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AN ENANTIOSELECTIVE SYNTHESIS OF (2S,3S)- AND (2R,3S)-3-HYDROXYLEUCINE

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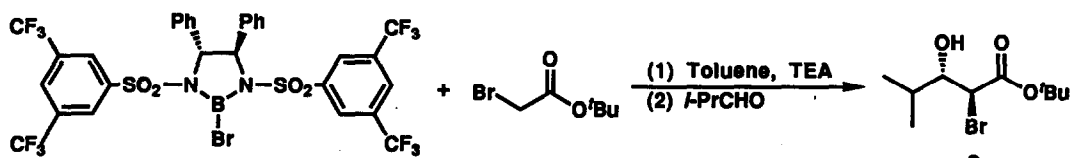
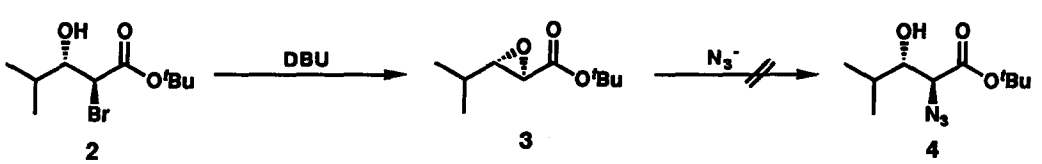
Summary : α-Bromo β-hydroxy ester 2 was prepared in a preparative scale by a 96 : 4 enantioselective aldol reaction of t-butyl bromoacetate with isobutyraldehyde and converted efficiently to either (2S,3S)- or (2R,3S)-3-hydroxyleucine (7 or 11).

In connection with the synthesis of neurologically active natural products, we required multigram quantities of (*2S,3S*)- and (*2R,3S*)-3-hyroxyleucines.[1] In this paper, we report the application of recently described methodology[2] to this problem and improvements for larger scale reactions.

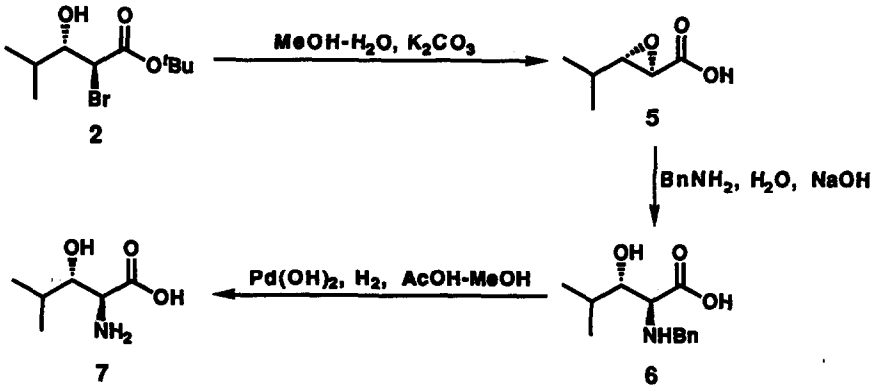
The reaction of *t*-butyl bromoacetate with (*R,R*)-bromoborane **1** (R_2^*BBr) and triethylamine in toluene at -78 °C for 5 h produced the (*Z*)-boron enolate (OBR_2^* and Br are *trans* to each other) stereoselectively.[3] Addition of isobutyraldehyde (0.9 equiv) and reaction at -78 °C for 5 h followed by quenching with CH_3OH at -78 °C, extractive isolation, recovery of the *bis*-sulfonamide precursor of bromoborane **1** (85 %) and silica gel purification afforded α–bromo β-hydroxy ester **2** in excellent yield (90 %), ee (92 %), and diastereoselectivity (*anti* : *syn* = 98 : 2)[4] in a 13 mmol scale reaction.



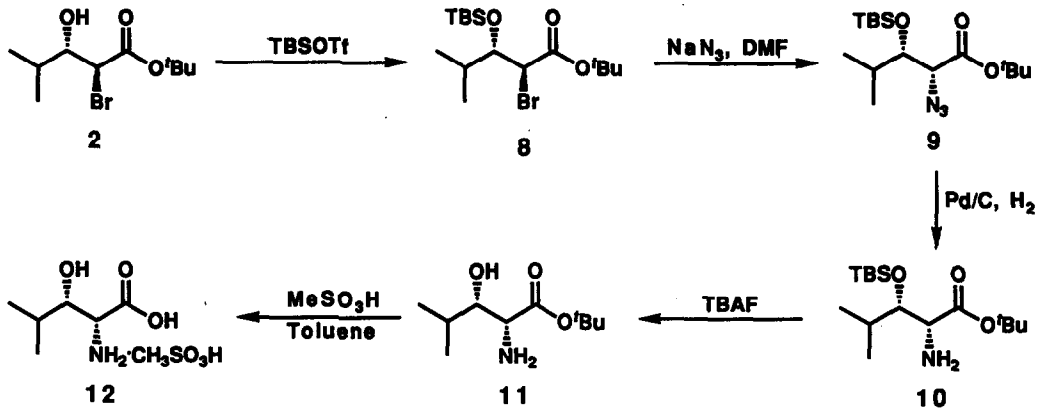
The α-bromo β-hydroxy ester **2** was readily converted to the α,β-epoxy ester **3** (DBU, CH_2Cl_2, rt, 66 %). However, attempts to displace epoxide by azide at the α-position to produce the α-azido β-hydroxy ester **4** were unsuccessful under a variety of reaction conditions.[5]



