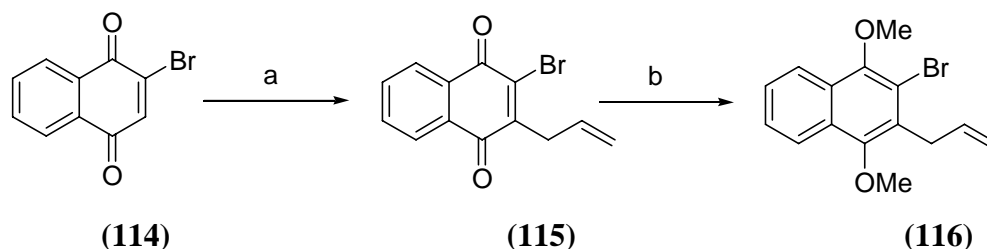


Synthesis of 2-allyl-3-bromo-1,4-naphthoquinone (116)

The 2-allyl-3-bromo-1,4-naphthoquinone (116) was synthesized from (114) in two steps as shown in Scheme 8 (De Kimpe *et al.*, 1999).



Scheme 8

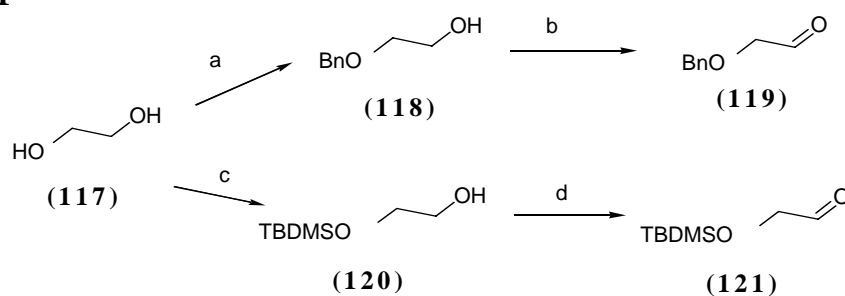
Reagents and conditions:

- a. vinyl acetic acid, AgNO₃, ammonium persulfate, H₂O, MeCN, 60-70 °C, 72%¹⁾
- b. SnCl₂, HCl, EtOH, 50 °C then dimethyl sulfate, 50% KOH, 65 °C, 75%¹⁾

Preparation of benzyloxyacetaldehyde (119) and (tert-butyldimethylsilyloxy)-acetaldehyde (121)

Benzyloxyacetaldehyde (119) (Kusakabe *et al.*, 1987; Hon *et al.*, 1995) and (tert-butyldimethyl silyloxy)acetaldehyde (121) (Enders and Schusseler, 2002; Brown *et al.*, 2000) were synthesized by using two different methods and the synthetic methodologies were described in Scheme 9 and 10.

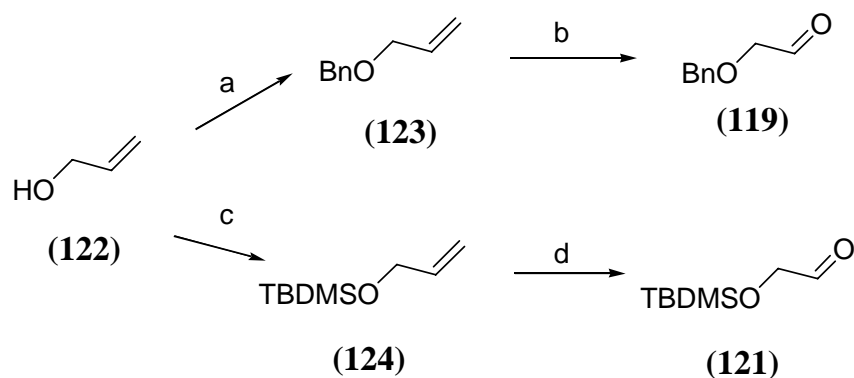
Method 1



Scheme 9

Reagents and conditions:

