Tetrahedron Vol. 47, No. 26, pp. 4619-4630, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

REACTIONS OF FLUOROBENZENE TRICARBONYLCHROMIUM COMPLEXES WITH ANIONS FROM SCHIFF BASES OF α-AMINO ESTERS ; ENANTIOSELECTIVE SYNTHESIS OF α-ARYL AMINO ACIDS

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(*Received in Belgium* 21 *February* 1991)

Abstract : We report here a convenient synthesis of α-substituted aryl amino acids via the addition of α-imino esters to fluorobenzene tricarbonylchromium complexes. Optically pure α-aryl amino acids have been prepared by enantioselective substitution of fluorobenzene complexes using Schiff bases of L-alanine, leucine and valine methyl esters and (1R,2R,5R)-2-hydroxypinan-3-one.

INTRODUCTION :

Non proteinogenic α-amino acids, like α-arylglycines derivatives, are of pharmacological importance as drugs[1] and they can also be introduced in peptides for giving indications on their structure and biological activity. For example p-hydroxyphenylglycine is a side-chain constituant of ß-lactam antibiotic amoxicillin.[2] Highly functionalized arylglycines are found in numerous peptide and glycopeptide antibiotics such as the vancomycins.[3]

Recently reported synthesis of α-arylglycines including asymmetric Strecker reactions,[4] Friedel-Crafts addition to chiral cationic glycine equivalents,[5] cuprate or Friedel-Crafts coupling to chiral bromoglycinates,[6] encounters several problems such as numerous synthetic steps or poor yields. O'Donnell *et al.*[7] have also described a new route to α-phenyl-α-substituted amino acids using Barton's phenylating reagent, triphenylbismuth carbonate.

In a preliminary communication[8] we have shown that α-aryl amino esters can be obtained from anions of α-imino esters and halogenobenzene tricarbonylchromium complexes, after decomplexation and hydrolysis, in moderate to good yields. This represents a new and simple general method for the synthesis of these compounds. Next we have reported some preliminary data for the diastereoselective arylation of chiral enolates by fluoroarene tricarbonylchromium complexes.[9] In this article we will present our full results from the reactions of complexes 1[10] and several anions of Schiff bases 2 and 5.

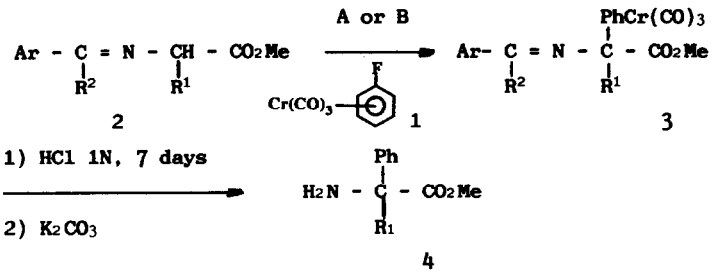
RESULTS :

Schiff bases of p-chlorobenzaldehyde and benzophenone.

First our synthesis was perfected following the method of Stork[11] from Schiff bases prepared with p-chloro benzaldehyde or benzophenone imine[12] and methyl esters of different amino acids (Gly, Ala, Leu, Val) in the presence of LDA in THF at -78°C (Method A, table).

In the first step (scheme 1) the presence of cosolvent is essential: in its absence the yield fell dramatically. The imines 3 are sufficiently stable to be purified by flash chromatography, analytical data and spectral analysis are in agreement with the assigned structures.

The arylation is completely regioselective from Schiff bases of glycine and alanine ; it affects only the α carbon. It presents a neat regioselectivity in the same sense for the Schiff base of leucine. On the contrary for valine this regioselectivity is completely reversed, this result is ascribed to the steric bulk of the isopropyl group. It can be compared with the results of Koga[13] who has shown that the Schiff base of the t.butyl ester of valine and cyclohexanone led exclusively to α-alkyl cyclohexanones after alkylation in the presence of LDA and hydrolysis.



