UNNATURAL AMINO ACIDS

STEREOSELECTIVE ENZYMATIC SYNTHESIS

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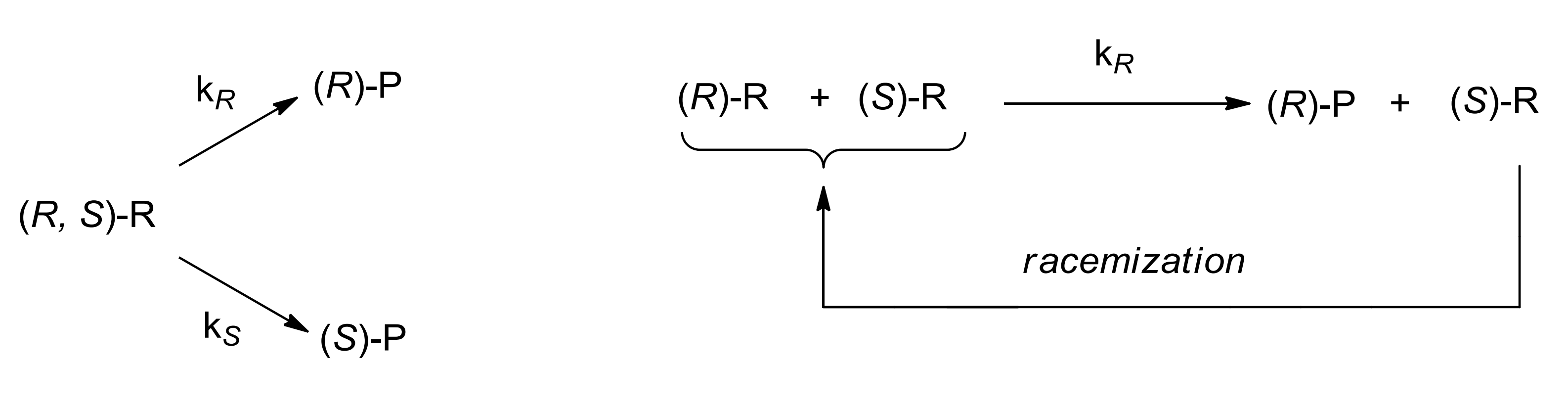
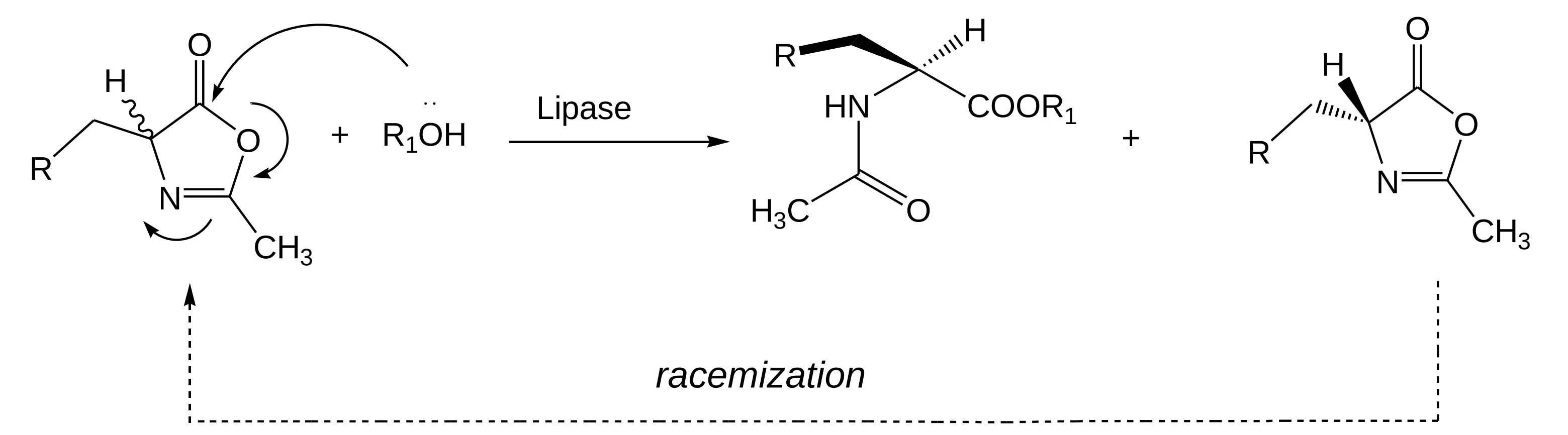
Introduction

Presently, an important direction in the area of organic and pharmaceutical chemistry consists in the synthesis of unnatural amino acids in homochiral form which proved to play an important part in drug design and synthesis of biologically and medically relevant molecules [1]. Moreover, aryl-thiophenes were found to be constituents of several important classes of pharmacologically active compounds, being associated with activities like lipoxygenase inhibitors and antiarrhythmics [2]. Thus, the synthesis of enantiopure aryl-thiophene alanines represents an attractive goal. For obtaining both enantiomerically enriched (*R*)- and (*S*)-5-aryl-2-thiophene alanines, biocatalytic approaches (enzymatic kinetic and dynamic kinetic resolutions) will be used (Scheme 1). It has been previously reported [3, 4] the efficient lipase-catalysed DKR of oxazolones as a key step in the synthesis of optically pure amino acids (Scheme 2).



