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# Efficient large (ca. 40 g) laboratory scale preparation of (*S*)- and (*R*)-valine *tert*-butyl esters

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**Abstract**—A large laboratory scale (ca. 40 g) method for the preparation of enantiomerically pure (*S*)- and (*R*)-valine *tert*-butyl esters has been developed. The method involves three steps: preparation of *N*-TFA-valines, preparation of valine *tert*-butyl esters using 2-methylpropene in dioxane in the presence of sulfuric acid, and isolation of the target compounds as the acetate derivative. The overall yield is up to 70% relative to the starting valine, ee being more than 98% (by HPLC). 

## 1. Introduction

At present we are witnesses of continuing growth in the production enantiopure compounds, which is caused by the demands of modern drug industry. However, not all of the experimental procedures can be extended to multi-gram processes and solving the problems associated with large scale preparations of enantiopure compounds sometimes requires the development of special approaches to provide the target products in a combination of high yields and high enantiomeric purities.

(*S*)- and (*R*)-Valine and their alkyl esters are commonly used as starting materials both in asymmetric synthesis,[1] and peptide and peptidomimetic synthesis.[2] *tert*-Butyl esters are of specific interest since the *tert*-butyl ester can be removed easily and selectively in acidic media, and amino acid *tert*-butyl esters are stable in the free base form to *N*-condensation reactions.

Though the protocols for amino acid *tert*-butyl esters are well documented,[3] problems arise during large scale preparation. Usually, *tert*-butyl esters are prepared starting from both *N*-protected (usually *N*-Cbz or *N*-Boc) and free amino acids. The known literature methods for preparation of *tert*-butyl esters consist of reaction of the free amino acid with 2-methylpropene in a mixture of 1,4-dioxane and sulfuric acid,[4] where the yield of the *tert*-butyl ester is dependant on the solubility of the amino acid in the dioxane–$H_2SO_4$ mixture. In the case of valine the yield ranged from 45[4a] to 65%.[4b,4d]

Synthesis of amino *tert*-butyl esters also could be performed by reaction of the free amino acid with *tert*-BuOAc in the presence of perchloric acid.[5] We carried out the preparation of valine *tert*-butyl ester as described in previously,[5c] the yield being 70%. It should be noted that although the yield from this method is rather high, applying this procedure to the large scale production of valine *tert*-butyl ester is not promising due to the high volume of the reaction mixture ($\sim$128 mL of *tert*-BuOAc per 1 g of valine), which requires a large-scale process with 50 g valine to be carried out in a 10 L reactor.

Some literature methods for preparing amino *tert*-butyl esters describe the condensation of *N*-protected amino acids with *tert*-BuOH in the presence of various carbodiimides and 4-dimethylaminopyridine as a catalyst followed by removal of protecting group.[6] However, these methods require an additional protecting group removal step.

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## 2. Results and discussion

Herein, we suggest the trifluoroacetate ester (TFA) as a useful protecting group: It can be removed smoothly by alkali treatment of the reaction mixture after interaction with 2-methylpropene. The use of the TFA group makes it possible to avoid the problems related to the poor solubility of valine in dioxane–$H_2SO_4$ mixture during esterification with 2-methylpropene, and therefore to drastically decrease the reactor volume. Davidovich et al. described the preparation of glycine *tert*-butyl ester by the reaction of *N*-TFA-glycine with 2-methylpropene in the presence of $H_2SO_4$ in overall yield of about 76%.[7] However, in the preparation of valine *tert*-butyl esters using this approach, the risk of enantiomeric purity loss exists due to the possibility of racemization at any of the steps.

The (*S*)- and (*R*)-*N*-TFA-valines **2** were obtained from free valines **1** according to the published procedure[8] in 84–90% yield. Esterification of *N*-TFA-valines by 2-methylpropene was carried out in dioxane–$H_2SO_4$ (10:1 v/v) while shaking the reaction mixture in a glass pressure bottle during 70–80 h at room temperature. Then the cooled reaction mixture was treated with 2N NaOH and stirred for 2 h to remove the *N*-TFA protecting group (with yields of ca. 95%). Based on the $^1$H NMR spectra we have observed that the products isolated from reaction mixture contain from 5 to 20 mass% of the solvents (1,4-dioxane and hexane) as impurities. In our hands, further evaporation of the solvents and drying under reduced pressure resulted in considerable loss of the product due to its high volatility. Therefore, purification was performed by isolation of the *tert*-butyl esters **4** as the acetates **5**[5c] in 84–88% yield. The overall yield of the target products in large-scale preparation (starting from 30–50 g of valine) was up to 70% (Scheme 1).