Scheme 1

Substrate	Ar	R^1	R^2	Method	3(Yield %)	4(Yield %)
2a	2-Cl-C6H4	H	H	A	3a (62)	4a (56)
2a	2-Cl-C6H4	H	H	B	3a (40)	4a (37)
2b	Ph	H	Ph	A	3b (58)	4a (52)
2b	Ph	H	Ph	B	3b (35)	4a (32)
2c	2-Cl-C6H4	Me	H	A	3c (76)	4b (70)
2d	Ph	Me	Ph	A	3d (68)	4b (62)
2d	Ph	Me	Ph	B	3d (32)	4b (29)
2e	2-Cl-C6H4	iBu	H	A	3e (48)	4c (45)
2f	Ph	iBu	Ph	A	3f (43)	4c (39)
2g	2-Cl-C6H4	iPr	H	A	3g (10)	4d (09)

Table: α-phenyl amino acids prepared by phenylation using 1

The decomplexation of the aromatic ring is accomplished by oxidation whith iodine at -78°C, but can also be performed without other treatment during hydrolysis of the imine. In this case the yield is better than 90%. The synthesis of α-aryl amino esters 4 can be also carried out directly in a one pot reaction without isolation of 3.

O'Donnell[14] has developed a general synthesis of amino acids based on catalytic phase-tranfer (PTC) alkylation of the benzophenone imine or aldimine. In contrast to known anhydrous alkylative routes the PTC method involves a simple reaction procedure, mild conditions, inexpensive and safe reagents and solvents. Arylation of 2 was also accomplished by catalytic solid-liquid phase transfer arylation using mixture of powdered KOH and K_2CO_3 (1/3) in acetonitrile at 15-20°C with 10% Bu_4NBr as the phase-transfer catalyst (method B, Table 1). The crude arylated derivatives 3 obtained as oils with moderate to low yields were chromatographed and hydrolysed by mild acid hydrolysis during one week. The decomplexation is achieved by air exposure in the same time to give amino ester 4.

Schiff bases of 2-hydroxypinan-3-one.

In our laboratory we have developed a general and efficient method for diastereoselective alkylation of chiral Schiff bases prepared from 2-hydroxypinan-3-one.[15] This chiral auxiliary is very attractive because it is easily obtained by permanganate oxidation of α-pinene.[16] Schiff bases 5 were prepared in good yields in refluxing benzene containing boron trifluoride etherate.[17]

To two equivalents of lithium diisopropylamide (prepared from BuLi in ether) in THF, Schiff bases 5 (1 equivalent) were added in an inert atmosphere at -75°C or -100°C. After 30 min and dilution with 10 equivalents of HMPA, the aromatic complex (20% excess) was slowly added; the temperature maintained at -75°C or -100°C during 1 h and allowed to reach room temperature in 15 h with stirring.

In all cases at -75°C arylated lactones were isolated (scheme 2). From **5a** two isomeric lactones were obtained in 58% global yield: **6a** (60%) in a single diastereomeric form and **6b** (40%) arylated on the pinane ring*; **5b** gave a mixture of two diastereomeric lactones: **7a** (71%) and **7b** (23%) with 55% overall yields. Finally from **5c** the sole arylated lactone **8** was isolated in poor yield (15%).

It is interesting to note that for the three reactions, anisole tricarbonyl chromium,[10] (which arises from substitution of the fluorine of **1** by methoxy liberated during lactonisation), is also isolated (15-20%).

