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CHIRAL FERROCENYLALKYLAMINES FROM (-)-MENTHONE

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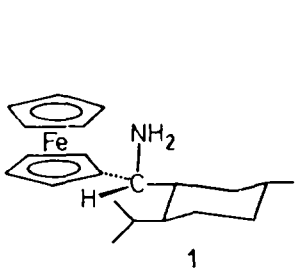
Abstract
Three enantiomerically pure α-ferrocenylalkylamines are directly obtained from (-)-menthone. The isomerizations of the α-ferrocenylalkyl carbocation intermediates are studied and exploited in stereoselective syntheses. These carbocations are the basis of the configurational assignment of the amines. Their usefulness as chiral templates of stereoselective four component condensations is demonstrated by the synthesis of a model compound for peptides.

The importance of chiral products led to a growing interest in asymmetric syntheses[1]. Catalytic systems[2] and recoverable chiral templates[3-5,7,8] are the main areas of research. Many syntheses, and very often the most elegant, have made use of the natural 'chiral pool'.

Chiral α-ferrocenylalkylamines, the starting materials for chelating chiral phosphane ligands in hydrogenation catalysts[2,6] and chiral templates in peptide synthesis by stereoselective four component condensation (4CC)[7,8], were only accessible via resolution of the racemates[9,10,11]. The resolution procedures are generally cumbersome processes and involve losses of resolving agent and amine. Accordingly we tried to prepare chiral ferrocenylalkylamines directly from materials belonging to the chiral pool. (-)-Menthol and (-)-menthone appeared favorable as starting materials, since they are inexpensive enantiomerically pure chiral compounds.



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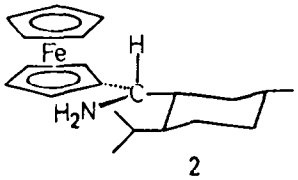

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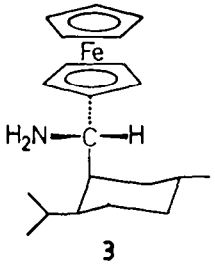

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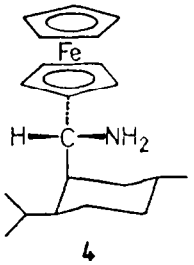


