Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2573-2576, 1996
Copyright © 1996 Published by Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

S0040-4039(96)00393-0

Stereocontrolled Synthesis of α,α-Disubstituted α-Aminoaldehydes and α-Aminoacids using a [3,3] Allylic Trichloracetimidate Rearrangement

Hassan Imogaï, Yves Petit and Marc Larchevêque*

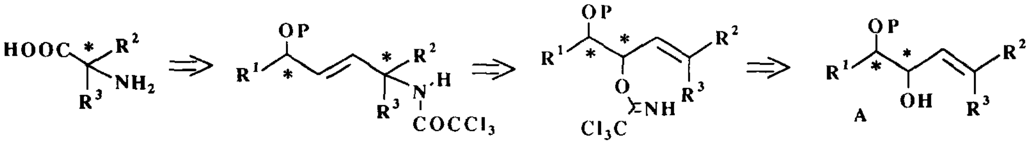
Laboratoire de Synthèse Organique associé au CNRS
ENSCP, 11 rue Pierre et Marie Curie; 75231 Paris Cedex 05 - France

Abstract: Sigmatropic rearrangement of trichloracetimidates derived from *syn* monoprotected allylic diols **3** resulting from the condensation of vinylalanes or cuprates with α-alkoxyaldehydes afforded diastereomerically pure allylic amines **6**. The oxidative cleavage of these amines allowed the access to α,α-disubstituted α-aminoacids in high enantiomeric purity. Copyright © 1996 Published by Elsevier Science Ltd

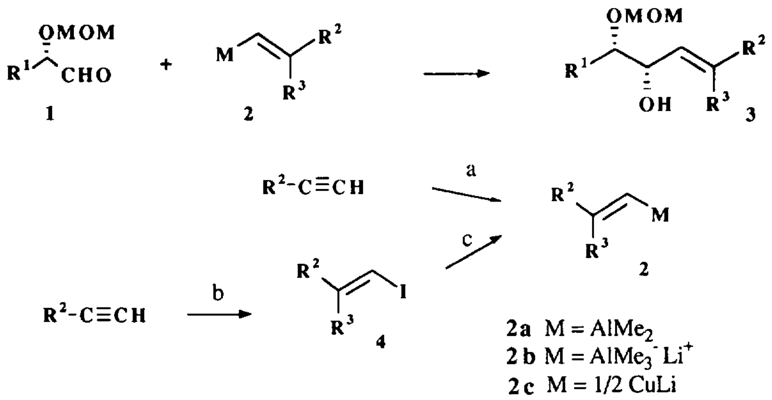
Owing to their biological properties, α,α-disubstituted-α-aminoacids constitute an important class of non-proteinogenic aminoacids. Incorporation of these compounds into peptides results in conformational restrictions and increased rigidity leading to enhanced resistance towards protease enzymes[1], and to the favoring of particular secondary structures[2]. Because of this range of biological activities, a wide variety of synthetic approaches to these compounds have been developed[3].

We wish to report here a new approach based on the [3,3] sigmatropic rearrangement of trichloracetimidates derived of trisubstituted monoprotected allylic diols **A** which allows the access to α,α-dialkylated α-aminoacids in high enantiomeric purity.

The thermal or Pd (II) catalyzed rearrangement of allylic trichloracetimidates into N-trichloroacetyl allylic amines was reported some years ago by Overman[4]. This rearrangement was shown to proceed by a six center cyclic transition state. Moreover, when applied to trichloracetimidates derived from secondary optically active allylic alcohols, it was shown to lead to products of (*E*) configuration exclusively with a high level of transfer of chirality[5]. An interesting application of this reaction was found in the oxidative cleavage of the double bond of the resulting allylic amines which allows the access to α-aminoacids[6].



We thought that the rearrangement of trisubstituted unsaturated alcohols such as **A** (available by condensation of a vinylic organometallic compound on an α-alkoxyaldehyde) would furnish an attractive route towards α-alkylated aminoacids. The stereochemistry of the products obtained from such a rearrangement being highly dependent on the stereochemistry of the double bond of the starting compound, we decided in a first attempt to study the condensation of vinylalanes on the aldehydes **1**[7]. In order to obtain the required trisubstituted vinylic compounds, we used the Zr catalysed addition of trimethylaluminium on an alkyne developed by Negishi[8]. The reaction of O-protected aldehydes **1** with the alanates **2b** obtained by addition of an organolithium compound[9] on vinyl alanes **2a** afforded the allylic alcohols **3** in satisfactory



Scheme 1: a) Me_3Al, cat. Cp_2ZrCl_2;
b) R_3MgX, CuI then I_2; c) nBuLi then 1/2 CuBr-Me_2S.

yields[10] (Table). However, It must be outlined that the vinylalanes prepared in the presence of a small amount of water[11] do react with the aldehydes **1** and give the corresponding alcohols in very good yields. In most cases, the *syn* monoprotected diols **3** were obtained in high distereoselectivity, the best results being observed with the aldehyde derived from mandelic acid (entries 4 and 8).