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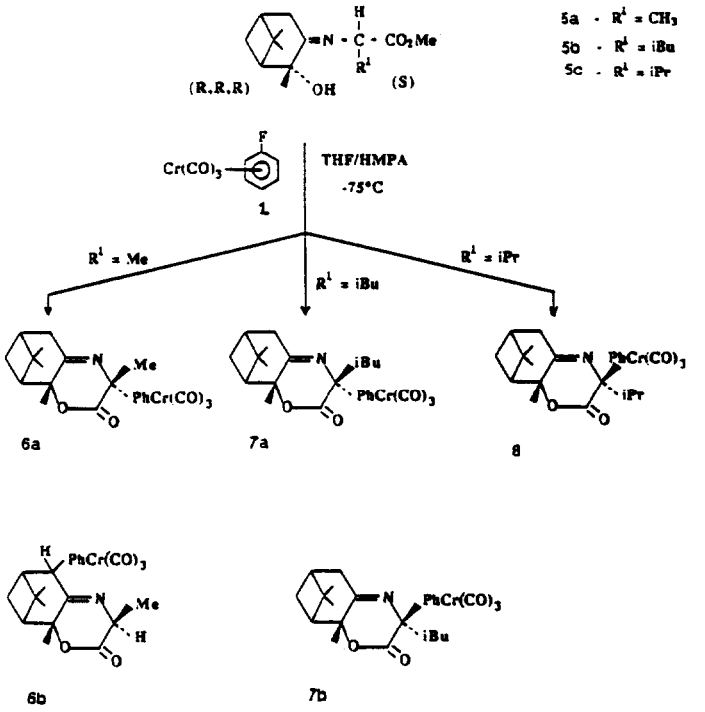
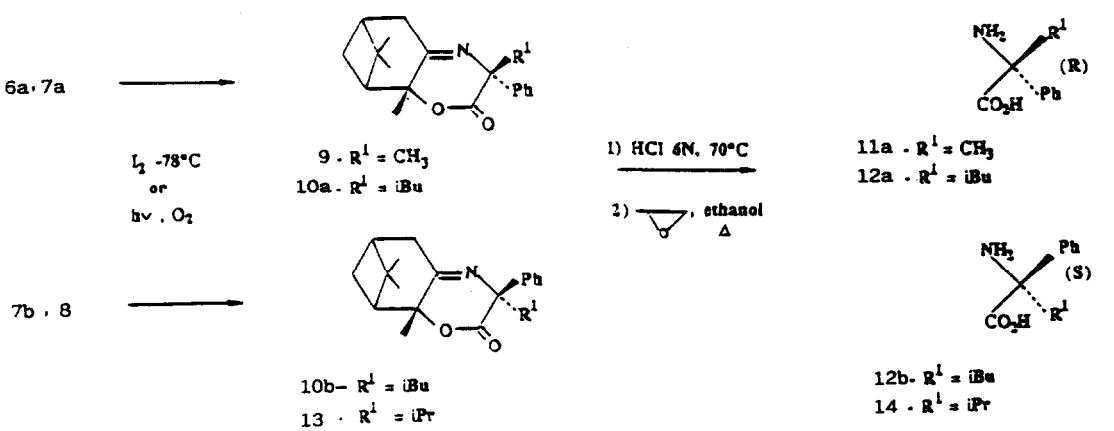
*) Arylation on the pinane ring results from the existence of different limit forms for the anion. Structure and stereochemistry of **6b** were established from 360 MHz spectra. In particular the proton α to the carbonyl function gave a quartet arising from the coupling with the geminal methyl group. It has been shown[18] that in this configuration this proton did not show the homoallylic coupling with the proton on the terpene ring α to the C=N bond. It implies for this compound a reprotonation with retention of configuration. A similar result was observed by Roumestant[19] for certain Schiff bases.



Scheme 2



Scheme 3

The structures of lactones **6-8** were established from spectral and analytical data (360 MHz NMR, mass spectra). They were then decomplexed by oxidation by iodine at -78°C, or by stirring in a mixture of ether-THF, in the light, during one week to give the products **9,10a,10b** and **13**. These new lactones were hydrolysed by heating at 70°C during 5 hours in presence of 6N HCl and led to aminoesters hydrochlorides liberated by boiling during 30 minutes in ethanol in the presence of propylene oxide (scheme 3).

The stereochemistry of the α asymmetric carbon of **6a** was deduced from the structure of the hydrolysed product **11a**. Indeed this last product gives the physical and spectral data of (R)-2-methyl-2-phenylglycine.[20]

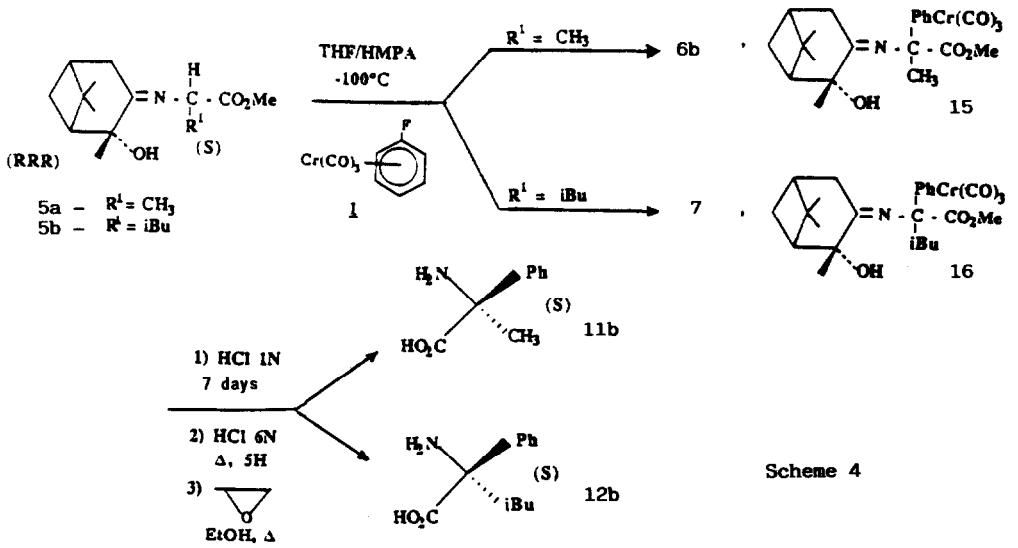
Analogy of NMR spectra, especially for the chemical shift of the methyl group at the junction of the cycles (1.42 ppm for **6a**, 1.45 ppm for **7a**; 1.75 ppm for **7b** and 1.72 ppm for **8**) led to assignment of the same configuration to α carbons of **6a** and **7a** on the one hand and of **7b** and **8** on the other . Examination of Dreiding models of these molecules shows that the diamagnetic-anisotropic effect of the aromatic ring can affect this methyl group, which is deshielded for **7b** and **8**, only if these two groups are syn. This fact is corroborated by X ray crystallography of lactones analogs.[21] Decomplexation followed by hydrolysis gives (R)-2-phenylleucine **12a** from **7a**, (S)-2-phenylleucine **12b** from **7b** and (S)-2-phenylvaline **14** from **8** (scheme 3).