The transformation of the α-bromo β-hydroxy ester **2** into the α,β-epoxy acid **5** (glycidic acid) was readily and quantitatively effected by reaction with 3 equiv of K_2CO_3 in CH_3OH-H_2O (60 : 1) at rt for 9 h. Position-selective attack at the α-position of the epoxide **5** by benzylamine[1c,6] ($BnNH_2$-H_2O, NaOH, reflux, 2 h) proceeded smoothly to give the N-benzyl amino acid **6** (60 %); The NMR spectrum of the product showed it to be a single compound, free of the position isomer or the epimer at C-2. Hydrogenolysis of the N-benzyl group in **6** using Pearlman's catalyst[7] (20 % $Pd(OH)_2$ on C, 40 psi of H_2, AcOH-MeOH, rt, 10 h) afforded 94 % of (*2S,3S*)-3-hydroxyleucine (**7**)[8] after filtration and precipitation of the product with MeOH.



The conversion of the α-bromo β-hydroxy ester **2** into (*2R,3S*)-hydoxyleucine *t*-butyl ester (**11**) was accomplished in 4 steps. Protection of the β-hydroxy group in **2** as the *t*-butyldimethylsilyl ether (*t*-butyldimethylsilyl triflate and 2,6-lutidine in CH_2Cl_2 at 0 °C for 1 h, quantitative) and reaction of **8** with 5 equiv. of sodium azide in dimethylformamide at 65 °C for 15 h afforded 95 % of the α-azido β-silyloxy ester **9**. The reaction of the bromide **2** and sodium azide without protection of the β-hydroxy group gave not only the desired



α-azido β-hydroxy ester but also the diastereomer at C-2 and the epoxide **3**. Reduction of **9** (Pd/C, 40 psi of H_2, THF, rt, 85 %) and deprotection of **10** (TBAF, THF, rt, 1 hr) produced (*2R,3S*)-3-hydroxyleucine *t*-butyl ester (**11**), $[\alpha]_D^{20}$= - 11.6° (c 0.7, $CHCl_3$), in 90 % yield. Refluxing **11** in toluene with 1 equiv of methanesulfonic acid for 1 h afforded (*2S,3S*)-3-hydroxyleucine **12** as its amine salt form.

In conclusion, the α-bromo β-hydroxy ester **2** can be conveniently prepared in multigram quantities and serves as a common intermediate for the synthesis of (*2S,3S*)- and (*2R,3S*)-3-hydroxyleucine (**7** and **11**). A detailed experimental procedure, which includes key modifications[9] of the original process, follows.

