SIMPLE HETEROCYCLE, 2-OXAZOLONE, AS VERSATILE BUILDING BLOCK FOR 2-AMINO ALCOHOLS. CHIRAL SYNTHESIS OF POLYHALOTHREONINES

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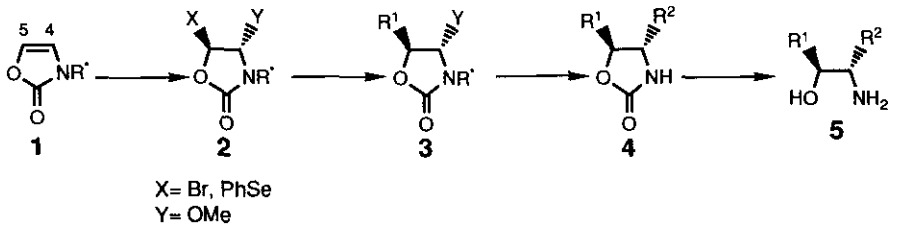
Abstract - Smooth radical-initiated addition of CCl_4 and CCl_3Br to 3-[(1*S*)-ketopinyl]-2-oxazolone gives a 1 : 1 mixture of readily separable (4*S*, 5*R*)- and (4*R*, 5*S*)-4-halogeno-5-trichloromethyl-2-oxazolidinone derivatives, which serve for facile preparation of polychlorothreonines including 4,4-dichloro-2-amino-3-hydroxybutyric acid, known as antimicrobial armentomycin analog.

There have appeared a number of strategies for stereocontrolled construction of the 2-amino alcohol skeletons found in bioactive natural products such as peptidic enzyme inhibitors and amino sugar antibiotics.[1] Most of the methods appear of limited use in terms of synthetic versatility. We previously reported a promising methodology for versatile synthesis of 2-amino alcohols to utilize the simple heterocycle, 2-oxazolone (**1**), as a building block, which involves stepwise conversion of the chiral synthon (**2**) functionalized by easily replaceable groups (X=Br, PhSe, Y=OMe) at both 4- and 5-positions [2] (Scheme 1).

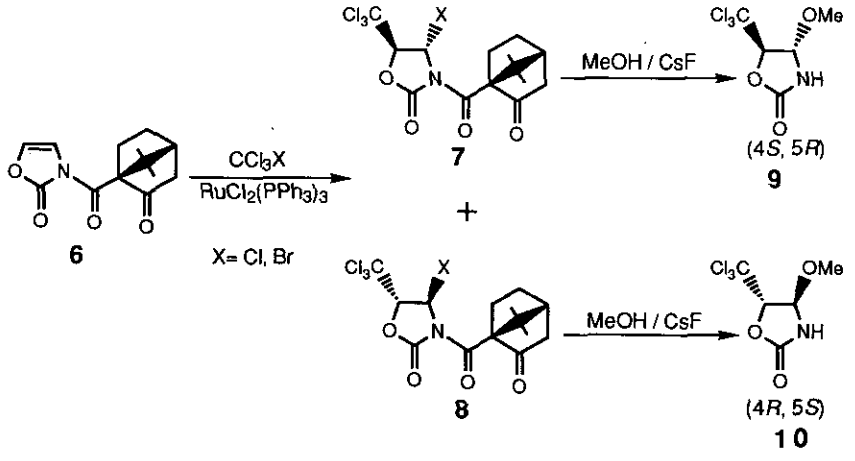


Scheme 1.

* Dedicated to Prof. Edward C. Taylor on the occasion of his 70 th birthday.

This paper describes an alternative route for chiral preparation of polychlorothreonines which involves direct introduction of carbon substituents at the 5-position to give the chiron (**3**) by the use of radical addition of polyhalomethanes to the 2-oxazolones. The method permits chiral facile synthesis of a variety of halogenated 2-amino alcohols, which occasionally act as antagonists or agonists of medicinal interest. Of the halogeno-α-amino acids isolated from natural sources, (2*S*)-2-amino-4,4-dichlorobutanoic acid is known as armentomycin with interesting growth inhibitory activity against certain microorganisms.[3] The 3-hydroxylated analog, *threo*-2-amino-4,4-dichloro-3-hydroxybutyric acid, was proved to exhibit a stronger growth inhibition against *Pseudomonas aeruginosa* than armentomycin itself.[4]