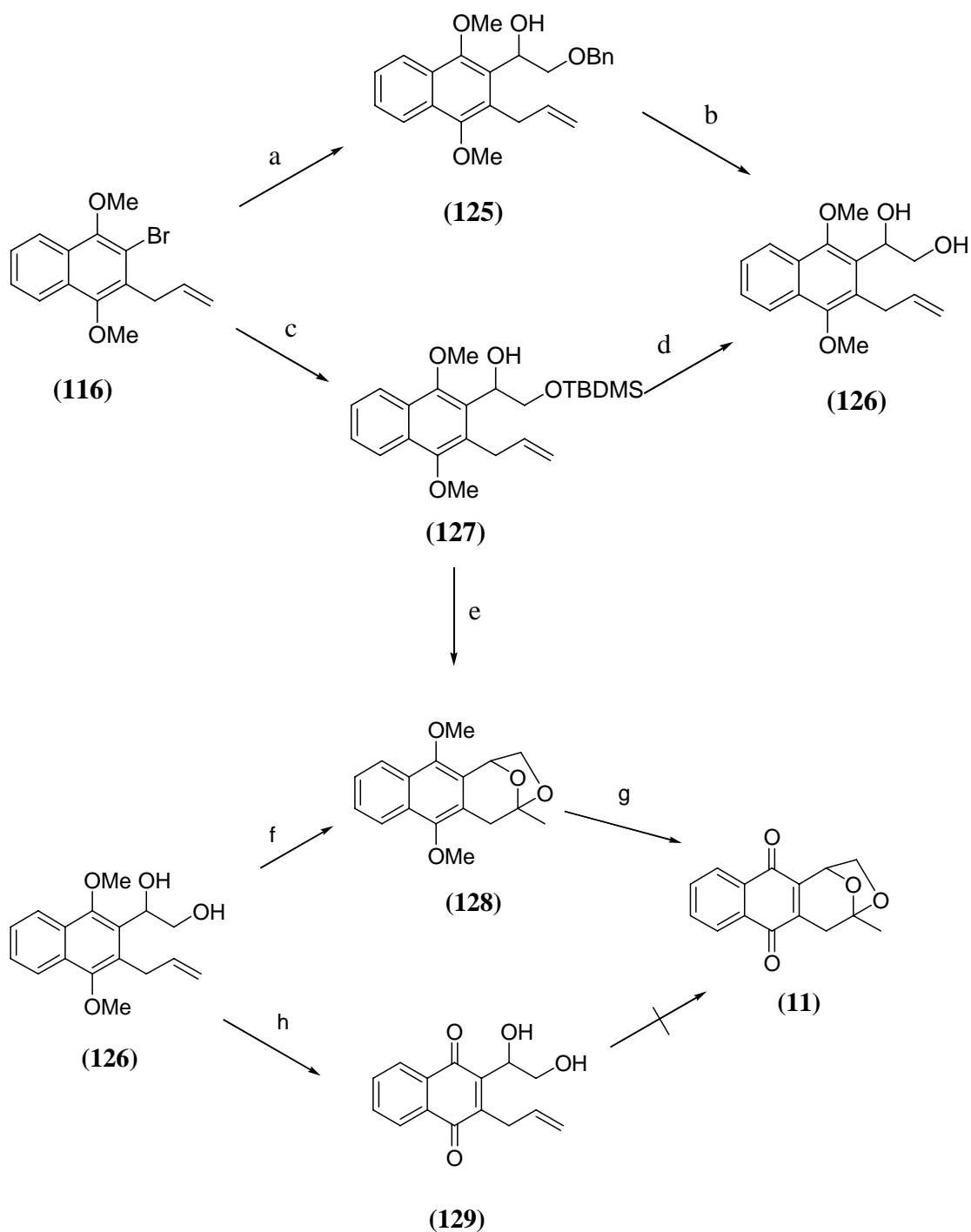
- KOH, Benzyl chloride, 90 °C, 51%¹⁾
- oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, -78 °C, 81%¹⁾
- NaH, TBDMSCl, THF, rt, 73%¹⁾
- Oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, -78 °C, 76%¹⁾

Method 2**Scheme 10**Reagents and conditions:

- NaH, BnCl, THF, rt, 84%¹⁾
- O₃, CH₂Cl₂, -78 °C then PPh₃, rt, 82%¹⁾
- TBDMSCl, imidazole, CH₂Cl₂, rt, 73%¹⁾
- O₃, CH₂Cl₂, -78 °C then PPh₃, rt, 76%¹⁾

Synthesis of isagarin (11)

The synthesis of isagarin (11) from 2-allyl-3-bromo-1,4-naphthoquinone (116) is shown in Scheme 11.



