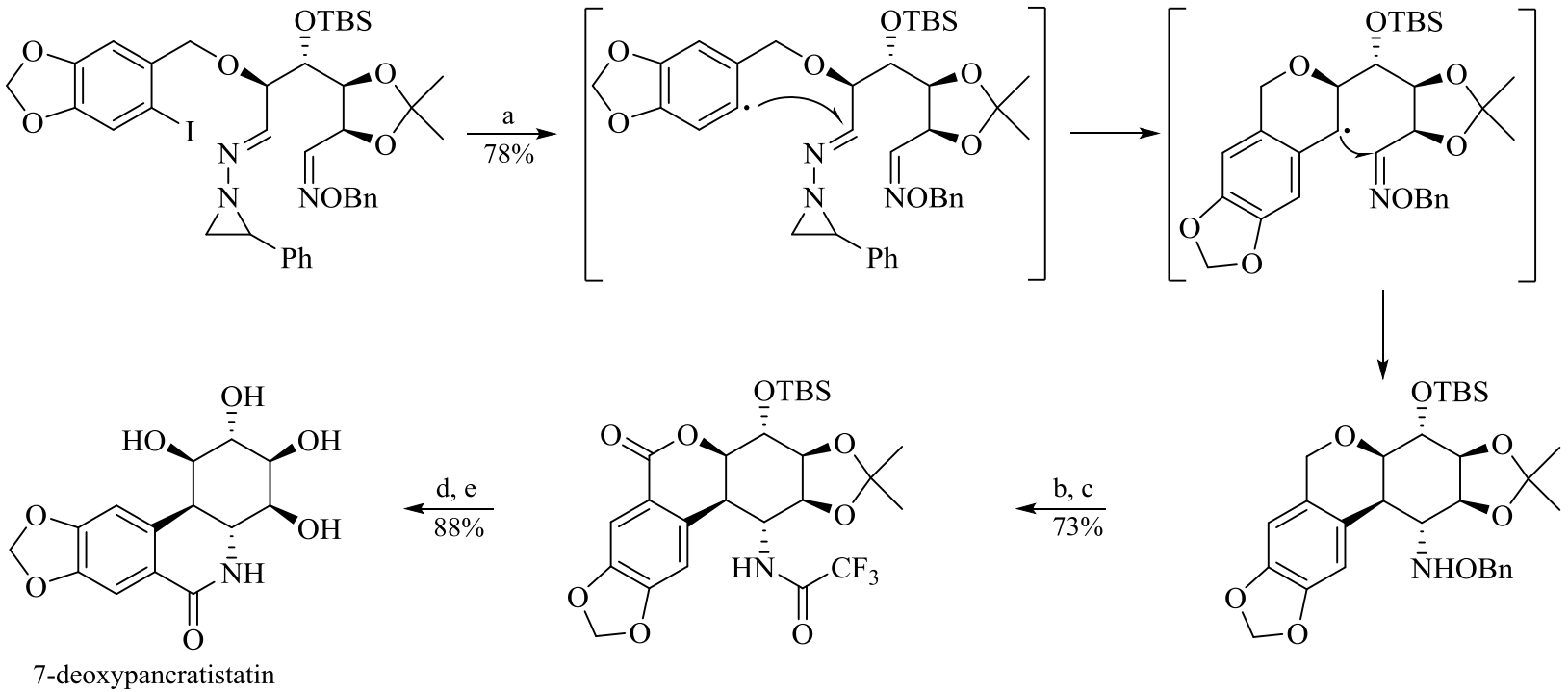
Reagents and conditions: a) DMP, acetone, *p*-TsOH (cat.); **b)** $NaIO_4$, methyl carbamate, MeOH, 0 °C to rt, 60% (2 steps); **c)** *t*-BuLi, $B(OEt)_3$, THF, -78 °C, 97%; **d)** $Pd(PPh_3)_4$ (0.03%), Na_2CO_3, C_6H_6, EtOH, H_2O, reflux; $Mo(CO)_6$, reflux, 45%; **e)** $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 80%; **f)** DEAD, Bu_3P, BzOH, THF, 75%; **g)** Dowex 50X8-100, MeOH; Ac_2O, py, DMAP, 70% **h)** Tf_2O, DMAP, CH_2Cl_2, 0 °C 41% ; **i)** Amberlyst A21, MeOH, 80%; **j)** LiCl, DMF, 120 °C, 20%.