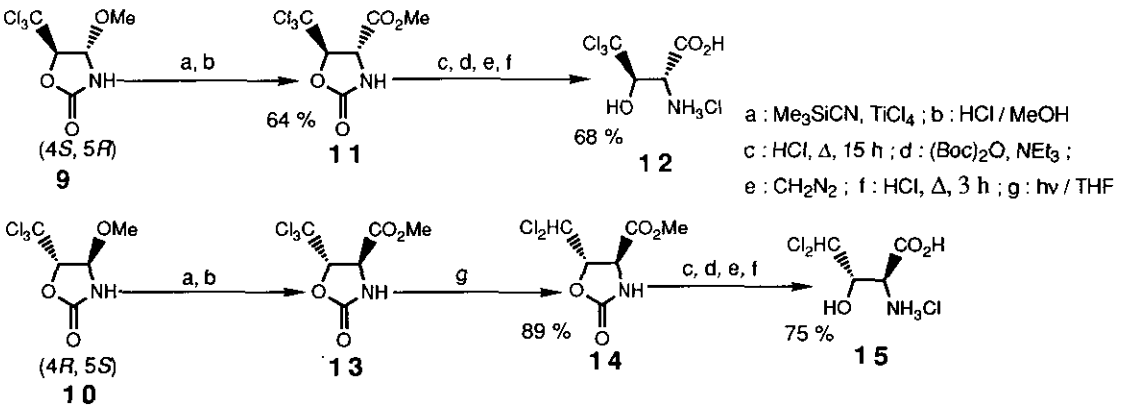
In contrast with the radical addition of carbon tetrachloride to *N*-acetyl-2-oxazolone in the presence of benzoyl peroxide which yielded a mixture of lower telomers,[5] the 1 : 1 *trans*-adducts were exclusively formed without any *regio*-isomers by the use of dichlorobis(triphenylphosphine)ruthenium (II) [$RuCl_2(PPh_3)_3$] as a catalyst. The *trans*-stereochemistry of the adducts was based on small coupling constants, $J_{4,5} < 1.5$ Hz. This reaction was applied to 3-[(1*S*)-ketopinyl]-2-oxazolone (**6**), readily obtainable from diphenylphosphoryl oxa-zolone [6] (DPPOx) and (1*S*)-ketopinic acid,[7] to give the 1 : 1 mixture of (4*S*, 5*R*)- and (4*R*, 5*S*)-4-chloro-5-trichloro-methyl-2-oxazolidinone derivatives (**7** and **8**, X=Cl) in good yield. These diastereomers were easily separated by column chromatography on silica gel. Similarly, bromotrichloromethane gave the adducts (**7** and **8**, X=Br) more smoothly as a mixture of readily separable diastereomers. Polyhalomethyl compounds such as trichloroacetonitrile and methyl trichloroacetate also reacted with 3-[(1*S*)-ketopinyl]-2-oxazolone (**6**) only sluggishly to give the adducts in *regio*- and *trans*-selective addition mode but with poor diastereoselectivity as well.



Scheme 2.

These adducts (**7** and **8**) reacted with boiling MeOH in the presence of CsF to yield (4*S*, 5*R*)- and (4*R*, 5*S*)-4-methoxy-5-trichloromethyl-2-oxazolidinones (**9** and **10**), respectively, accompanied by smooth recovery of the sterically congested ketopinyl moiety as methyl ester. Both enantiomers of the *trans*-4-methoxy derivatives (**9** and **10**), thus obtained in optically pure form, serve as good synthetic intermediates for chiral halogenated 2-amino alcohols, since a reliable method is available for direct substitution of 4-methoxy groups by a wide variety of alkyls, alkenyls and aryls.[8]

The 4-methoxy-5-trichloromethyl-2-oxazolones (**9** and **10**) smoothly reacted with trimethylsilyl cyanide in the presence of $TiCl_4$ to yield 4-cyano-5-trichloromethyl derivatives which were converted without purification to *trans*-4-methoxycarbonyl-5-trichloromethyl derivatives (**11** and **13**) by hydrogen chloride in MeOH with full retention of configurations.