Scheme 11

Reagents and conditions:

a. *n*-BuLi, THF then (119), -78 °C, 44%¹⁾

b. Li, naphthalene, THF, -78 °C, 41%¹⁾

c. *n*-BuLi, THF then (121), -78 °C, 70%¹⁾

d. TBAF, THF, rt, 87%¹⁾

e. PdCl₂, CuCl₂, DME, O₂, 65 °C, 67%¹⁾

f. PdCl₂, CuCl₂, DME, O₂, 65 °C, 71%¹⁾

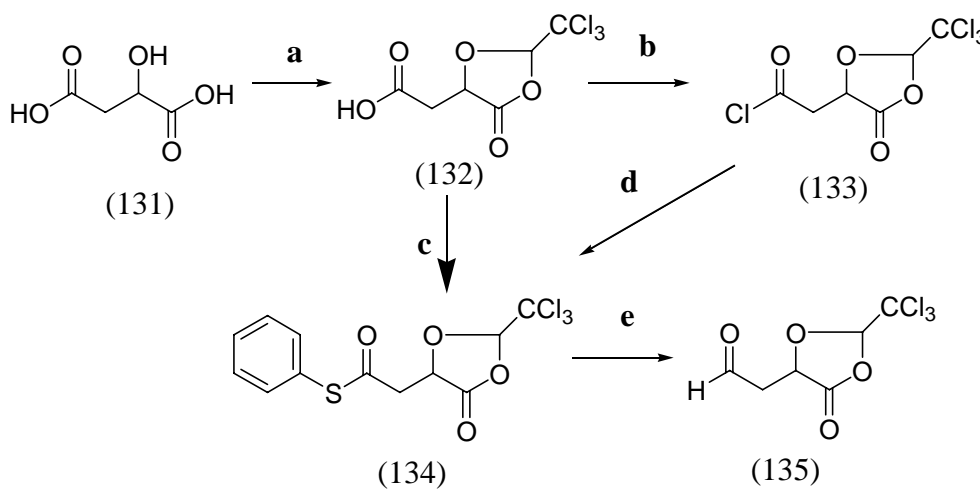
g. CAN, MeCN, H₂O, 0 °C, 95%¹⁾

h. CAN, MeCN, H₂O, 0 °C, 95%¹⁾

Synthesis of (±)-marticin and (±)-isomarticin

Preparation of (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl chloride (133).

Acid chloride (133) (Shih *et al.*, 1989) and aldehyde (135) were prepared from *dl*-malic acid (131) in good yield as shown in Scheme 12.



Scheme 12

Reagents and conditions:

a. *dl*-Malic acid, H₂SO₄, CCl₃CHO, 79%³⁾

b. SOCl₂, reflux, 2 days, 98%²⁾

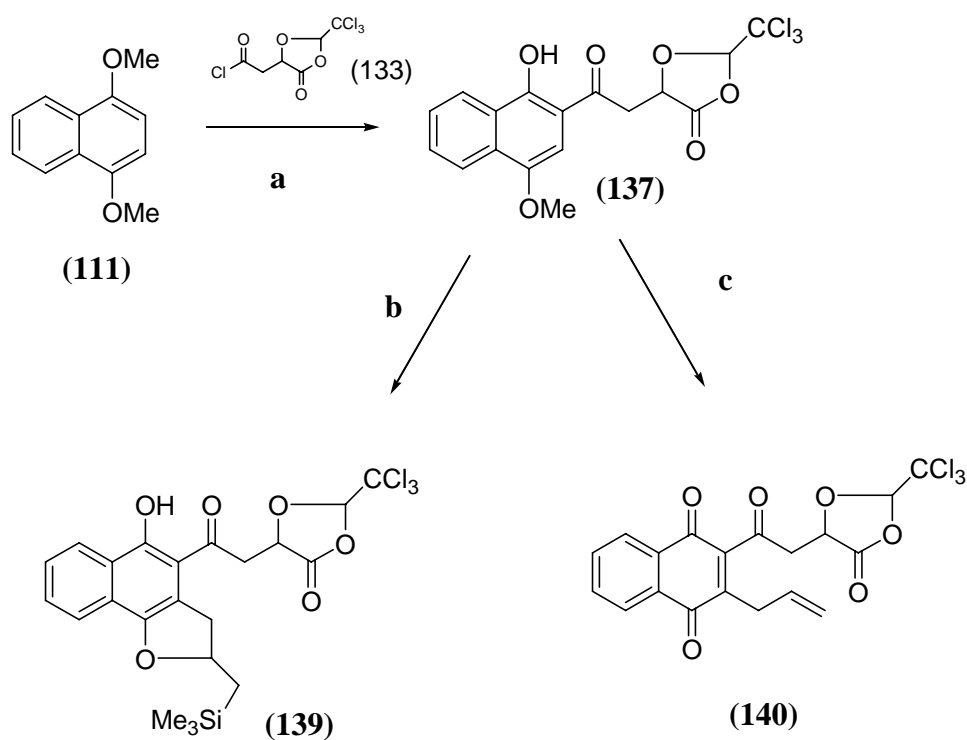
c. DCC, CH₂Cl₂, DMAP, thiophenol, 79%¹⁾

d. thiophenol, pyridine, rt, 85%¹⁾

e. Et_3SiH , Pd/C, rt, 98%¹⁾

Model synthesis of marticin

The synthesis of 2-allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphthoquinone (140) from 1,4-methoxynaphthalene (111) was shown in Scheme 13.



Scheme 13

Reagents and conditions:

a. (133), AlCl_3 , CH_2Cl_2 , rt, 0 °C, 43%¹⁾

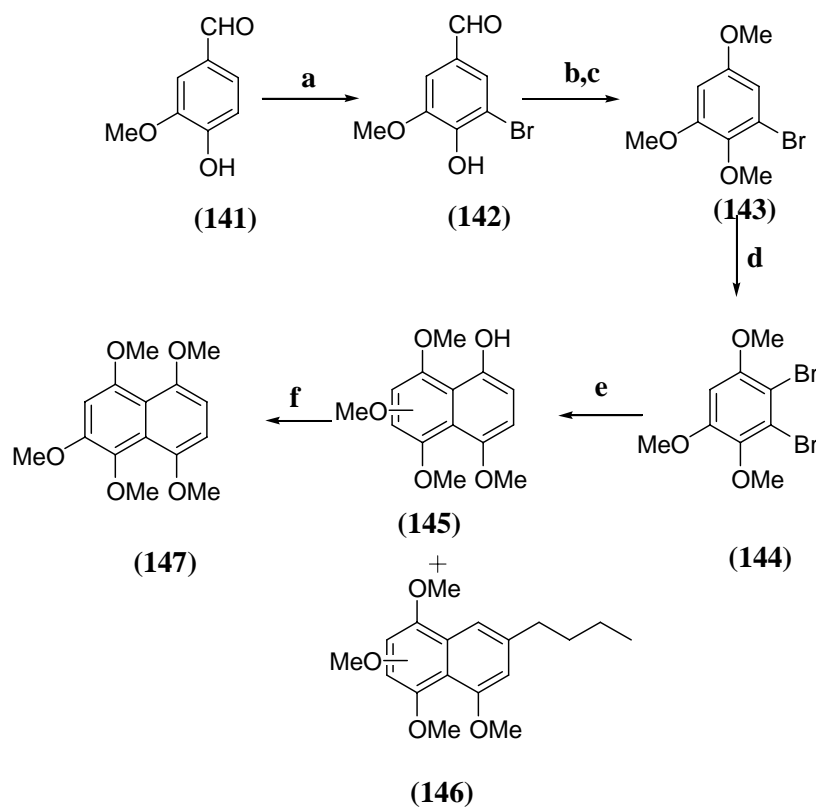
b. CAN, MeCN, H_2O ; allyl trimethylsilane, SnCl_4 , dry CH_2Cl_2 , 78 °C, N_2 , 56% over two steps¹⁾

c. CAN, MeCN, H_2O ; vinyl acetic acid, AgNO_3 , ammonium persulfate, H_2O , MeCN, 60-70 °C, 55% yield¹⁾

Synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147)

The synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147) using two different methods were shown in Scheme 14 (Giles *et al.*, 1988) and 15.

