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SYNTHESIS OF CHIRAL 2-CHLOROACRYLIC ESTERS

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Abstract: A convenient synthesis of chiral 2-chloroacrylic esters in two consecutive steps is described.

New routes for the asymmetric synthesis of amino acids continue to present a challenge for the synthetic organic chemist[1]. Because of the key role of carbon-carbon bond formation in organic synthesis the development of new and versatile chiral anionic[2] and cationic[3] amino acids equivalents is an important area of research.

Due to their structure 2-chloroacrylic esters are potential α-amino acid precursors as they can act as acceptors in conjugate addition-enolate trapping reactions to afford 3-substituted-2-chloropropanoic esters which can be easily transformed into the corresponding α-amino acids[4]. For example methyl 2-chloroacrylate reacts with phenylmagnesium bromide in the presence of copper (I) iodide to afford

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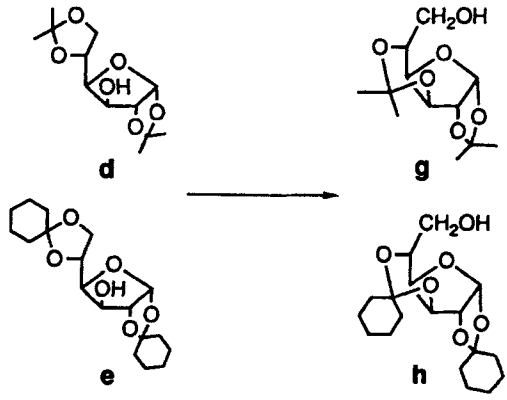
after protonation the corresponding phenylalanine precursor methyl 3-phenyl-2-chloropropanoate[5]. So chiral 2-chloroacrylic esters are new and versatile chiral anionic amino acid equivalents and we have focused our attention on the development of a convenient synthesis of them.

Although many methods of preparation have been described, the esterification of 2-chloroacrylic acid is problematic as this compound and its derivatives easily polymerize as pure liquids or in solution in the presence of ultraviolet light, heat or acidic media[6], and acid catalysing esterification or transesterification reactions cannot be applied. In addition, 2-chloroacryloyl chloride explodes, and another route based on the condensation of acids with alcohols promoted by N,N'-dicyclohexylcarbodiimide and 4-dimethylaminopyridine does not work well with sterically hindered alcohols[7]. So it is advisable to make the chiral ester moiety in a process prior to the formation of the double bond.

We would like to report here a convenient preparation of optically active 2-chloroacrylic esters from bulky chiral alcohols with different morphological and electronic characteristics by a general procedure involving two consecutive steps.

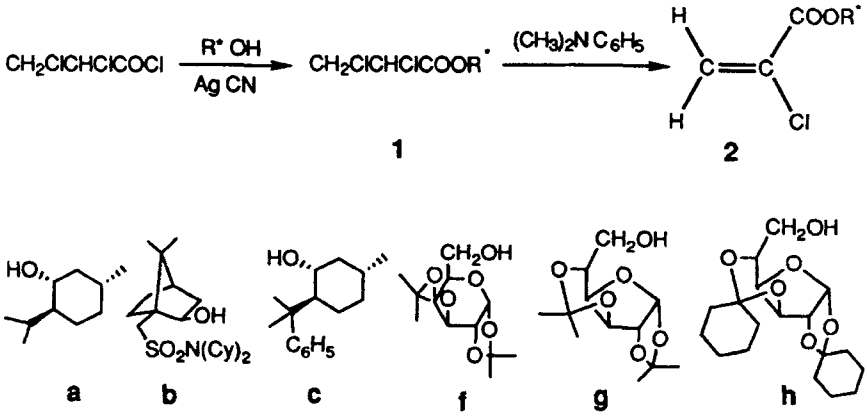
Chiral sterically-hindered 2,3-dichloropropionic esters can be easily prepared (Table 1) from commercially available 2,3-dichloropropionyl chloride and the corresponding alcohol in the presence of silver cyanide[8]. The yields obtained depend on the structure and morphological aspect of the alcohol and concave alcohols[9] give better results than convex ones, i.e. the yield decreases with the increase in steric shielding of the hydroxy group.



Scheme 1

In these conditions the reaction of 2,3-dichloropropionyl chloride with 1,2:5,6-diisopropylidene and 1,2:5,6-dicyclohexylidene-D-glucofuranose affords unexpected 2,3-dichloropropionic esters which were hydrolysed and the alcohols characterised analytically and spectroscopically as 1,2:3,5-diisopropylidene and 1,2:3,5-dicyclohexilydene-D-glucofuranose; it can be concluded that in the reaction medium these carbohydrate derivatives undergo a previous transacetalization process. All attempts to avoid these undesired reactions were unsuccessful and a mixture of the two possible esters in which the 1,2:3,5 derivative predominated was obtained.