Scheme 3.

(2*R*, 3*R*)-Trichlorothreonine (**12**) was readily obtained by hydrolytic cleavage of the 2-oxazolidinone (**11**). Trichloromethyl groups of **11** and **13** were easily reduced to dichloromethyl groups by uv irradiation in tetrahydrofuran. Compound (**14**), thus formed, was hydrolyzed with hydrochloric acid to the (2*S*, 3*S*)-4,4-dichlorothreonine hydrochloride (**15**) as an armentomycin analog. The optical purity was shown above 99 % e.e. by the Mosher's method.[9] The dichlorothreonine (**15**) was reductively converted to (2*S*, 3*R*)-threonine by catalytic hydrogenation, providing unambiguous evidence for the configuration.

The present route may be widely applicable to the facile synthesis of halogenated 2-amino alcohols including the fluoro derivatives of biological interest.

EXPERIMENTAL

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded in $CDCl_3$, unless other specified, at 400 MHz and 60 MHz on JEOL GX400 and Hitachi R-24B instruments, respectively, with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-370 polarimeter. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). All the solvents were distilled before use ; THF over Na / benzophenone, CH_2Cl_2 and benzene over CaH_2, CCl_4 over P_2O_5 and MeOH over MeONa.

4-Chloro-3-[(1*S*)-ketopinyl]-5-trichloromethyl-2-oxazolidinones (7 and 8, X=Cl).

To a solution of 3-[(1*S*)-ketopinyl]-2-oxazolone (**6**) (1.53 g, 6.1 mmol) in CCl_4 (8.3 ml) was added $RuCl_2(PPh_3)_3$ (466 mg, 0.49 mmol) and the whole was refluxed for 7 days under argon atmosphere. Concentration of the mixture *in vacuo* followed by silica gel column chromatography (hexane : CH_2Cl_2 = 3 : 2) gave (4*S*, 5*R*)-4-chloro-5-trichloromethyl-derivative (**7**, lower polarity) (984 mg, 40 %) and the (4*R*, 5*S*)-isomer (**8**, higher polarity) (1.01 g, 41 %) both as colorless crystals.

(4*S*, 5*R*)-Isomer (**7**, X=Cl) : mp 183-186 °C (hexane- CH_2Cl_2) ; $[\alpha]_D^{20}$ +77.3 ° (c 1.0, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ 1.136 (s, 3H), 1.256 (s, 3H), 1.53-1.61 (m, 1H), 2.01-2.18 (m, 4H), 2.43 (ddd, 1H, J=2.4 Hz, 4.9 Hz, 18.3 Hz), 2.98-3.06 (m, 1H), 5.13 (d, 1H, J=1.5 Hz), 6.43 (d, 1H, J=1.5 Hz) ; Anal. Calcd for $C_{14}H_{15}NO_4Cl_4$: C, 41.71 ; H, 3.75 ; N, 3.48. Found : C, 41.58 ; H, 3.71 ; N, 3.37.

(4*R*, 5*S*)-Isomer (**8**, X=Cl) : mp 180-183 °C (hexane- CH_2Cl_2) ; $[\alpha]_D^{26}$ -17.0 ° (c 1.0, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ 1.186 (s, 3H), 1.230 (s, 3H), 1.51-1.55 (m, 1H), 2.05-2.15 (m, 4H), 2.48-2.55 (m, 1H), 2.77-2.81 (m, 1H), 5.16 (d, 1H, J=1.3 Hz), 6.39 (d, 1H, J=1.3 Hz) ; Anal. Calcd for $C_{14}H_{15}NO_4Cl_4$: C, 41.71 ; H, 3.75 ; N, 3.48. Found : C, 41.75 ; H, 3.81 ; N, 3.48.

4-Bromo-3-[(1*S*)-ketopinyl]-5-trichloromethyl-2-oxazolidinones (7 and 8, X=Br).