In previous cases, during alkylation reactions, the formation of lactones was never observed. Moreover synthesis of lactones starting from 2-hydroxypinan-3-one and α-aminoesters was accomplished in a very low yield. We have also observed that lactonisation does not precede arylation because non-arylated lactones have never been isolated. For these arylation reactions it is clear that the arene tricarbonylchromium complex favours for the anion a cis geometry that during arylation permits cyclisation. It implies in aggregates a strong interaction between the anion and the electrophile, perhaps by means of a complexation with chromium by exchange of a CO ligand.

Finally we observed three different results for the stereochemistry of the α-carbon which is governed by the crowding of the R^1 group initially present on the Schiff base. For R^1= Me or iBu approach occurs exclusively or preferably on the opposite side of the gem-dimethyl bridge as it was noted in the laboratory for alkylation of the lactone prepared from glycine.[18] For R^1= iPr, the yield is low and the reverse approach is exclusive.

We have achieved this same reaction at -100°C on Schiff bases **5a** and **5b** (the reactivity of the valine Schiff base being too low, arylation was not attempted on **5c**). In these conditions the arylated Schiff bases (**15** and **16**, respectively) are major products (scheme 4). From **5a** the overall yield of the reaction is 70% and the lactone **6b** (22% of the mixture) is also obtained; from **5b** the yield is 75% and the lactone **7a** (18% of the mixture) is also isolated.

The stuctures of **15** and **16** were established from spectral and analytical data. The configuration of α-asymmetric carbon can be assigned as previously described by identification of the hydrolysed products.Thus, compound **15**, after hydrolysis of the imine and decomplexation and hydrolysis of the ester leads to (S)-2-methyl-2-



Scheme 4

phenylglycine **11b**, the enantiomer of **11a**, though **16** gives, under the same experimental conditions, (S)-2-phenylleucine **12b** already obtained from **7b**.

We find again the observation made previously in this laboratory:[19] the reactivity of the Schiff bases of 2-hydroxypinan-3-one depends highly on the stereochemistry of the starting product.

CONCLUSION

In summary, reactions of arene tricarbonylchromium with the anion of α-iminoester provide racemic or optically pure α-aryl aminoester. This is a very attractive route to these compounds because of the availibity of the starting substrates, the simplicity of the reaction procedure, workup and product purification. It's an original synthesis which is accomplished from Schiff bases of 2-hydroxypinan-3-one in good chemical yields and excellent diastereomeric excesses (> 98%). At this stage of our work, it seems to be limited only by the steric encumbrance on the α-carbon of the imino ester as shown by the results obtained from valine.

Efforts to optimize and further expand the scope (in particular with heteroaromatic compounds) of this methodology are presently under investigation.

EXPERIMENTAL SECTION

Melting points are uncorrected. Reagents and solvents were purified in the usual way. All reactions involving lithium derivatives were carried out under anhydrous conditions in nitrogen atmosphere. LDA was prepared from BuLi in ether. Spectra were recorded with the following instruments: IR Perkin Elmer

spectrophotometer 298; ^{1}H-NMR : Varian EM-360; Bruker 360 WB and AC 250; Mass Spectra Jeol JMS DX 300. Optical rotations were determined with a Perkin Elmer Model 241 polarimeter. Routine analyses agree with calculated values within 0.3%.