Regioselective hydrogen chloride β-elimination can be conveniently achieved simply by heating the corresponding 2,3-dichloro ester at 100 ºC with dimethylaniline in nitrogen atmosphere to afford chiral 2-chloroacrylic esters in moderate to high yields and without undesired polymerization (scheme 2). In spite of using two consecutive



Scheme 2

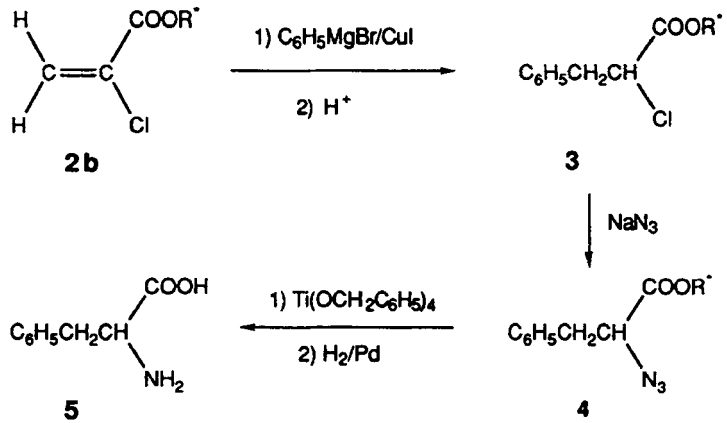
steps, the sufficiently high overall yields, procedural simplicity and use of easily accessible chemicals make this procedure a suitable one for the synthesis of chiral 2-chloroacrylic esters.

The results are summarised in Table 1. All new compounds are characterised spectroscopically.

In order to test the validity of these new compounds as α-amino acid precursors we performed the reaction of **2b** with phenylmagnesium bromide promoted by copper (I) iodide and subsequent diastereoselective protonation of the enolate using saturated aqueous ammonium chloride solution to afford the corresponding 2-chloro-3-phenylpropanoic ester **3** in a good chemical yield (65%) and a moderate diastereomeric excess (23%, determined in the crude reaction 200 MHz ^{1}H NMR spectrum). This compound can easily be converted into the corresponding α-amino acid according to the method previously

TABLE 1

Product	Procedure	Yield	Product	Yield
1a	**A**	94%	**2a**	93%
1b	**B**	69%	**2b**	86%
1c	**A**	67%	**2c**	41%
1f	**A**	97%	**2f**	87%
1g	**B**	65%	**2g**	67%
1h	**B**	67%	**2h**	68%



Scheme 3

reported[4] by W. Oppolzer and co-workers: treatment of chloride **3** with NaN_3 in DMF furnishes smoothly azide **4** in 80% yield, $Ti(OCH_2C_6H_5)_4$ mediated transesterification and concomitant hydrogenolyses of the benzyloxy and azide groups with 5% Pd/SO_4Ba under H_2 (1atm)

furnishes α-phenylalanine in 80% overall yield and regenerates the chiral auxiliary.

Although there still appears to be room for improvement of diastereoselectivity this is only an example of how it should be possible to prepare a wide variety of α-amino acids from a single and easily available starting material choosing a suitable nucleophilic reagent and electrophile.

EXPERIMENTAL

All the melting points were taken using a Buchï 510 capillary melting point apparatus and are uncorrected. IR spectra were obtained using a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian XL 200 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Microanalyses were carried out using a Perkin-Elmer 240-C element analyzer.

Dichloropropionic esters (1) General procedure

Method A: In a typical procedure 2,3-dichloropropionyl chloride (12 mmol) was added by means of a syringe to a stirred mixture of silver cyanide (9 mmol) and the chiral alcohol (6 mmol) in toluene (60 ml) under argon. The mixture was heated at 100 °C for 8 h. (**1a**, **1f**) or 24 h. (**1b**). The reaction mixture was filtered, washed successively with a 10% aqueous sodium hydrogenecarbonate solution and water, dried with magnesium sulfate and chromatographed.

Method B: In a typical procedure 2,3-dichloropropionyl chloride (12 mmol) was added by means of a syringe to a stirred mixture of silver cyanide (9 mmol) and the chiral alcohol (6 mmol) in toluene (60 ml) under argon. The mixture was heated at 100 °C for 24 h. and another

addition of 2,3-dichloropropionyl chloride (12 mmol) in toluene (10 ml) is made, the solution is then stirred at 100 ºC for 48h. The reaction mixture was filtered, washed successively with a 10% aqueous sodium hydrogenecarbonate solution and water, dried with magnesium sulfate and chromatographed.