In the same manner as above, a solution of 3-[(1*S*)-ketopinyl]-2-oxazolone (**6**) (6.8 g, 27.3 mmol) and $RuCl_2(PPh_3)_3$ (1.0 g, 1.0 mmol) in bromotrichloromethane (27 ml, 274 mmol) and benzene (5 ml) was heated at 105 °C for 36 h to give (4*S*, 5*R*)-4-bromo-5-trichloromethyl-derivative (**7**, X=Br) (4.75 g, 39 %) and the (4*R*, 5*S*)-isomer (**8**, X=Br) (4.75 g, 39 %) as colorless crystals.

(4*S*, 5*R*)-Isomer (**7**, X=Br) : mp 188-191 °C (hexane- CH_2Cl_2) ; $[\alpha]_D^{20}$ +112.8 ° (c 1.1, $CHCl_3$) ; ^{1}H-nmr (400MHz) δ 1.136 (s, 3H), 1.257 (s, 3H), 1.53-1.57 (m, 1H), 1.96-2.05 (m, 4H), 2.43 (dd, 1H, J=4 Hz,

18.3 Hz), 3.01 (m, 1H), 5.30 (d, 1H, J=1.3 Hz), 6.51 (d, 1H, J=1.3 Hz) ; Anal. Calcd for $C_{14}H_{15}NO_4Cl_3Br$: C, 37.58 ; H, 3.35 ; N, 3.13. Found : C, 37.77 ; H, 3.41 ; N, 2.87.

(4*R*, 5*S*)-Isomer (**8**, X=Br) : mp 182-185 °C (hexane- CH_2Cl_2) ; $[\alpha]_D^{26}$ -40.4 ° (c 1.1, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ 1.185 (s, 3H), 1.189 (s, 3H), 1.51-1.55 (m, 1H), 2.02-2.11 (m, 4H), 2.48-2.54 (m, 1H), 2.75 (m, 1H), 5.33 (d, 1H, J=1.5 Hz), 6.46 (d, 1H, J=1.5 Hz) ; Anal. Calcd for $C_{14}H_{15}NO_4Cl_3Br$: C, 37.58 ; H, 3.35 ; N, 3.13. Found : C, 37.85 ; H, 3.34 ; N, 2.88.

(4*S*, 5*R*)-4-Methoxy-5-trichloromethyl-2-oxazolidinone (9).

a) A solution of (4*S*, 5*R*)-4-chloro-3-[(1*S*)-ketopinyl]-5-trichloromethyl-2-oxazolidinone (**7**, X=Cl) (289 mg, 0.72 mmol) and CsF (131 mg, 0.86 mmol) in MeOH (18 ml) was refluxed for 48 h. Removal of the solvent *in vacuo* followed by column chromatography on silica gel (CH_2Cl_2 : AcOEt = 9 : 1) yielded **9** (124 mg, 68 %) as colorless oil : $[\alpha]_D^{19}$ -68.5 ° (c 1.3, $CHCl_3$) ; ^{1}H-nmr (60 MHz) δ 3.43 (s, 3H), 4.78 (br.d, 1H, J=1.0 Hz), 5.08 (d, 1H, J=1.0 Hz), 7.75-8.05 (br.s, 1H).

b) On the similar treatment, (4*S*, 5*R*)-4-bromo-3-[(1*S*)-ketopinyl]-5-trichloromethyl-2-oxazolidinone (**7**, X=Br) (3.80 g, 8.5 mmol) gave **9** (1.34 mg, 67 %) as colorless oil.

(4*R*, 5*S*)-4-Methoxy-5-trichloromethyl-2-oxazolidinone (10).

a) (4*R*, 5*S*)-4-Chloro-3-[(1*S*)-ketopinyl]-5-trichloromethyl-2-oxazolidinone (**8**, X=Cl) (303 mg, 0.75 mmol) was treated as above to yield **10** (150 mg, 85 %) as colorless oil : $[\alpha]_D^{21}$ +70.5 ° (c 1.0, $CHCl_3$). The ^{1}H-nmr spectrum was identical with that of the (4*S*, 5*R*)-isomer (**9**).

b) (4*R*, 5*S*)-4-Bromo-3-[(1*S*)-ketopinyl]-5-trichloromethyl-2-oxazolidinone (**8**, X=Br) (2.24 g, 5.0 mmol) gave the 2-oxazolidinone (**10**) (820 mg, 70 %) as colorless oil.

(4*R*, 5*R*)-4-Methoxycarbonyl-5-trichloromethyl-2-oxazolidinone (11).

