p38 was identified as a member of the mitogen activated protein (MAP) kinase superfamily.\textsuperscript{1,2} MAP kinases are important signalling molecules which are activated by a number of extracellular stress stimuli. The actual activation of p38 occurs by dual phosphorylation of conserved threonine and tyrosine residues by upstream activators such as MAP kinase kinases (MKKs) upon receiving extracellular signals. The downstream events that are subsequently regulated by p38 lead to the production of cytokines such as TNF-\(\alpha\) and IL-1\(\beta\) and these are the causative agents for rheumatoid arthritis and other inflammatory disease. A small molecule inhibitor that can selectively block p38 will prevent this signal transduction cascade from producing harmful cytokines and eventually alleviate the onset of disease.

Research at Merck has identified compound 1 as a potent p38 MAP kinase inhibitor (Figure 1). The compound contains a naphthyridone core, which showed a good activity against kinases.\textsuperscript{3} To further the studies of this compound, an efficient synthesis is required for large-scale production.

![Figure 1: p38 MAP Kinase Inhibitor 1](image)

Questions:

1) Please identify the key components in the structure of inhibitor 1;

2) Please suggest possible retrosynthetic analysis from components identified from Q1.
An early synthesis of 1 involved a multi-step synthetic procedure in its longest linear sequence with an overall yield of approximately 2% (Schemes 1).

(a) (i) HNO3; (ii) NaNO2; (iii) POCl3; (b) ArB(OH)2, Cs2CO3, Pd(PPh3)4, toluene, MeOH, H2O; (c) (i) RaNi; (ii) Br2, HCl; (iii) tBuONO; (d) NBS, (BzO)2, CCl4; (e) tBuOAc, LiHMDS, THF, -78 °C; (f) (i) TFA, anisole; (ii) TMS-CH2N2, C6H6, MeOH; (iii) AlMe3, CH2Cl2, dichloroaniline; (g) Cul, K2CO3, DMF, 160 °C; (h) (i) NBS, AIBN, CCl4, heat; (ii) DBU.

Scheme 1: Early Synthesis of 1

Questions:
3) Please provide mechanisms for steps a to h;
4) Please discuss the drawbacks in this route which limited a large-scale synthesis.

References:
(2) Han, J.; Lee, J.-D.; Bibbs, L.; Ulevitch, R. J. Science 1994, 265, 808.
Bingli’s Problem Session_Part2

Design and Development of a p38 MAP Kinase Inhibitor

Researchers at Merck predicted the mode of binding of dihydroquinazolinone derived inhibitors like 1 in the hopes that the 3 H-bondings might improve the potency and functional activity (Figure 1).

**Figure 1:** Schematic representation of predicted bonding of 1 to p38

**Question:**
(1) Please suggest suitable substituents for R group indicated in Figure 3.

**Figure 3:** Dihydroquinazolinone derived p38 inhibitor 3

(2) Please suggest suitable substituents for R’ group indicated in Figure 3.