Due to the fact that this reaction allows the obtention of methyl substituted vinylic compounds only, in a second approach we studied the condensation of vinyl cuprates **2c** which were easily prepared by lithiation with n-butyllithium[12] of the trisubstituted vinylic iodides **4**[13] followed by reaction with a cuprous salt. The *syn* diastereomers were again obtained in a *syn/anti* ratio better than 94/6.

The trichloracetimidates **5** derived from the pure *syn* alcohols isolated after flash-chromatography[14] were then obtained in nearly quantitative yields by reaction with trichloracetonitrile in the presence of a base[15].

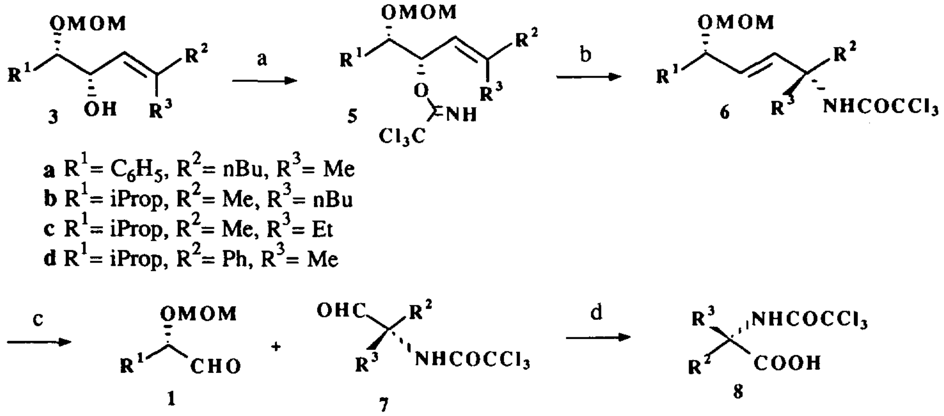
The imidates derived from lactaldehyde (R^1 = Me) were rather unstable and could not be submitted to

Table Reaction of aldehydes **1** with trisubstituted vinylic organometallic compounds **2**

	Aldehyde **1**	Organometallic compound **2**			Diol **3**	
	R^1	R^2	R^3	M	Yield%	*syn/anti*
1	CH_3	*n*-C_4H_9	CH_3	$AlMe_3^-Li^+$	65	92/8
2	i-C_3H_7	*n*-C_4H_9	CH_3	$AlMe_2$ [a]	92	96/4
3	i-C_4H_9	*n*-C_4H_9	CH_3	$AlMe_3^-Li^+$	62	92/8
4	C_6H_5	*n*-C_4H_9	CH_3	$AlMe_3^-Li^+$	55	100/0
5	i-C_3H_7	C_6H_5	CH_3	$AlMe_2$ [a]	93	80/20
6	i-C_3H_7	CH_3	C_2H_5	1/2CuLi	78	96/4
7	i-C_3H_7	CH_3	*n*-C_4H_9	1/2CuLi	75	94/6
8	C_6H_5	CH_3	*n*-C_4H_9	Cu [b]	63	98/2

a. The carboalumination was achieved in the presence of 1.5 eq of water before adding the aldehyde.
b. 1 equivalent of $ZnBr_2$ was added before the condensation.

rearrangement. However, with a more hindered R^1 group, the stability of these imidates was greatly enhanced and thermal rearrangements were then achieved in satisfactory yields[16].



a $R^1 = C_6H_5$, $R^2 =$ nBu, $R^3 =$ Me
b $R^1 =$ iProp, $R^2 =$ Me, $R^3 =$ nBu
c $R^1 =$ iProp, $R^2 =$ Me, $R^3 =$ Et
d $R^1 =$ iProp, $R^2 =$ Ph, $R^3 =$ Me

Scheme 2: a) DBU,CH_2Cl_2, -78°C, 1 hour; b) Xylene, 140°C, 4 hours; c) O_3, Me_2S, 12 hours; d) Jones reagent, 20 mn.