1a: This compound was obtained as an oil; IR (nujol) 1745 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.77(d, 3H, J = 7); 0.90(d, 3H, J = 6); 0.92(d, 3H, J = 6); 0.96-1.18(m, 2H); 1.39-1.58(m, 2H); 1.60-1.67(m, 2H); 1.72-1.78(m, 1H); 1.85-1.89(m, 1H); 1.89-2.06(m, 1H); 3.74-4.01(m, 2H); 4.35-4.43(m,1H); 4.78(dt, 1H, J = 4.5, J = 10.9), eluting agent chloroform. Found: C, 55.67; H, 7.93%. $C_{13}H_{22}Cl_2O_2$ requires C, 55.52; H, 7.88%.

1b: m.p. 123 ºC; IR (nujol) 1755 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.91(s, 3H); 1.05(s, 3H); 1.08-2.10(m, 27H); 2.65(d, 1H, J = 13); 3.12-3.37(m, 2H); 3.41(d, 1H, J = 13); 3.67-4.13(m, 2H); 4.32-4.55(m,1H); 4.87-5.12(m, 1H), eluting agent chloroform. Found: C, 57.54; H, 7.96; N, 2.49%. $C_{25}H_{41}Cl_2NO_4S$ requires C, 57.46; H, 7.91; N, 2.68%.

1c: This compound was obtained as an oil; IR (nujol) 1745 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.89(d, 3H, J = 6); 1.22(s, 3H); 1.32(s, 3H); 0.95-2.30(m, 8H); 3.39-3.57(m, 2H); 3.62-3.68(m, 1H); 4.89(dt, 1H, J = 4.4, J = 10.7); 7.07-7.34(m, 5H), eluting agent chloroform/hexane 1:4. Found: C, 63.75; H, 7.57%. $C_{19}H_{26}Cl_2O_2$ requires C, 63.87; H, 7.33%.

1f: This compound was obtained as an oil; IR (nujol) 1750 cm^{-1}; ^1H-NMR ($CDCl_3$) 1.32(s, 6H); 1.43(s, 3H); 1.48(s, 3H); 3.74-3.86(m, 1H); 3.92-4.10(m, 2H); 4.23-4.36(m, 3H); 4.42-4.54(m, 2H); 4.58-4.68(m, 1H); 5.53(d, 1H, J = 3.6), eluting agent chloroform/diethyl ether 4:1. Found: C, 46.55; H, 6.01%. $C_{15}H_{22}Cl_2O_7$ requires C, 46.77; H, 5.75%.

1g: This compound was obtained as an oil; IR (nujol) 1755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.33(s, 3H); 1.35(s,3H); 1.36(s, 3H);1.48(s, 3H); 3.71-3.84 (m, 2H); 3.92-4.02(m, 1H); 4.23(d, 1H, J=3.8); 4.30-4.38(m, 2H); 4.44-4.51(m, 2H); 4.58(d, 1H, J = 3.6); 6.00(d, 1H, J = 3.6), eluting agent chloroform/diethyl ether 9:1. Found: C, 46.90; H, 5.83%. $C_{15}H_{22}Cl_2O_7$ requires C, 46.77; H, 5.75%.

1h: This compound was obtained as an oil; IR (nujol) 1755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.35-1.70(m, 20H); 3.75-3.88(m, 2H); 3.92-4.05(m, 1H); 4.23(d, 1H, J=3.8); 4.28-4.38(m, 2H); 4.46-4.53(m, 2H); 4.59(d, 1H, J = 3.6); 6.02(d, 1H, J = 3,6), eluting agent chloroform/diethyl ether 9:1. Found: C, 54.59; H, 6.41%. $C_{21}H_{30}Cl_2O_7$ requires C, 54.20; H, 6.50%.

2-chloroacrylic esters (2). General procedure

In a typical procedure 2-chloroacrylic esters were prepared by heating the dichloroester (5 mmol) and dimethylaniline (10 mmol) together at 100 ºC for 6-9 h. [5 days in the case of **2b**].

The reaction mixture was dissolved in 50 ml of chloroform and this solution was washed thoroughly with 5 % hydrochloric or sulphuric acid to remove any traces of amine. The chloroform solution was then dried over anhydrous sodium sulfate, evaporated and cromatographed.

2a: This compound was obtained as an oil; IR (nujol) 1730, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.76(d, 3H, J = 7); 0.89(d, 3H, J = 6); 0.91(d, 3H, J = 6); 0.96-1.14(m, 2H); 1.36-1.56(m, 2H); 1.60-1.69(m, 2H); 1.70-1.76(m, 1H); 1.81-1.96(m, 1H); 1.98-2.08(m, 1H); 4.77(dt, 1H, J = 4.5, J = 11); 5.97(d, 1H, J=1.2); 6.48(d, 1H, J=1.2), eluting agent dichloromethane/hexane 1:1. Found: C, 63.90; H, 8.79%. $C_{13}H_{21}ClO_2$ requires C, 63.79; H, 8.65%.