Enantiomeric purity was checked by ^{1}N-NMR spectroscopy on the aminoester (0.15-0.2M $CDCl_3$/TMS in the presence of 0.2-0.6 mole equivalent of d.Eu(hfc)$_3$).

General procedure for arylation of Schiff bases **2a-2g** *with fluorobenzene tricarbonyl chromium.*

Method A

The Schiff base (4 mmol) was added under nitrogen at -80°C to a stirred suspension of LDA (4.1 mmol) in dry THF. The mixture was stirred for 30 min more. After dilution with HMPA (5eq HMPA/1eq Schiff base) and addition of the flurorobenzene chromium complexe (4,4 mmol), the mixture was stirred 30 min at -80°C then 16 to 20 hr at RT. The reaction was followed by T.L.C. (Kieselgel Merck 60). The mixture was poured into a solution of NH_4Cl (20 ml), the aqueous phase extracted with ether (3 x 100 ml). the organic layer was dried ($MgSO_4$), evaporated (t<50°C) and the residue was purified by flash chromatography (silica gel 60, eluant : ether/hexane 1/3).

Method B

A solution of the Schiff base (0.018 ml) and the fluorobenzene chromium complexe (0.02 mol) in CH_3CN (35ml) was dropped rapidly into a stirred suspension of Bu_4NBr (0.0027 mol) and powdered mixture of K_2CO_3/KOH (3/1), (0.054 mol), in CH_3CN (15ml) at 5°C. When addition was complete the mixture was allowed to warm to room temperature. The progress of the reaction was monitored by T.L.C.. The mixture was diluted with Et_2O (100 ml), filtered through a thin bed of celite and concentrated in vacuo to a thick oil which was dissolved by stirring with a mixture of 100 ml Et_2O and 40ml 0.1% aqueous $NaHCO_3$. The ethereal fraction was washed with 0.1N aqueous $NaHCO_3$ and saturated aqueous NaCl and concentrated to yield a viscous oil which was chromatographed over silica gel (30 parts).

Products **3** have the following characteristics (yields are given in the table):

3a: mp 66°C. Anal. Calcd for $C_{19}H_{14}NO_5ClCr$: C, 53.90; H, 3.30; N, 3.30. Found: C, 53.99; H, 3.21; N, 3.37. ^{1}H-NMR ($CDCl_3$) δ : 3.74(s,CH_3); 4.65(s,CH); 5.35(m,4H); 5.80(m,1H); 7.43(AB,2H); 7.83(AB,2H). MS(EI) m/z: 423 (M^+).

3b: mp 122°C. Anal. Calcd for $C_{25}H_{19}NO_5Cr$: C, 64.52; H, 4.09; N, 3.01. Found: C, 64.39; H, 4.17; N, 2.92. ^{1}H-NMR ($CDCl_3$) δ : 3.75(s,CH_3); 5.00(s,CH); 5.20(m,3H); 6.10(m,2H); 7.3-7.9(m,10H). MS(EI) m/z: 465 (M^+).

3c: oil. ^{1}H-NMR ($CDCl_3$) δ : 1.83(s,CH_3); 3.80(s,CH_3); 5.84(m,3H); 5.93(m,2H); 7.50(AB,2H); 7.86(AB,2H); 8.38(s,CH_3); MS(EI) m/z: 437 (M^+).

3d: mp 125°C. Anal. Calcd for $C_{26}H_{21}NO_5Cr$: C, 65.14; H, 4.38; N, 2.92. Found: C, 64.61; H, 4.36; N, 2.88. ^{1}H-NMR ($CDCl_3$) δ : 1.71(s,CH_3); 3.45(s,CH_3); 5.2(m,3H); 6.1(m,2H); 7.2-7.9 (m,10H). MS(EI) m/z: 479 (M^+).

3e: mp 88°C. Anal. Calcd for $C_{23}H_{22}NO_5ClCr$: C,57.62; H, 4.59; N, 2.92. Found: C, 57.70; H, 4.49; N, 2.96. ^{1}H-NMR ($CDCl_3$) δ : 0.83(d,6H); 1.66(m,CH); 2.13(br d. CH_2); 3.85(s,CH_3); 5.40(m,4H); 6,00(m,1H); 7.50(AB,2H); 7.93(AB,2H); 8.43(s,CH).6. MS(EI) m/z: 479 (M^+).