Method 1

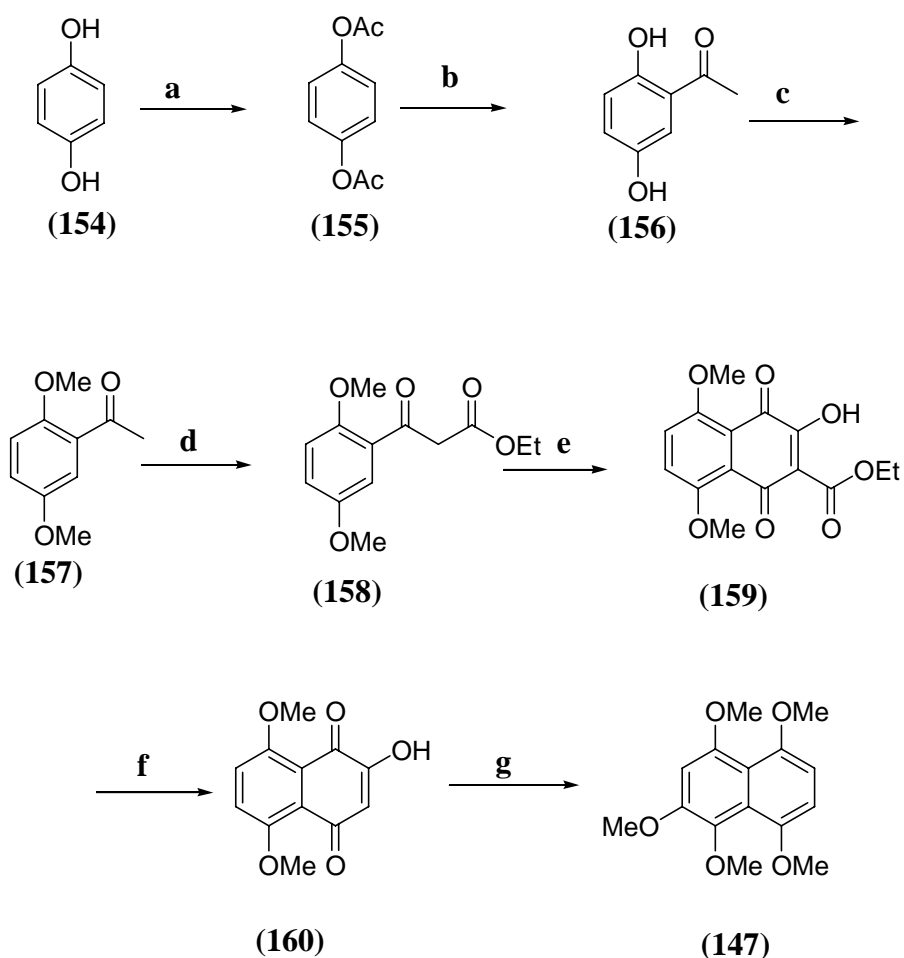


Scheme 14

Reagents and conditions:

- a. Br₂, acetic acid, 0 °C, 95%¹⁾
- b. H₂O₂, NaOH, 0 °C
- c. Dimethyl sulfate, K₂CO₃, dry acetone, reflux, 81% yield over two steps¹⁾
- d. Br₂, benzene, 81%¹⁾
- e. 2-Methoxyfuran, *n*-BuLi, dry THF, -78 °C, (145) (43%) and (146) (27%)¹⁾
- f. Dimethyl sulfate, K₂CO₃, dry acetone, reflux, 70%¹⁾