Keck's synthesis of 7-deoxypancratistatin:



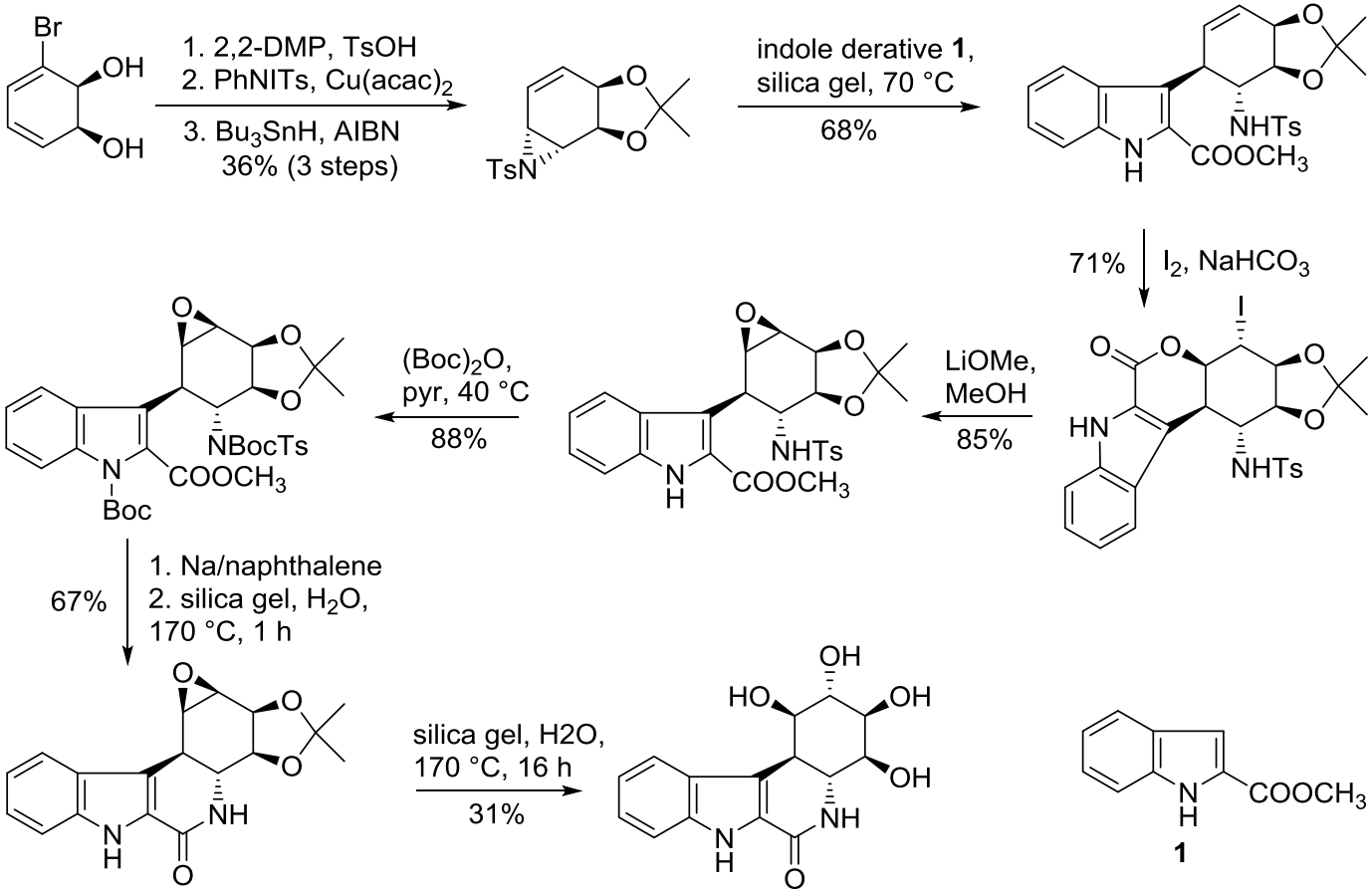
Reagents and conditions: a) 2,2-dimethoxypropane, acetone, *p*-TSOH, 79%; **b)** HOAc, H_2O, 79%; **c)** TBSCl, imidazole, DMF, -40 °C, 71%; **d)** 6-iodopiperonol, NaH, CCl_3CCN, 0 °C; **e)** TfOH, THF, 0 °C, 75% (over 2 steps); **f)** L-selectride, CH_2Cl_2, -78 °C; **g)** HCl•H_2NOBn, py, 96% (over 2 steps); **h)** TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; **i)** HF•py, THF, 84% (over 2 steps); **j)** TPAP, NMO, 4 Å molecular sieves; **k)** 1-amino-2-phenylhydrazine, EtOH, 0 °C, 83% (over 2 steps).