3f: mp 139°C. Anal. Calcd for $C_{29}H_{27}NO_5Cr$: C, 66.79; H, 5.18; N, 2.69. Found: C, 66.66; H, 5.12; N, 2.75. ^{1}H-NMR ($CDCl_3$) δ : 0.78(d,CH_3); 0.85(d,CH_3); 1.58(m,CH); 2.15(br d,CH_3); 5.30(m,3H); 6.05(m,2H); 7.2-7.9(m,10H). MS(EI) m/z: 521 (M^+).

3g: mp 145°C. Anal. Calcd for $C_{22}H_{20}NO_5ClCr$: C, 56.77; H, 4.30; N, 3.01. Found: C, 56.65; H, 4.25; N, 3.16. ^{1}H-NMR ($CdCl_3$) δ : 0.83 (d,CH_3); 0.96(d,CH_3); 2.63(m,CH); 3.91(s,CH_3); 5.33(m,3H); 5.93(m,2H); 7.43(AB,2H); 7.90(AB,2H); 8.56(s,CH). MS(EI) m/z: 465 (M^+).

3h: mp 156°C. Anal. Calcd for $C_{28}H_{25}NO_5Cr$: C, 66.27; H, 4.93; N, 2.76. Found: C, 65.98; H, 4.99; N, 2.69. ^{1}H-NMR ($CDCl_3$) δ : 0.85(d,CH_3); 0.95(d,CH_3); 2.63(m,CH); 3.91(s,CH_3); 5.33(m,3H); 5.93(m,2H); 7.43(AB,2H); 7.90(AB,2H); 8.56(s,CH). MS(EI) m/z: 507 (M^+).

General procedure for hydrolysis and decomplexation.

a) Hydrolysis and decomplexation.

The compound **3** (3 mmole) was dissolved in ether (30 ml) and treated by 1N HCl solution (10 ml) during 6 days under stirring. After extraction with ether, the aqueous layer was neutralised with a saturated solution of K_2CO_3 and extracted several times with ether. After drying, filtration over celite and concentration **4** was obtained in 90-95% yield.

b) Oxidation by iodine and hydrolysis.

After the arylation reaction, the mixture (3 mmoles) was cooled at -78°C and iodine (10 mmole) in THF (40 ml) was added. The mixture was stirred 3h at room temperature, treated at 0°C with 30% solution of K_2CO_3 and extracted with ether. The organic layers were washed 5 times in turn with a 5% solution of $NaHSO_3$ and with water. After normal workup **4** was obtained in 80% yield.

Products **4** give the following characteristics (yields are given in a table):

4a: Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.41; H, 6.61; N, 8.55. ^{1}H-NMR ($CDCl_3$) δ : 1.86(br s,NH_2); 3.70(s,CH_3); 4.51(s,CH); 7.36(br s,5H).MS (EI) m/z: 165 (M^+).

4b: Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 66.88; H, 7.21; N, 7.92. ^{1}H-NMR ($CDCl_3$) δ : 1.70(s,CH_3); 2.08(br s, NH_2); 3.71(s,CH_3); 7.41(m,5H). MS(EI) m/z: 179 (M^+).

4c: Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60; N, 6.33. Found: C,70.43; H, 8.49; N, 6.40. ^{1}H-NMR ($CDCl_3$) δ : 0.70(d,CH_3); 0.83(d,CH_3); 1.2-1.8(m,CH_2,CH); 1.84(br s,NH_2); 3.63(s,CH_3); 7.33(m,5H). MS(EI) m/z: 221 (M^+).

4d: Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.57; H, 8.21; N, 6.76. Found: C, 69.67; H, 8.18; N, 6.62. ^{1}H-NMR ($CDCl_3$) δ : 0.57(d,CH_3); 0.90(d,CH_3); 1.70(br s,NH_2); 2.70(m,CH); 3.63(s,CH_3); 7.30(m,3H); 7.60(m,2H) MS(EI) m/z: 207.

3) General procedure for arylation of Schiff bases **5**.

They were performed using the general procedure described for the Schiff bases **2** ; except two equivalents of base were used.

a) Arylation at -75°C (in all cases anisole tricarbonylchromium was first isolated in 15-20% yield).