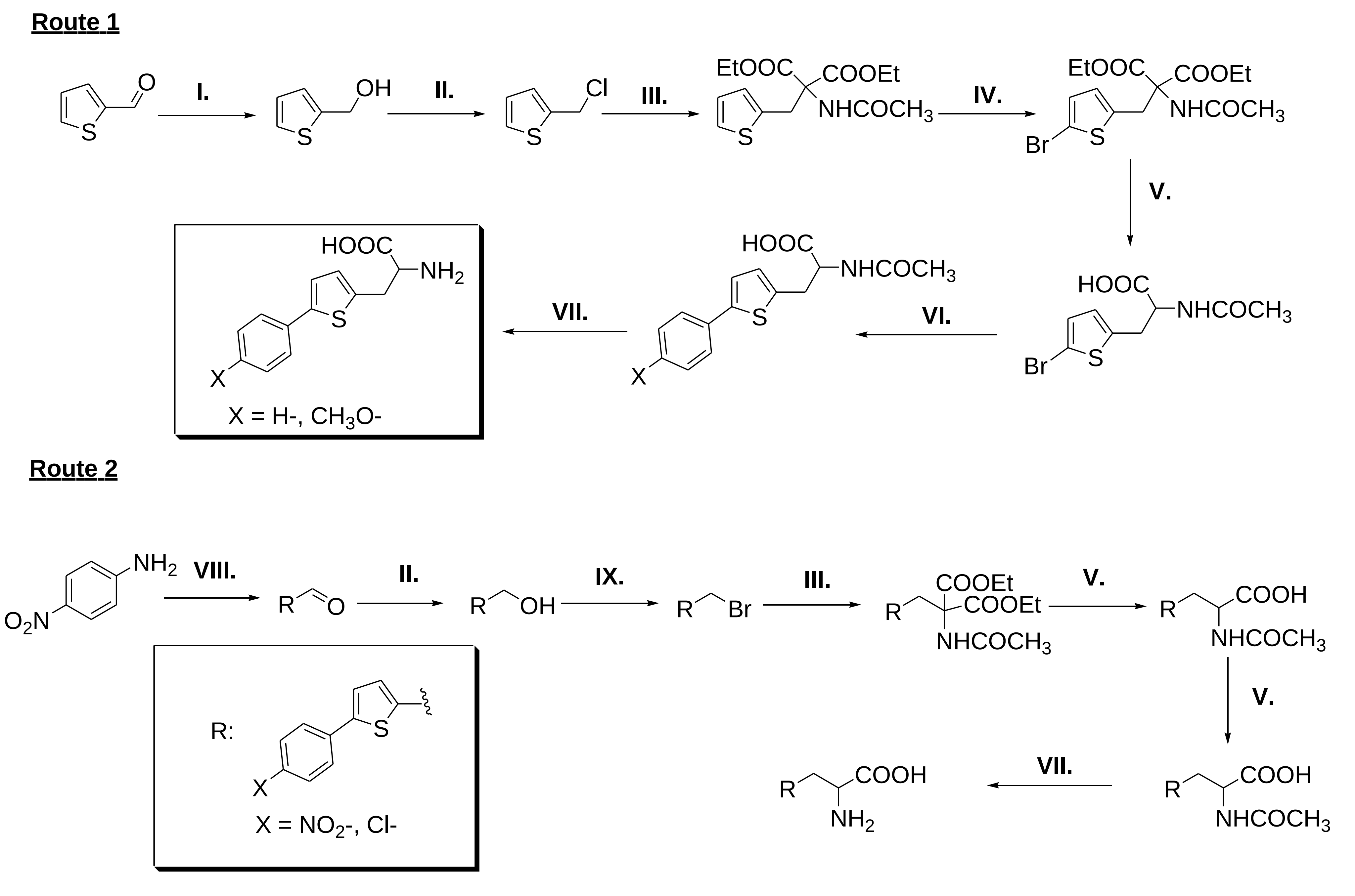
Scheme 1. Kinetic resolution vs. dynamic kinetic resolution



Scheme 2. Lipase mediated DKR of oxazolones

Experimental

The synthesis of four 5-aryl-2-thiophene alanines bearing one or no substituent in the *para* position of the phenyl ring was performed using two different approaches (Scheme 3). The *p*-methoxy-substituted and the unsubstituted derivatives were obtained through the Suzuki coupling method [5], which consists in the formation of a C-C bond between the corresponding aryl boronic acids and the 5-bromo-thiophene derivative (Route 1). For the synthesis of *p*-nitro- and *p*-chloro-substituted derivatives, the corresponding thiophenecarboxaldehydes used as starting materials were prepared by the Meerwein method [6] from the diazonium salts of the substituted anilines and the commercially available 2-thiophenecarboxaldehyde (Route 2).



I. $NaBH_4$, CH_3OH, r.t.; **II.** $SOCl_2$, benzotriazole/CH_2Cl_2; **III.** NaH, $CH_3CONH(CO_2Et)_2$, DMF, 60^oC; **IV.** NBS, $HClO_4/CCl_4$, r.t; **V.** a) 10% NaOH, reflux; b) toluene, reflux; **VI.** $XC_6H_4B(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$/toluene/ethanol, reflux; **VII.** 10% HCl, reflux; **VIII.** a) $NaNO_2$, HCl/ H_2O, 0-5^oC; b) thiophene-2-carbaldehyde, $CuCl_2$, acetone, 1 day, r.t; **XII.** NBS, PPh_3/CH_2Cl_2, r.t;

Scheme 3. Synthesis plane of 5-aryl-2-thiophene alanines

References

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