A single diastereoisomer (as indicated by the NMR data) was isolated even when the two R^2 and R^3 substituents were very similar (methyl and ethyl for instance in **5c**)[17]. Furthermore, the inversion of R^2 and R^3 groups in the trichloracetimidates **5** afforded a similar inversion for **6**.

We attempted also to achieve these rearrangements by using a catalytic amount of Pd (II) or Hg (II) salts. In contrast with the trichloracetimidates derived from allylic alcohols with a disubstituted double bond which are easily rearranged in the presence of a catalytic amount of palladium acetate[5c,6b,18], we only isolated a mixture of dienes resulting from the elimination of trichloracetamide.

The configuration of the new chiral center was determined by comparison of the rotatory power of the aminoacid obtained after oxidative cleavage of **6b** and deprotection with the value previously reported.

In a first experiment, the oxidative cleavage was achieved by using $RuCl_4$-$NaIO_4$; however, the result was rather disappointing. Better results were obtained with ozone, the use of which allowed to isolate the aldehydes **7** in excellent yields[19]. Simultaneously, the aldehydes **1** could be regenerated. The protected α-aminoacids **8** were then obtained in nearly quantitative yields by Jones oxidation[20] and could be isolated in free form by basic hydrolysis (KOH 1M, 50°C) followed by chromatography of the hydrochlorides on an exchange-ion resin (Dowex 50X8)[21]. A high enantiomeric purity was observed for all these compounds[22]. Thus, these results were consistent with a concerted rearrangement proceeding via a six-center chairlike transition-state.

In summary, the thermal rearrangement of the imidates derived from the stereochemically pure monoprotected allylic diols **3** easily prepared from α-alkoxyaldehydes allowed the synthesis of dialkylated or aryl substituted aminoacids in high enantiomerical purities.

References and notes

1. Khosla, A.; Stachowiak, K.; Smeby, R.R.; Bumpus, F.M.; Piriou F.; Lintner, K.; Fermandjian, S. Proc. Natl. Acad. Sci. USA 1981, 78, 757-760; Toniolo, C.; Crisma, M.; Pegoraro, S.; Valle, G.; Bonora, G.M.; Becker, E.; Polinelli, S.; Boesten, W.H.J.; Schoemaker, H.E.; Meijer, E.M.; Kamphuis, J.; Freer, R. *Peptide Res.* **1991**, *4*, 66-71.