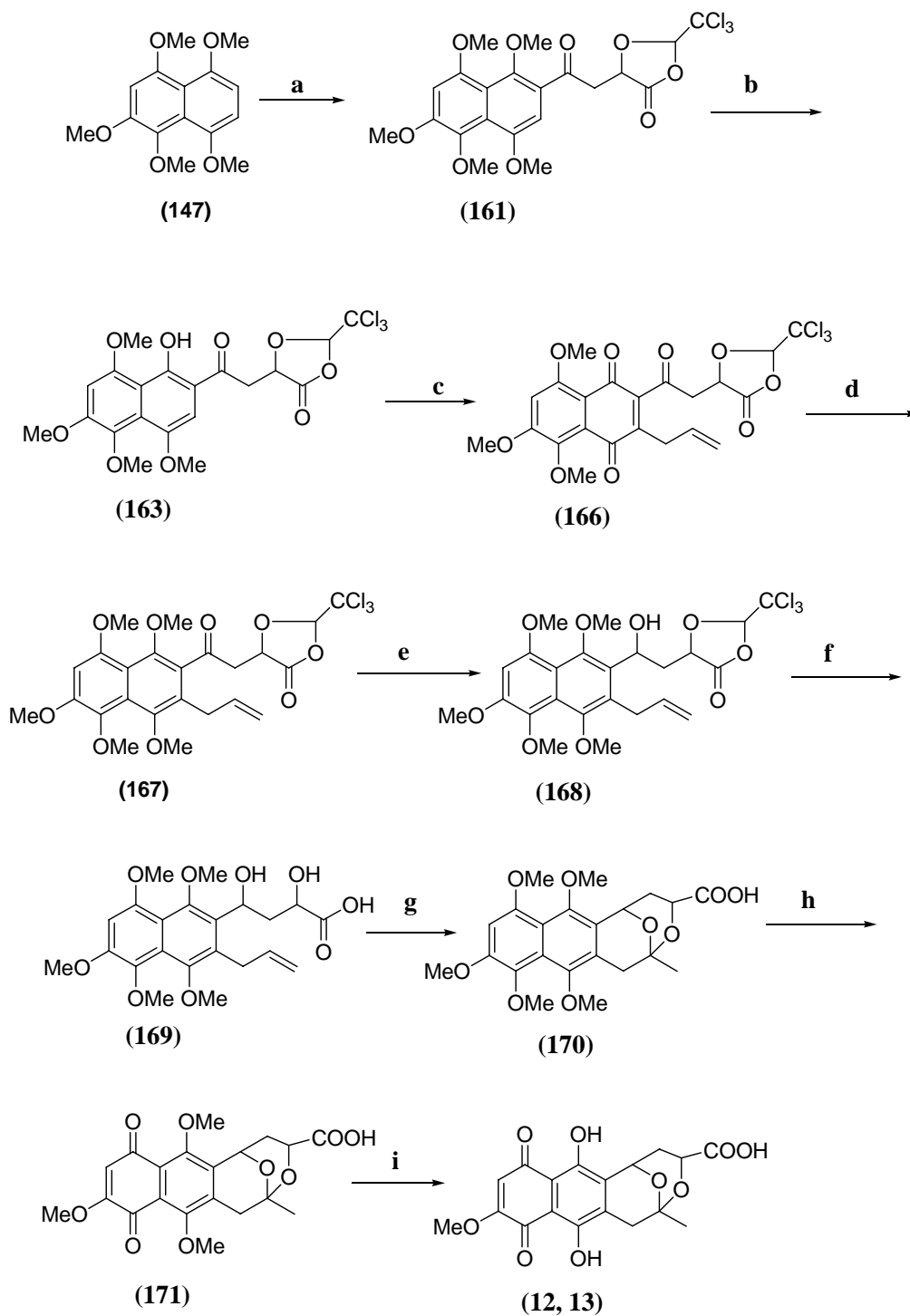
Method 2

**Scheme 15**Reagents and conditions:

- Ac₂O, H₂SO₄, 100%¹⁾
- AlCl₃, 165 °C, 71%
- dimethyl sulfate, K₂CO₃, dry acetone, reflux, 72%¹⁾ or dimethyl sulfate, KOH, TBAI, H₂O, THF, rt, 71%¹⁾
- diethyl carbonate, NaH, benzene, reflux, 77%¹⁾
- oxalyl chloride, AlCl₃, MeNO₂, reflux, 67%¹⁾
- 5% KOH 65 °C then 10% HCl, 65 °C, 73%¹⁾
- dimethyl sulfate, Na₂S₂O₄, KOH, TBAI, H₂O, THF, rt, 71%¹⁾

Marticin (12)

The synthesis of (±)-marticin (12) from 1,2,4,5,8-pentamethoxynaphthalene (147) is shown in Scheme 16.

**Scheme 16**

Reagents and conditions:

- a. TFAA, CH₂Cl₂, 0 °C, 55%¹⁾
- b. BBr₃, CH₂Cl₂, -78 °C, 71%¹⁾
- c. CAN/ MeCN/ H₂O, 0 °C; vinyl acetic acid, AgNO₃, ammonium persulfate, H₂O, MeCN, 60-70 °C, 50%¹⁾
- d. Dimethyl sulfate, Na₂S₂O₄, K₂CO₃, TBAI, H₂O, THF, rt, 55%¹⁾
- e. NaBH₄, EtOH, 0 °C
- f. NaOH, EtOH, 62% over two steps¹⁾
- g. PdCl₂, CuCl₂, DME, O₂, 65 °C, 67%¹⁾
- h. CAN/ MeCN/ H₂O, 0 °C
- i. BBr₃, CH₂Cl₂, -78 °C, 52 % over two steps¹⁾

- 1) yield refers to chromatographic product
- 2) yield refers to crude product
- 3) yield refers to crystallized product