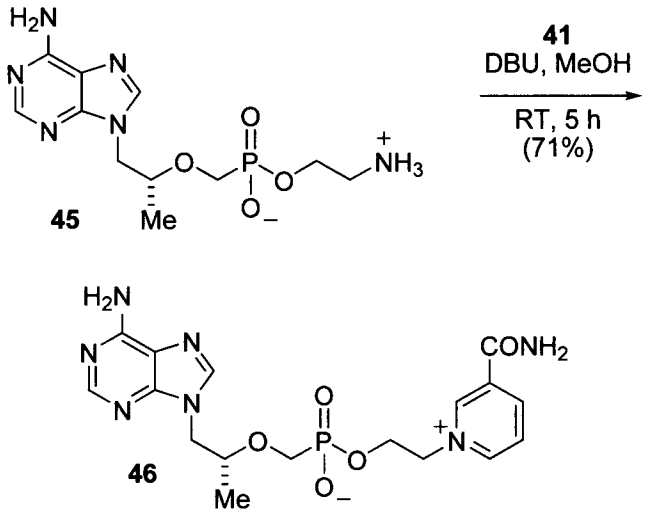
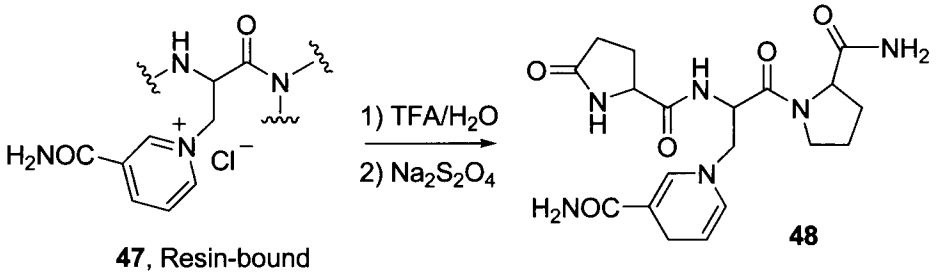


Solid-phase Zincke reaction was applied for the search of activators of the cystic fibrosis transmembrane conductance regulator protein.[40] On the other hand, the tripeptide TRH (pGlu–His–Pro–NH_2) was shown to be a hypothalamic releasing factor for the regulation of pituitary function.[41] A solid-phase Zincke reaction was used to prepare analogues of TRH having the central histidine replaced with a 1,4-dihydropyridine unit (such as **48**).[41] Compound **48** was expected to cross the hydrophobic blood–brain barrier (BBB) but to be trapped within the central nervous system upon oxidation to the hydrophilic pyridinium form.



A redox system (**50/51**) to affect brain delivery of γ-aminobutyric acid (GABA) derivatives and analogues was also developed.[26a,42] Zincke reaction of **41** with acetal **49** followed by dithionite reduction afforded the 1,4-dihydropyridine prodrug **50**, which was hydrolyzed and oxidized *in vivo* to the active GABA analogue **51**. The neutral and lipophilic 1,4-dihydropyridine **50** can penetrate the blood–brain barrier (BBB), whereas the oxidized pyridinium salt **51** is retained in the brain for an extended period and then eliminated.