2. Mutter, M. *Angew. Chem. Int. Ed. Engl.* **1985**, *97*, 639-653; Toniolo, C. *CRC Critical Rev. Biochem.* **1980**, *9*, 1-44; Karle, I.L.; Balaram, P. *Biochemistry* **1990**, 29, 6747-6756; Benedetti, E.; Toniolo, C.; Hardy, P.; Barone, V.; Bavoso, B.; di Blasio, B.; Grimaldi, P.; Lelj, F.; Pavone, V.; Pedone, C.; Bonora, G.M.; Lingham, I. *J. Am. Chem. Soc.* **1984**, *106*, 8146-8152; Crisma, M.; Valle, G.; Bonora, G.M.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternali, F.; Hardy, P.M.; Maia, H.L.S. *Biopolymers* **1991**, *31*, 637-641.
3. For overviews, see Williams, R.M. Synthesis of Optically Active Amino Acids, Pergamon Press, Oxford, 1989; Heimgartner, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238-264. For recent synthesis, see: Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K.; Heimgarten, H.; Stierli, F. *Helv. Chem. Acta* **1992**, *75*, 1666-1696; Colson, P.J.; Hegedus, L.S. *J. Org. Chem.* **1993**, *58*, 5918-5924; Cativiela, C.; Diaz-de-Villegas, M.D.; Galvez, J.A. *Tetrahedron:Asymmetry* **1994**, *5*, 261-268; Berkowitz, D.B.; Smith, M.K. *J. Org. Chem.* **1995**, *60*, 1233-1238; Jung, M.E.; D'Amico, D.C. *J. Am. Chem. Soc.* **1995**, *117*, 7379-7388.
4. Overman, L.E. *J. Am. Chem. Soc.* **1976**, *98*, 2901-2910; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579-586.
5. (a) Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247-3249; (b) Savage, I.; Thomas, E.J. *J. Chem. Soc., Chem. Commun.* **1989**, 717-719; (c) Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313-4316.
6. (a) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 770-771; (b) Metz, P.; Mues, C.; Schoop, A. *Tetrahedron*, **1992**, *48*, 1071-1080; (c) Chen, A.; Savage, I.; Thomas, E.J.; Wilson, P.D. *Tetrahedron Lett.* **1993**, *34*, 6769-6772.
7. The aldehydes **1** were synthesized by DIBAL-H reduction of the corresponding O-protected α-hydroxyesters directly issued from the chiral pool or prepared by nitrous deamination of the corresponding α-aminoacids: Li, W.R.; Ewing, W.R.; Harris, B.D.; Joullié, M.M. *J. Am. Chem. Soc.* **1990**, *112*, 7659-7672.
8. Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333-2356.
9. Zweifel, G.; Steele, R.B. *J. Am. Chem. Soc.* **1967**, *89*, 2754-2755.
10. The vinyl alanes **2a** prepared according the conventional manner were not reactive enough to react with aldehydes.
11. Wipf, P.; Lim, S. *Angew. Chem. Int. Ed. Engl* **1993**, *32*, 1068-1071.
12. Normant, J.F.; Cahiez, G.; Chuit, C.; Villiéras, J. *J. Organomet. Chem.* **1974**, *77*, 269-279.
13. Cahiez, G.; Bernard, D.; Normant, J.F. *Synthesis* **1976**, 245-248.
14. $[\alpha]_D^{20}$ +13 (c=1.0, $CHCl_3$): **3** (R^1=i-Prop, R^2 = Me, R^3= Et); $[\alpha]_D^{20}$ +5 (c=1.0, $CHCl_3$): **3** (R^1=i-Prop, R^2 = Me, R^3= nBu); $[\alpha]_D^{20}$ +8 (c=2.3, $CHCl_3$), **3** (R^1=i-Prop, R^2 = Me, R^3= Ph)
15. The imidates were prepared by reaction of alcohols **3** with trichloracetonitrile in the presence of a catalytic amount of HNa[4], or with an equivalent of DBU at low temperature[5c]. Yields in purified products (after a rapid chromatography on carbonated silica gel) were in all cases better than 95%.
16. Thermal rearrangements were performed by refluxing trichloracetimidates in xylene for 4 to 10 hours. Yields %: **6a**: 98; **6b**: 62; **6c**: 60; **6d**: 70.
17. In all cases, the stereochemistry of the double bond was purely E.
18. Doherty, A.M.; Kornberg, B.E.; Reily, M.D. *J. Org. Chem.* **1993**, *58*, 795-798; Gonda, J.; Helland, A.C.; Ernst, B.; Bellus, D. *Synthesis*, **1993**, 729-733.
19. With R^1 = iProp, the aldehyde **1** was isolated after chromatography on silicagel in 77-99% yield; for aldehydes **7**: **7b**: $[\alpha]_D^{20}$ -21.2 (c=1.03, $CHCl_3$), 85%; **7c**: $[\alpha]_D^{20}$ -8.8 (c=2.17, CH_2Cl_2), 81%; **7d**; $[\alpha]_D^{20}$ -154.2 (c=2.01, CH_2Cl_2), 98%.
20. Physical data for **8** (as methyl esters): **8b**: $[\alpha]_D^{20}$ -23.2 (c=2.1,CH_2Cl_2); **8c**: $[\alpha]_D^{20}$ -10.7 (c=1.55, $CHCl_3$); **8d**: $[\alpha]_D^{20}$ +66.8 (c=2.05, CH_2Cl_2)
21. $[\alpha]_D^{20}$ -10.5 (c=2, H_2O) for the (*R*)-2-amino-2-methylpentanoic acid (as hydrochloride) obtained after cleavage of **6b**; $[\alpha]_D^{20}$ +8.1 (c=2, H_2O) for the *S* acid: Kolb, M.; Barth, J. *Angew. Chem. Int. Ed. Engl* **1980**, *19*, 725-726.
22. The enantiomeric purities were measured on a β-cyclodextrin stationary phase: Cydex-B from SGE (50 m) for the aldehydes **7** isolated after flash-chromatography and by NMR in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium III for the esters **8**. They were found better than 98%.

(Received in France 5 *December* 1995; *accepted* 27 *February* 1996)