6a: (35%). Rf(ether 1/hexane 1) = 0.62. mp 178°C. Anal. Calcd for $C_{22}H_{23}NO_5Cr$: C, 60.97; H, 5.31; N, 3.23. Found: C, 60.56; H, 5.17; N, 3.33. ^{1}H-NMR ($CDCl_3$) δ : 1.10(s,CH_3); 1.24(d,CH,J=12Hz); 1.38(s,CH_3); 1.42(s,CH_3); 1.87(s,CH_3); 2.16(m,2H); 2.42(m,1H); 2.84(AB system,2H,J=17.5Hz); 5.10, 5.55, 6.08(m,C_6H_5). MS(EI) m/z: 433 (M^+).

6b: (24%). Rf(ether 1/hexane 1) = 0.48. mp 113°C. Anal. Calcd for $C_{22}H_{23}NO_5Cr$. Found: C, 61.12; H, 5.18; N, 3.31. ^{1}H-NMR ($CDCl_3$) δ : 1.15(s,CH_3); 1.37(s,CH_3); 1.62(s,CH_3); 1.71(d,CH_3,J=7.5Hz); 1.58-2.56(m,5H); 4.69(q,CH,J=7.5Hz); 5.10-6.20(m,C_6H_5). MS(EI) m/z: 433 (M^+).

7a: (40%). Rf(ether 1/hexane 1) = 0.60. mp 193°C. Anal. Calcd for $C_{25}H_{29}NO_5Cr$: C, 63.16; H, 6.11; N, 2.95. Found: C, 63.41; H, 6.19; N, 3.02. ^{1}H-NMR ($CDCl_3$) δ : 0.85(s,CH_3); 0.94(s,CH_3); 1.07(s,CH_3); 1.22(d,CH); 1.38(s,CH_3); 1.45(s,CH_3); 1.83(sept.,CH); 2.04(dd,CH); 2.10(m,CH); 2.18(m,CH); 2.40(m,2H); 2.91(AB system, 2H).MS(EI) m/z: 475 (M^+).

7b: (16%). Rf(ether 1/hexane 1) = 0.74. mp 153°C. Anal. Calcd for $C_{25}H_{29}NO_5Cr$. Found: C, 63.35; H, 6.23; N, 3.01. ^{1}H-NMR ($CDCl_3$) δ = 0.80(d,CH_3); 0.97(d,CH_3); 1.16(s,CH_3); 1.25(d,CH); 1.46(s,CH_3); 1.78(s,CH_3); 1.80(m,2H); 2.13(m,2H);

2.38(m,1H); 2.65(m,1H); 2.95(AB,system, 2H); 5.12, 5.48,6.08 (m,C_6H_5). MS(EI) m/z :475 (M^+).

8: (15%).Rf(ether 1/hexane 1) = 0.71. mp 200°C(decomp.). Anal. Calcd for $C_{24}H_{27}NO_5Cr$: C, 62.47; H, 5.86; N, 3.04. Found: C, 61.98, H, 5.79; N, 3.16. ^{1}H-NMR ($CDCl_3$) δ 0.87(d,CH_3); 1.03(d,CH_3); 1.13(s,CH_3); 1.28(d,CH); 1.40(s,CH_3); 1.72(s,CH_3); 1.85(m,2H); 2.10(m,CH); 2.15(m,CH); 2.20(m,CH); 2.70(m,1H); 2.92(AB system,2H); 5.10, 5.40, 5.98 (m,C_6H_5). MS(EI) m/z: 461 (M^+).

b) Arylation at-100°C.

15: (50%). Rf(ether 1/hexane 1) = 0.55. oil. ^{1}H-NMR ($CDCl_3$) δ :0.85(s.CH_3); 1.32(s,CH_3); 1.56(s,CH_3); 1.66(s,CH_3); 2.05-2.76(m,7H); 3.78(s,CH_3); 5.10-6.10(m,5H). MS(FAB) m/z: 466 $(M+H)^+$.

16: (45%). Rf(ether 1/hexane 1) = 0.59. oil. ^{1}H-NMR ($CDCl_3$) δ : 0.43(d,CH_3); 0.50(d,CH_3); 0.88(s,CH_3); 1.31(s,CH_3); 1.60(s,CH_3); 2.01-3.06(m,9H); 3.76(s,CH_3); 5.05-6.08(m,5H). MS(FAB) m/z :508 $(M+H)^+$.

4) Decomplexation of lactones.

The purified arylated lactone (2 mmole) was dissolved in THF (10 ml) or ether and the mixture was stirred at room temperature for one week. The progress of the decomplexation was monitored by TLC. After filtration over celite and concentration the residue was purified by column chromatography on silica gel.