Keck's synthesis of 7-deoxypancratistatin:

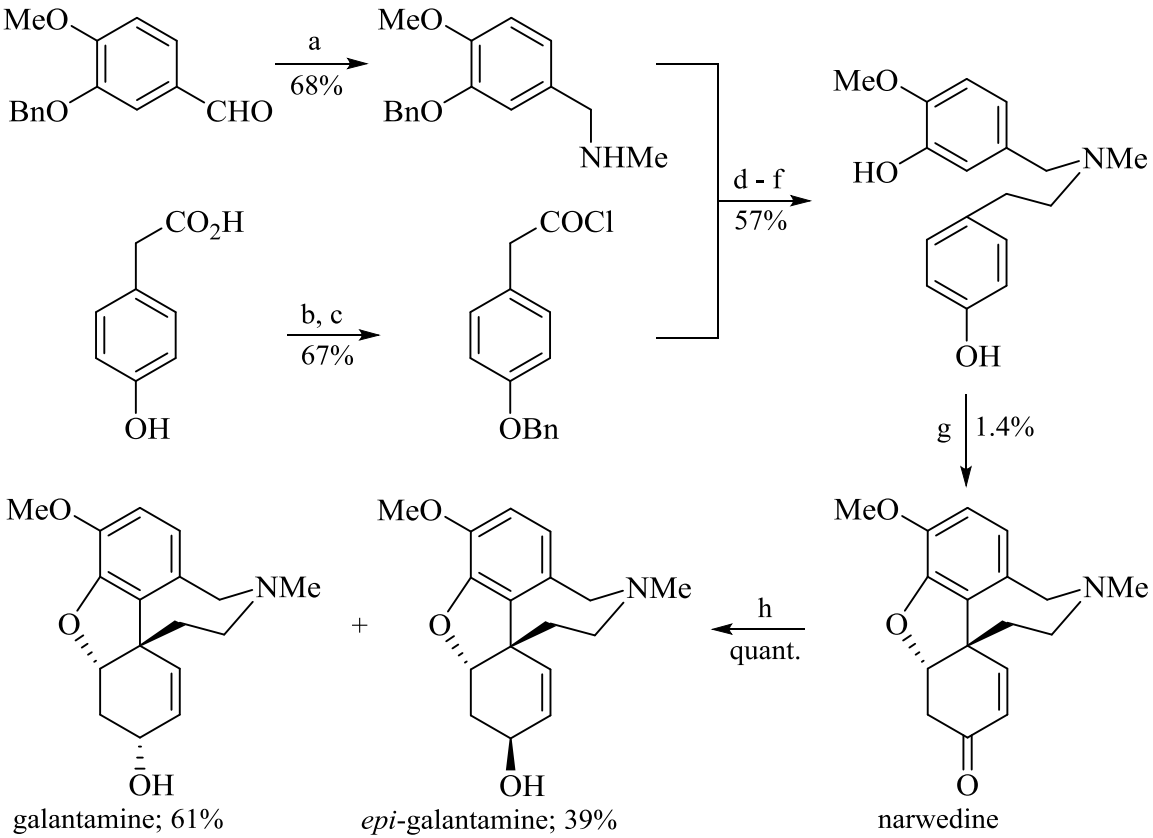


Reagents and conditions: a) Ph_3SnH, AIBN, C_6H_6, reflux, 78%; **b)** SmI_2; TFAA, THF, 60 °C, 88%; **c)** PCC, CH_2Cl_2, 83%; **d)** BF_3•Et_2O; **e)** K_2CO_3, MeOH, 88% (2 steps).

Hudlicky/Rinner's synthesis of 7-deoxypancratistatin:



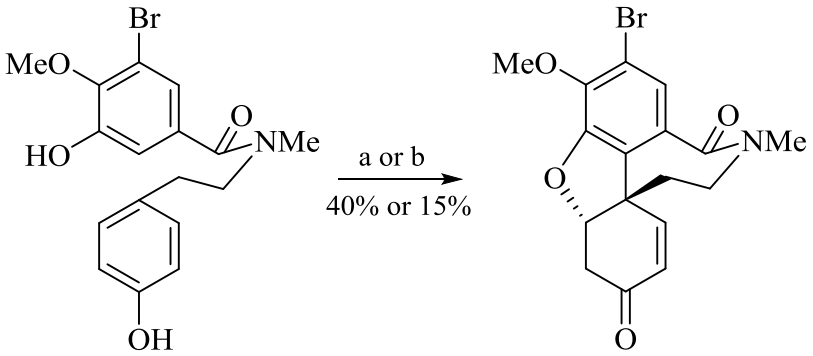
Barton and Kirby's synthesis of galantamine:



Reagents and conditions: a) $MeNH_2$, MeOH; KBH_4, 67%; **b)** KOH, BnCl, EtOH, reflux, 67%; **c)** $(COCl)_2$, C_6H_6, quant.; **d)** C_6H_6, 85%; **e)** LAH, Et_2O, reflux, 88%; **f)** H_2, Pd/C, MeOH, H_2O, HCl; $NaHCO_3$, 76%; **g)** $K_3Fe(CN)_6$, H_2O, $NaHCO_3$, 1.4%; **h)** LAH, Et_2O quant.