To a solution of (4*S*, 5*R*)-4-methoxy-5-trichloromethyl-2-oxazolidinone (**9**) (646 mg, 2.8 mmol) and trimethylsilyl cyanide (548 mg, 5.5 mmol) in CH_2Cl_2 (20 ml) was added $TiCl_4$ (0.3 ml, 2.7 ml) at 0 °C under argon atmosphere and the whole was stirred at room temperature for 12 h. After removal of the solvent *in vacuo*, the residue was dissolved in MeOH (5 ml) saturated with HCl gas and the solution was stirred at room temperature for 12 h. Evaporation *in vacuo* followed by silica gel column chromatography (CH_2Cl_2 : AcOEt = 9 : 1) gave the methyl ester (**11**) (336 mg, 48 %) as colorless crystals : mp 120-121 °C (hexane - CH_2Cl_2) ; $[\alpha]_D^{28}$ -81.5 ° (c 1.0, $CHCl_3$) ; ^{1}H-nmr (60 MHz) δ 3.88 (s, 3H), 4.51 (d, 1H, J=3.5 Hz), 5.21 (d, 1H, J=3.5 Hz),

6.90-7.25 (br.s, 1H) ; Anal. Calcd for $C_6H_6NO_4Cl_3$: C, 27.46 ; H, 2.30 ; N, 5.34. Found : C, 27.47 ; H, 2.32 ; N, 5.09.

(2*R*, 3*R*)-2-Amino-3-hydroxy-4,4,4-trichlorobutyric acid hydrochloride (12).

A solution of (4*R*, 5*R*)-4-methoxycarbonyl-5-trichloromethyl-2-oxazolidinone (**11**)(424 mg, 1.6 mmol) in 6M HCl (40 ml) was stirred at 130 °C for 15 h in sealed tube. After evaporation *in vacuo*, di-*tert*-butyl dicarbonate (529 mg, 2.4 mmol) and NEt_3 (326 mg, 3.2 mmol) were added to the residue dissolved in aqueous dioxane (15 ml) and the whole was stirred at room temperature overnight. The mixture was acidified with citric acid and extracted with AcOEt (30 ml x 3). The organic solution was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. Treatment of the residue with CH_2N_2 followed by silica gel column chromatography (hexane : CH_2Cl_2 = 3 : 2) yielded methyl (2*R*, 3*R*)-2-[(*tert*-butoxycarbonyl)amino]-4,4,4-trichloro-3-hydroxybutanoate (250 mg, 46 %) as colorless oil : ^{1}H-nmr (400 MHz) δ 1.45 (s, 9H), 3.819 (s, 3H), 4.57 (br.s, 1H), 4.73 (br.s, 1H), 5.12 (d, 1H, J=9.5 Hz), 5.47 (d, 1H, J=9.5 Hz).

A solution of the methyl ester, thus obtained, (131 mg, 0.39 mmol) in 6M HCl (40 ml) was stirred at 130 °C in sealed tube for 3 h. Evaporation of the solvent *in vacuo* gave the hydrochloride(**12**)(69 mg, 68 %) as colorless crystals : mp 140-143 °C ; $[\alpha]_D^{30}$ +7.2 ° (c 1.0, H_2O) ; ^{1}H-nmr (60 MHz, CD_3OD) δ 4.62 (d, 1H, J=2.0 Hz), 4.85 (d, 1H, J=2.0Hz) ; Anal. Calcd for $C_4H_7NO_3Cl_4$: C, 18.56 ; H, 2.73 ; N, 5.41. Found : C, 18.65 ; H, 3.03 ; N, 5.70.

(4*S*, 5*S*)-4-Methoxycarbonyl-5-trichloromethyl-2-oxazolidinone (13).

On similar treatment as the (4*S*, 5*R*)-isomer (**9**), (4*R*, 5*S*)-4-methoxy-5-trichloromethyl-2-oxazolidinone (**10**) (620 mg, 2.7 mmol) gave the methyl ester (**13**) (424 mg, 64 %), enantiomeric with **11**, as colorless crystals : mp 121-122 °C (hexane-CH_2Cl_2) ; $[\alpha]_D^{18}$ +78.0 ° (c 1.0, $CHCl_3$). The ^{1}H-nmr spectrum was identical with that of the (4*R*, 5*R*)-isomer (**11**).