2b: This compound was obtained as an oil; IR (nujol) 1730, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.90(s, 3H); 1.03(s, 3H); 1.07-2.05(m, 27H); 2.65(d, 1H, J = 13); 3.12-3.27(m, 2H); 3.28(d, 1H, J = 13); 5.09-5.18(m, 1H); 5.94(d, 1, J=1.2H); 6.52(d, 1H, J=1.2), eluting agent diethyl ether/hexane 2:3. Found: C, 61.97; H, 8.37; N, 3.01%. $C_{25}H_{40}ClNO_4S$ requires C, 61.78; H, 8.29; N, 2.88%.

2c: This compound was obtained as an oil; IR (nujol) 1730, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.88(d, 3H, J = 6); 1.20(s, 3H); 1.30(s, 3H); 0.98-2.30(m, 8H); 4.87(dt, 1H, J = 4.5, J = 10.5); 5.6(d, 1H, J=1.2); 5.7(d, 1H, J=1.2); 7.12-7.32(m, 5H), eluting agent diethyl ether/hexane 1:9. Found: C, 71.39; H, 7.69%. $C_{19}H_{25}ClO_2$ requires C, 71.12; H, 7.85%.

2f: This compound was obtained as an oil; IR (nujol) 1735, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.32(s, 6H); 1.43(s, 3H); 1.48(s, 3H); 4.02-4.19(m, 2H); 4.21-4.45(m, 3H); 4.48-4.69(m, 1H); 5.48(d, 1H, J=3.6); 5.98(d, 1H, J = 1.2); 6.51(d, 1H, J=1.2), eluting agent diethyl ether/hexane 2:3. Found: C, 51.47; H, 6.24%. $C_{15}H_{21}ClO_7$ requires C, 51.66; H, 6.07%.

2g: This compound was obtained as an oil; IR (nujol) 1740, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.32(s, 3H); 1.36(s, 3H); 1.37(s, 3H);1.48(s, 3H); 3.83(dt, 1H, J=3.6, J=7.3); 4.23(d, 1H, J=3.7); 4.26-4.46(m, 3H); 4.58(d, 1H, J = 3.7); 6.01(d, 1H, J=3.7); 6.02(d, 1H, J=1.2); 6.53(d, 1H, J=1.2), eluting agent diethyl ether/hexane 2:3. Found: C, 51.40; H, 6.21%. $C_{15}H_{21}ClO_7$ requires C, 51.66; H, 6.07%.

2h: This compound was obtained as an oil; IR (nujol) 1740, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.35-1.69(m, 20H); 3.84(dt, 1H, J=3.7, J=7.3); 4.22(d, 1H, J=3.7); 4.28-4.45(m, 3H); 4.57(d, 1H, J = 3.7); 6.01(d, 1H, J = 3.7); 6.02(d, 1H, J = 1.2); 6.54(d, 1H, J= 1.2), eluting agent diethyl

ether/hexane 1:9. Found: C, 58.69; H, 6.99%. $C_{21}H_{29}ClO_7$ requires C, 58.81; H, 6.82%.

Conjugate addition of phenylmagnesium bromide and subsequent diastereoselective enolate protonation.

A stirred slurry of CuI (0.027 g, 0.14 mmol) in dry diethyl ether (10 ml) under an argon atmosphere cooled to 0 °C in an ice bath was added a solution of 3.0 M of phenylmagnesium bromide in diethyl ether (0.93 ml, 2.8 mmol). After 10 min **2b** (1.4 mmol) dissolved in diethyl ether (15 ml) was added dropwise and stirring was continued for additional 2h at 0 °C. The reaction mixture was then cooled to -80 °C and quenched with saturated aqueous NH_4Cl solution. The cold bath was removed after 5 min. and the mixture was extracted with ether. The organic phase was washed with water, dryed with $MgSO_4$, and evaporated to afford a mixture of diastereoisomers **3** (d.e. 23%) as a crude oil which was chromatographed on a silica gel column (230-400 mesh) eluting with methylene chloride/diethyl ether (9:1) (yield 65%). IR (nujol) 1750, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) of the mixture of diastereoisomers 0.78 and 0.87(s, 3H); 0.85 and 0.93(s, 3H); 1.06-1.99(m, 27H); 2.62(d, 1H, J=13); 3.09-3.29(m, 3H); 3.27(d, 1H, J=13); 3.40-3.52 (m, 1H); 4.22 and 4.48(m, 1H); 5.03(m, 1H); 7.23-7.29(m, 5H). Found: C, 65.97; H, 8.27; N, 2.41%. $C_{31}H_{46}ClNO_4S$ requires C, 65.99; H, 8.21; N, 2.48%.

Transformation into α-phenylalanine.

According to the previously described procedure[4] the ester **3** was converted into α-phenylalanine in 64% overall yield.

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