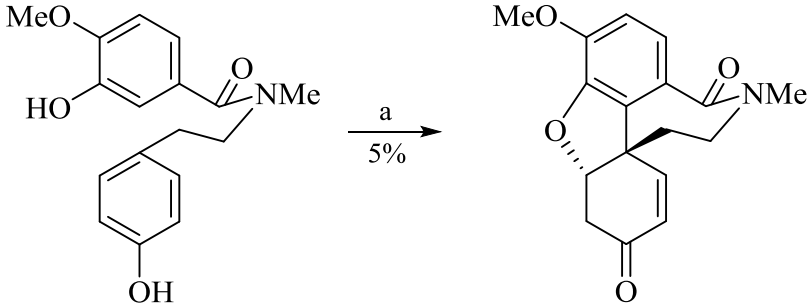
Galantamine served as model substrate for the development of oxidative coupling protocols:

Galantamine; Kametani, 1969; Vlahov, 1989:



Reagents and conditions: a) $K_3Fe(CN)_6$, H_2O, $NaHCO_3$, 60 °C, 1.5 h; 40%; **b)** same as a), 15%.

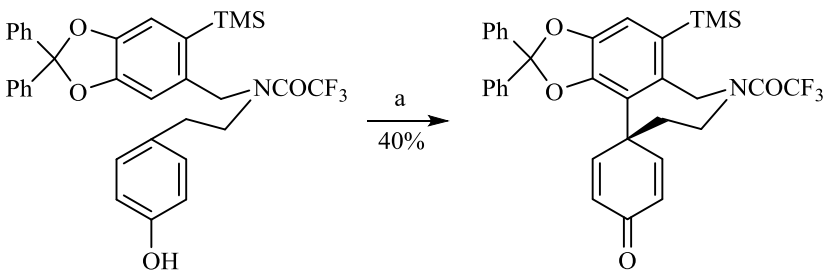
Galantamine; Kametani, 1971:



Reagents and conditions: a) $K_3Fe(CN)_6$, H_2O, $CHCl_3$, $NaHCO_3$, 60 °C, 1.5 h; 5%;

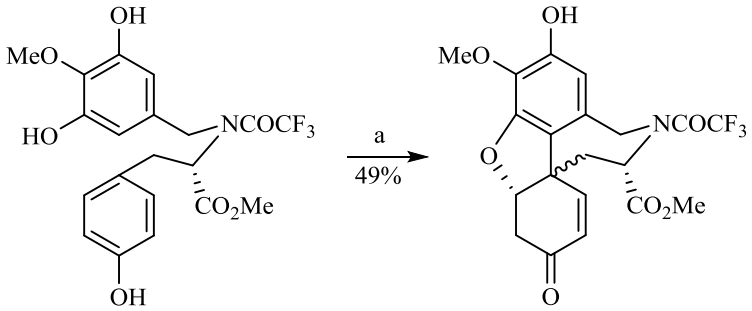
Galantamine served as model substrate for the development of oxidative coupling protocols:

Galantamine; Kita,1998:



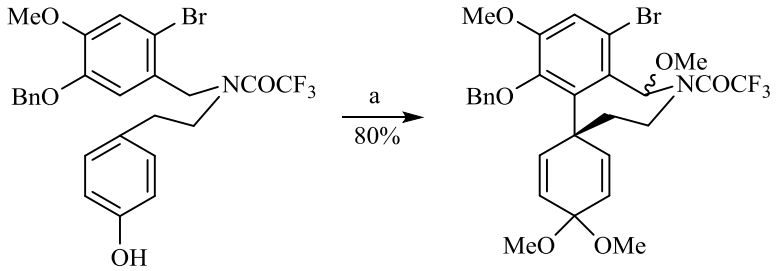
Reagents and conditions: a) PIFA, CF_3CH_2OH, -40 °C, 40%

Galantamine; Koga,1977:



Reagents and conditions: a) $Mn(acac)_3$, 49%.

Galantamine; Vlahov,1984:



Reagents and conditions: a) anodic oxidation 1.15V, Pt-electrode, MeOH, CH_3CN, $AgNO_3$, 80%.

Thank you for your interest