(4*S*, 5*S*)-5-Dichloromethyl-4-methoxycarbonyl-2-oxazolidinone (14).

A solution of (4*S*, 5*S*)-5-methoxycarbonyl-5-trichloromethyl-2-oxazolidinone (**13**) (112 mg, 0.43 mmol) in THF (3 ml) was uv irradiated (100W, high pressure Hg lamp) for 4 h in quartz flask. After removal of the solvent, purification by column chromatography on silica gel (CH_2Cl_2 : AcOEt = 9 : 1) gave the dichloro derivative (**14**) (70 mg, 72 %) as colorless oil : ^{1}H-nmr (60 NHz) δ 3.82 (s, 3H), 4.48 (d, 1H, J=4.0 Hz), 5.02 (t, 1H, J=4.0 Hz), 5.95 (d, 1H, J=4.0 Hz),7.0 (br.s, 1H).

(2*S*, 3*S*)-2-Amino-4,4-dichloro-3-hydroxybutanoic acid hydrochloride (15).

In analogy with the trichloro-derivative (**11**), (4*S*, 5*S*)-5-dichloromethyl-4-methoxycarbonyl-2-oxazolidinone (**14**) (135 mg, 0.52 mmol) was hydrolyzed in boiling 6M hydrochloric acid to give the dichlorothreonine (**15**) (45 mg, 46 %), which was purified *via* the *N*-Boc-4,4-dichlorothreonine methyl ester [$[\alpha]_D^{20}$ +2.0 ° (c 2.0, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ 1.463 (s, 9H), 3.52 (br.s, 1H), 3.801 (s, 3H), 4.39 (m, 1H), 4.83 (br.d, 1H, J=9.5 Hz), 5.67 (d, 1H, J=8.4 Hz)]. Recrystalization from AcOEt - MeOH gave colorless crystals : mp 159-162 °C (dec.)(EtOH) ; $[\alpha]_D^{28}$ -2.0 ° (c 1.0, H_2O) ; ^{1}H-nmr (60 MHz, CD_3OD) δ 4.25-4.50 (m, 2H), 6.05 (d, 1H, J=6 Hz) ; Anal. Calcd for $C_4H_8NO_3Cl_3$: C, 21.40 ; H, 3.59 ; N, 6.24. Found : C, 21.16 ; H, 3.43 ; N, 6.38.

(2*S*, 3*R*)- and (2*R*, 3*S*)-Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutanoates (*N*-Boc-L- and D-threonines).

a) To a solution of (2*S*, 3*S*)-2-amino-4,4-dichloro-3-hydroxybutanoic acid hydrochloride (**15**) (48 mg, 0.21 mmol) and $NaHCO_3$ (54 mg, 0.64 mmol) in H_2O (4 ml) was added 10 % Pd / C (100 mg) and the whole was stirred at room temperature under hydrogen atmosphere (4 kg / cm^2) for 3 h. The mixture was filtered through celite pad and then a solution of di-*tert*-butyl dicarbonate (55 mg, 0.25 mmol) and NEt_3 (43 mg, 0.42 mmol) in dioxane (2 ml) was added to the filtrate. After stirring at room temperature overnight, usual work-up followed by treatment with CH_2N_2 and purification by silica gel column chromatography gave methyl (2*S*, 3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutanoate (7 mg, 15 %) as colorless oil : $[\alpha]_D^{18}$ -18.8 ° (c 1.5, MeOH). The ^{1}H-nmr spectrum was identical with that of the authentic *N*-Boc-L-threonine methyl ester, $[\alpha]_D^{20}$ -20.2 ° (c 1.9, MeOH), which was synthesized from L-threonine by convensional method.

b) On the catalytic hydrogenation as above, (2*R*, 3*R*)-2-amino-4,4-dichloro-3-hydroxybutanoic acid hydrochloride (60 mg, 0.27 mmol) gave methyl (2*R*, 3*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutanoate (21 mg, 34 %) as colorless oil , $[\alpha]_D^{19}$ +19.0 ° (c 1.0, MeOH).

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