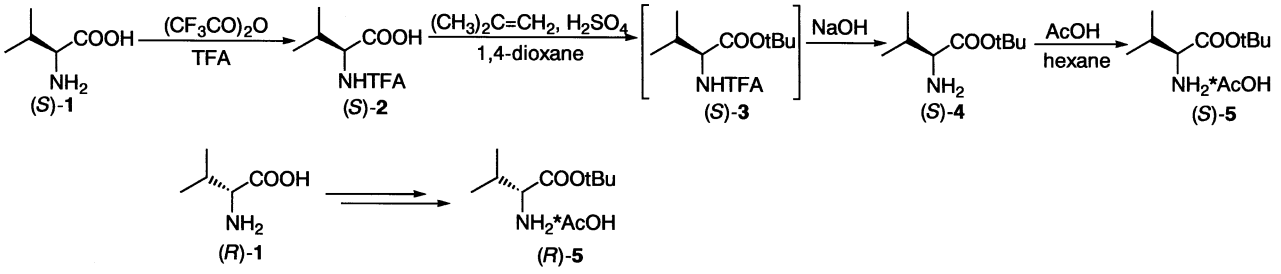
The enantiomeric purity of the obtained acetates could be determined from the specific rotation,[5c] but actually this method is not reliable. We therefore applied an HPLC technique with pre-column derivatization of acetates **5** with (*S*)-naproxen chloride[9] (Scheme 2).

Previously, we have shown that acylation of sterically hindered racemic amines by (*S*)-naproxen acyl chloride is accompanied by kinetic resolution.[10] So, the enantiomeric purity results from the HPLC analysis could be misjudged if the acylation is not complete. We performed HPLC determination of de values of amides **6** depending on the duration of the derivatization process. At the initial concentration of acetate **5** $C_0 = 0.2$ M, the reaction proceeds completely in 15 min and the ratio of (*S*,*S*)- and (*S*,*R*)-diastereoisomers **6** remains constant during 24 h. The enantiomeric excess (ee) of the synthesized acetates **5** was more than 98%.

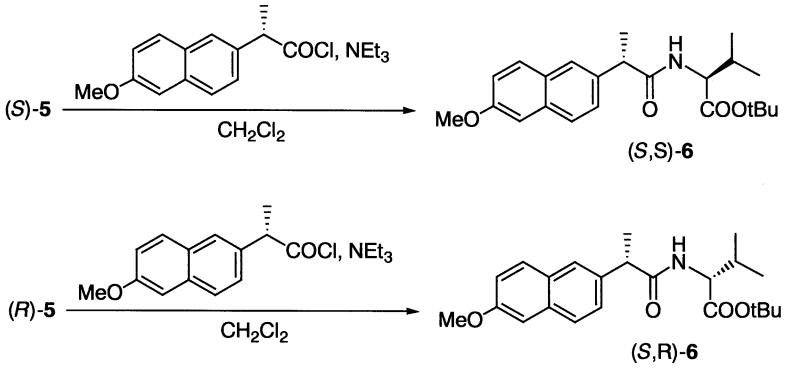
## 3. Experimental

### 3.1. General

Solvents were purified according to standard procedures. Routine monitoring of reactions was carried out using Silufol UV 254 (Kavalier) TLC aluminum plated silica gel. Melting points were determined on a Boetius melting point apparatus and are uncorrected. $^1$H NMR




**Scheme 1.** Synthesis of (*S*)- and (*R*)-valine *tert*-butyl esters.




**Scheme 2.** Derivatization of (*S*)- and (*R*)-valine *tert*-butyl ester acetates by (*S*)-naproxen chloride.

spectra were measured on a Bruker DRX 400 spectrometer. All signals are given in ppm ($\delta$) with TMS as an internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The de values of amides **6** were measured by HPLC on a Merck–Hitachi chromatograph with L-4000A Intelligent Pump, L-4000A UV Detector, and D-2500A Chromato-Integrator [Hibar Pre-packed Column RT250-4, Lichrosorb Si-60]; mobile phase: hexane: *i*-PrOH = 80:1, flow rate 1 mL/min; UV detection 230 nm; $\tau_{SS}$ 8.6 min, $\tau_{SR}$ 10.1 min.

2-Methylpropene was obtained according to the literature procedure[11] and was used as such in the subsequent step. (*S*)- and (*R*)-Valines were purchased from Lancaster Synthesis (UK). (*S*)-2-(6-Methoxynaphthyl-2)propionyl chloride [(*S*)-naproxen acyl chloride] was prepared from commercially available (*S*)-(+)-naproxen and oxalyl chloride.[12]

### 3.2. *N*-Trifluorocetyl (*S*)-valine, 2

*N*-TFA-(*S*)-Valine **2** was prepared from (*S*)-valine (31.8 g, 0.271 mol), trifluoroacetic anhydride and TFA as previously described in literature[12] (51.9 g, 90%). It was obtained as white crystals. Mp 84–86°C; $[\alpha]_D^{20}$ −15 (*c* 2, $H_2O$); $^1$H NMR ($CDCl_3$): 1.01 (d, $J$ = 7.0 Hz, 3H, $CH_3$), 1.03 (d, $J$ = 7.0 Hz, 3H, $CH_3$), 2.35 (sept d, $J$ = 6.9 and 4.8 Hz, 1H, CH), 4.64 (dd, $J$ = 8.6 and 4.5 Hz, 1H, $C_\alpha$H), 6.83 (br. d, $J$ = 8.3 Hz, 1H, NH), 8.29 (br. s, COOH). Anal. calcd for $C_7H_{10}F_3NO_3$: C, 39.44; H, 4.73; N, 6.57; F, 26.74. Found: C, 39.61; H, 4.77; N, 6.68; F, 26.70%.