9: (90%). mp 142°C. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.77; H, 7.74; N, 4.71. Found: 76.61; H, 7.78; N, 4.65. ^{1}H-NMR ($CDCl_3$) δ: 1.06(s,CH_3); 1.27(d,CH); 1.38(s,CH_3); 1.42(s,CH_3); 1.87(s,CH_3); 2.12(m,2H); 2.40(m,1H); 2.75(AB,2H); 7.40(m,C_6H_5). MS(EI) m/z: 297 (M^+).

10a: (98%). mp 153°C. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 77.88; H, 8.55; N, 4.13. Found: C, 77.55; H, 8.60; N, 4.10. ^{1}H-NMR ($CDCl_3$) δ : 0.86(d,CH_3); 0.88(d,CH_3); 1.01(s,$2CH_3$); 1.25(d,CH); 1.35(d,CH_3); 1.75(m,CH); 2.06(m,1H); 2.10(m,1H); 2.15(m,1H); 2.41(m,2H); 2.95(AB,2H); 7.42(m,C_6H_5). MS(EI) m/z: 339 (M^+).

10b: (92%). mp 163°C. Anal. Calcd for $C_{22}H_{23}NO_2$. Found: C, 78.05; H, 8.61; N, 4.29. ^{1}H-NMR ($CDCl_3$) δ: 0.80(d,CH_3); 0.86(d,CH_3); 1.16(s,CH_3); 1.27(d,CH); 1.45(s,CH_3); 1.76(s,CH_3); 1.85(m,2H); 2.15(m,2H); 2.40(m,1H) 2.60(m,1H); 2.95(AB system, 2H); 7.40(m,5H). MS(EI) m/z: 339 (M^+).

13: (92%). mp 167°C. Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.53; H, 8.31; N, 4.41. Found: C, 77.81; H, 8.45; N, 4.37. ^{1}H-NMR ($CDCl_3$) δ : 0.86(d,CH_3); 1.00(d,CH_3); 1.10(s,CH_3); 1.22(d,CH); 1.42(s,CH_3); 1.70(s,CH_3); 1.82(m,2H); 2.15(m,CH);

2.18(m,CH); 2.28(m,CH); 2.65(m,2H) 2.90(AB system, 2H); 7.43(m,5H). MS(EI) m/z: 325 (M^+).

5) Hydrolysis of lactones.

The lactone (2 mmole) was dissolved in THF then 10 ml of 6N HCl was added. The mixture was stirred at 70°C during 3h. The solution was extracted with ether. The aqueous layer was dried and refluxed 20 mn with 2 ml of propylene oxide and 6 ml of ethanol. After cooling the amino acid was filtered and purified.

11a: (65%). (R)-2-methyl-2-phenylglycine. mp 292°C (lit. 295°C); $[\alpha]_D^{20}$ = -86.9 (c=0.325 HCl 1N); (lit. -90.1, c=2.7, HCl 1N).

12a: (58%). (R)-2-phenylleucine. mp 270°C. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.57; H, 8.21; N, 6.76. Found: C, 69.88; H, 8.34; N, 6.61. $[\alpha]^{20}_D$ = -16.0(c=0.70,1N HCl). ^{1}H-NMR ($CDCl_3$) δ : 1.00 (d,6H); 1.50-2.15(m,3H); 7.56(br s,5H).

12b: (62%). (S)-2-phenylleucine. mp 272°C. Anal. Calcd for $C_{12}H_{17}NO_2$. Found: C, 69.90; H, 8.16; N, 6.84. $[\alpha]^{20}_D$ = +15.5 (c=0.58,1N HCl).

14: (60%). (S)-2-phenylvaline. mp 242°C. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.56; H, 7.66; N, 7.06. $[\alpha]^{20}_D$ = +20 (c=0.70, 1N HCl). ^{1}H-NMR ($CDCl_3$) δ : 0.95(d,6H); 2.16(m,1H); 7.52(br s,5H).

6) Hydrolysis of arylated Schiff bases 15 and 16.

They were performed using the general procedure described for the lactones.

11b: (67%). (S)-2-methyl-2 phenylglycine. (60%). mp 294°C (lit. 295°C). $[\alpha]^{20}_D$ = + 86.5 (c=0.52, 1N HCl); (lit. 90.1, c= 10 1N HCl).

12b: (65%). (S)-2-phenylleucine. mp 270-271°C. Anal. Calcd for $C_{12}H_{15}NO_2$. Found: C, 69.42; H, 8.44; N, 6.86. $[\alpha]^{20}_D$ = + 16,1 (c=0.390, 1N HCl).

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