***t*-Butyl (*2S,3S*)-(-)-2-Bromo-3-hydroxy-4-methylpentanoate (2).** To a 500 ml flame-dried and nitrogen-filled round bottomed flask was added (*R,R*)-bis{3,5-di(trifluoromethyl)benzenesulfonyl}-1.2-diamino-1,2-diphenylethane (precursor of **1**; 10 g, 13.1 mmol) and the flask was closed with dry septum. The ligand was dried further at 65 °C for 1 h under high vacuum (ca. 1 mm Hg; vacuum pump) and the flask was filled with nitrogen and then cooled to 23 °C. Freshly distilled dry methylene chloride (150 ml) was added and the homogeneous solution was treated with boron tribromide (2.0 M solution in methylene chloride, 10 ml, 20 mmol) at -78 °C. The reaction mixture was warmed slowly and stirred at ambient temperature for 18 h. Solvent was evaporated under reduced pressure (ca. 30 mm Hg) at 40 °C using calcium chloride and sodium hydroxide tubes in the line in order to prevent flow of moisture into the reaction flask. The vacuum was applied at 40 °C for additional 5 min after all the solvent was evaporated. Dry methylene chloride (30 ml) was added and evaporated as above. Low vacuum (ca. 30 mm Hg) and high vacuum (ca. 1 mm Hg) were applied to the resulting bromoborane **1** at 40 °C for 10 min each to remove any trace of HBr and especially boron tribromide (bp 90 °C) and then the reaction flask was flushed with nitrogen. Evacuation to 1 mm Hg and flushing with nitrogen were repeated 5 times. Toluene (300 ml) was added and the resulting mixture was warmed to effect complete solution. The homogeneous solution of bromoborane **1** was cooled to -78 °C, triethylamine (2.007 ml, 14.4 mmol) was added dropwise at - 78 °C and the mixture was stirred at -78 °C for 5 min. *t*-Butyl bromoacetate (2.008 ml, 12.4 mmol) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 5 h. Isobutyraldehyde (1.070 ml, 11.8 mmol) in toluene (10 ml; additional 3 ml for washing) was added at -78 °C down along the wall of the flask. The mixture was allowed to proceed at -78 °C for 5 h and then quenched with methanol (5 ml) at -78 °C. The mixture was diluted with ether (300 ml) and the organic layer was washed with brine (150 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 38 °C. The crude product was treated with methylene chloride (5 ml) and petroleum ether (100 ml), the resulting white suspension was stirred at rt for 1 h, and the white solid was filtered and washed with petroleum ether (100 ml) to afford the starting *bis*-sulfonamide (8.9 g, 89 % recovery). The filtrate was evaporated and the residue was separated by sgc (hexane in the first few tubes and then hexane : ether = 5 : 1) to yield pure bromo alcohol **2** (2.83 g, 90 %; *anti* : *syn* = 98 : 2; 92 % ee). $[\alpha]_D^{20}$ = - 10.9° (c 2.62, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (d, *J*=7.9 Hz, 1H), 3.78 (ddd, 1H), 2.66 (d, *J*=6.6 Hz, 1H), 2.13-2.07 (m, 1H), 1.50 (s, 9H), 1.01(d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2, 76.7, 47.2, 29.9, 27.8, 19.9, 15.5. IR (neat, cm^{-1}) : 3513, 2968, 2933, 1723. R_f : 0.49 (17% ethyl acetate in hexane).[10]

References and Notes

1. For previous asymmetric syntheses of α-amino β-hydroxy acids, see; (a) Schollkopf, U.; Groth, U.; Gull, M.-R.; Nozulak, J. *Liebigs Ann. Chem.* **1983**, 1133-1151 (b) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637-6640 (c) Caldwell, C. G.; Bondy, S. S. *Synth.* **1990**, 34-36 (d) Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067-1078 and references therein.
2. Corey, E. J.; Choi, S. *Tetrahedron Lett.* **1991**, *32*, 2857-2860.
3. Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976-4977.
4. (a) The absolute configuration was assumed from the results in ref. 2 and confirmed later by comparison of the optical rotation with that reported for the final product (*2S,3S*)-3-hydroxyleucine (**7**) (b) The enantiomeric purity (ee) was determined by conversion to MTPA ester (Dale, J.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512) followed by ^{1}H NMR analysis at 500 MHz in $CDCl_3$ solution. (c) The diastereoselectivity was determined by ^{1}H NMR analysis of the crude product at 500 MHz in $CDCl_3$ solution.
5. Several reaction conditions were tried : (a) NaN_3 in DMF, AcOH, or CF_3CO_2H (b) NaN_3-*i*-$PrNEt_2$·HCl in DMF. Generally, the starting material **3** remained unchanged when the reaction temperature was 70 °C and decomposed when it was heated to 90 °C-100 °C. Interestingly, reaction of **3** with benzylamine, which was successful with the corresponding acid **5**, failed to give the desired product.
6. For the related reactions, see; (a) Genet, J. P.; Durand, J. O.; Savignac, M.; Pons, D. *Tetrahedron Lett.* **1992**, *33*, 2497-2500 (b) Liwschitz, Y.; Rabinsohn,Y.; Perera, D. *J. Chem. Soc.* **1962**, 1116-1119 (c) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560-1563.
7. Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
8. Optical rotation and mp for compound **7** : $[\alpha]_D^{20} = +30°$ (c 0.57, 1N aq HCl) {Lit. $[\alpha]_D^{20} = +35.0°$ (c 0.41, 1N aq HCl)}, mp 219-224 °C (Lit. mp 218-222 °C); Sheehan, J. C.; Maeda, K.; Sen, A. K.; Stock, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1303-1305.
9. This new experimental procedure involves the use of toluene as solvent which gives comparable results in yield, ee, and diastereoselectivity with a minimum volume of solvent. Although bromoborane **1** is more soluble in CH_2Cl_2 than in toluene, the ee of the aldol product **2** was not acceptable (70 % ee). (2) In the original procedure, the ester was added to bromoborane **1** and then triethylamine was introduced later. The reverse order of addition which is used in this experiment is more reliable since acid sensitive esters can be cleaved by bromoborane **1**.
10. This research was assisted financially by a grant from National Institutes of Health.

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