### 3.3. *N*-Trifluorocetyl (*R*)-valine, 2

Following the above procedure, and starting with (*R*)-valine (35.8 g, 0.306 mol) the title compound was obtained as white crystals (55.4 g, 85%). Mp 85–87°C; $[\alpha]_D^{20}$ +15 (*c* 2, $H_2O$). Anal. calcd for $C_7H_{10}F_3NO_3$: C, 39.44; H, 4.73; N, 6.57; F, 26.74. Found: C, 39.71; H, 4.87; N, 6.67; F, 26.77%. $^1$H NMR see (*S*)-**2**.

### 3.4. (*S*)-Valine *tert*-butyl ester, 4

A solution of *N*-TFA-(*S*)-valine **2** (50 g, 0.234 mol) in a mixture of dry 1,4-dioxane (250 mL) and concentrated $H_2SO_4$ (25 mL) was placed in a 750 mL glass pressure bottle and cooled to −5 to 10°C, then freshly prepared 2-methylpropene (340 mL) was added to the reaction mixture. The reaction bottle was tightly sealed and then shaken in a shaking machine at rt for 70 h. The bottle was cooled before opening and cold 2N NaOH (630 mL) was carefully added to the reaction mixture under stirring. The mixture was stirred for 2 h at rt. The product was extracted with hexane (3×125 mL). The combined hexane solutions were dried ($Na_2SO_4$). Evaporation under reduced pressure (the bath temperature was maintained at about 30°C) followed by drying to constant weight at rt gave the title compound as a light yellow oil (39.8 g, 90%). The product contains dioxane (8.3%) according to $^1$H NMR spectrum. $^1$H NMR ($CDCl_3$): 0.90 (d, $J$ = 6.7 Hz, 3H, $CH_3$,), 0.97 (d, $J$ = 7.1 Hz, 3H, $CH_3$,), 1.47 (s, 9H, $(CH_3)_3$), 2.00 (sept d, $J$ = 6.9 and 4.9 Hz, 1H, CH,), 3.17 (d, $J$ = 4.8 Hz, 1H, $C_\alpha$H).

### 3.5. (*R*)-Valine *tert*-butyl ester, 4

Following the above procedure, and starting with *N*-TFA-(*R*)-valine **2** (50.0 g, 0.234 mol) the title compound was obtained as a light yellow oil (43.8 g, 95%). Dioxane content according to $^1$H NMR spectrum was 12%. For $^1$H NMR, see: (*S*)-**4** (Section 3.4).

### 3.6. (*S*)-Valine *tert*-butyl ester acetate, 5

To a solution of *tert*-butyl ester (*S*)-**4** (39.8 g, 0.211 mol) in hexane (200 mL) was added glacial AcOH (12.1 mL, 0.211 mol). The acetate was precipitated almost immediately. After stirring overnight at rt the precipitate was filtered off, and washed with hexane (2×15 mL). Drying the product gave (*S*)-**5** as colorless crystals (41.8 g, 85%). Mp 88–90°C; $[\alpha]_D^{20}$ +20.2 (*c* 2, EtOH); $^1$H NMR ($CDCl_3$): 0.92 (d, $J$ = 6.7 Hz, 3H, $CH_3$), 0.99 (d, $J$ = 6.9 Hz, 3H, $CH_3$), 1.48 (s, (9H, $(CH_3)_3$), 2.05 (s, 3H, $CH_3COO^-$), 2.06 (sept d, $J$ = 6.8 and 4.6 Hz, 1H, CH), 3.28 (d, $J$ = 4.7 Hz, 1H, CαH), 4.75 (br. s, 3H, $NH_3^+$). Anal. calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.68; H, 9.93; N, 5.98%. Enantiomeric purity: 98.1% (HPLC, de after pre-column derivatization with (*S*)-naproxen acyl chloride).

### 3.7. (*R*)-Valine *tert*-butyl ester acetate, 5

Following the above procedure, and starting with *tert*-butyl ester (*R*)-**4** (43.8 g, 0.222 mol) the title compound (45.6 g, 88%) was obtained as colorless crystals. Mp 90–91°C; $[\alpha]_D^{20}$ −20.4 (*c* 2, EtOH). Anal. calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.62; H, 9.95; N, 6.00%. Enantiomeric purity: 98.8% (HPLC, de after pre-column derivatization with (*S*)-naproxen acyl chloride). For $^1$H NMR, see: (*S*)-**5** (Section 3.6).

### 3.8. Derivatization with (*S*)-naproxen acyl chloride. General procedure

To a solution of acetate (*S*)-**5** or (*R*)-**5** (117 mg, 0.5 mmol) and pyridine (0.080 mL, 1.0 mmol) in dry dichloromethane (2.5 mL) was added a solution of (*S*)-naproxen acyl chloride (124 mg, 0.5 mmol) in the same solvent (2.5 mL). The reaction mixture was then stirred at rt for 15 min, filtered through silica gel and analyzed by HPLC.

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