4

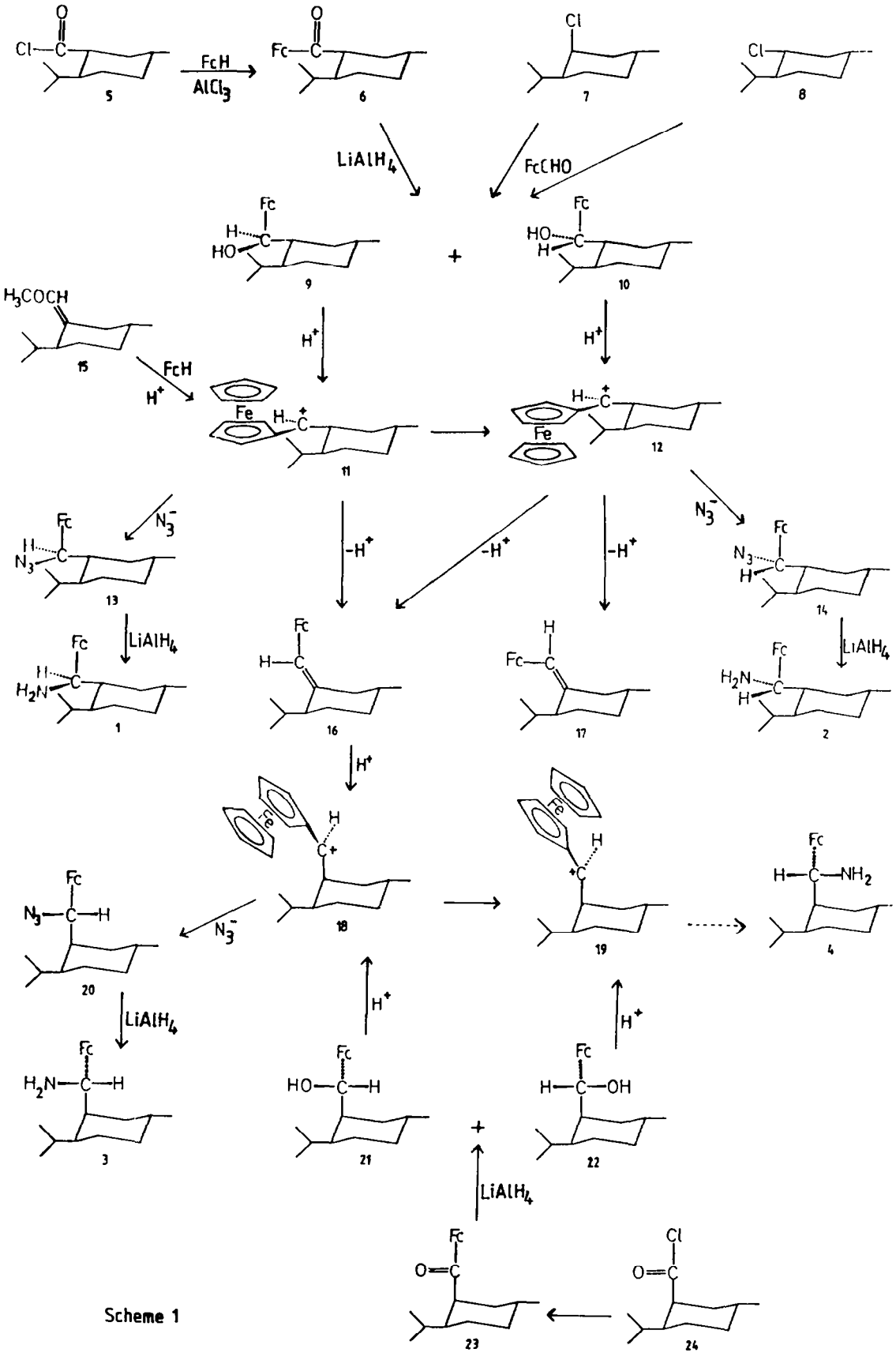
To ensure high enantiomeric excesses in asymmetric reactions, the amines should be of the type Fc-CH(NH_2)-R [11]. Four such diastereomeric amines may be obtained from (-)-menthol (compounds **1** - **4**).

The amines **1** and **2** are derived from the 'menthyl' system. They have all substituents of the cyclohexane system in equatorial positions, while **3** and **4** have the ferrocenylmethyl substituent in an axial position (the 'neomenthyl' system). The most straightforward approach to fix the position of the ferrocenylmethyl substituent would be a Friedel-Crafts acylation of ferrocene with 'menthyl' or 'neomenthyl' carboxylic acid chlorides, **5** or **24** respectively (see scheme 1). The corresponding acids **26** and **29** can be prepared from (-)-menthol in several steps[12]. The ferrocenyl menthyl (or neomenthyl) ketones **6** or **23** thus formed can be reduced to a mixture of diastereomeric alcohols **9** and **10** or **21** and **22**, respectively. While **9** and **10** can be separated by column chromatography, we found it impossible to separate the 'neomenthyl' alcohols **21** and **22**. The conversion of the alcohols to the amines proceeds with retention of the configuration[13] via the carbocations **11** and **12** (or **18** and **19** for the 'neomenthyl' system) with azide anion as a scavenger[11,14]. While the amines **1** and **2** can thus be prepared as pure enantiomers by reducing the azides **13** and **14**, **3** and **4** are obtained only as a hard to separate mixture of diastereomers. The reaction of ferrocene carboxaldehyde with the Grignard reagents from both 'menthyl' and 'neomenthyl' chlorides **7** and **8** yields the same diastereomeric mixture of the 'menthyl' alcohols **9** and **10** exclusively and can therefore not be considered as practical alternative. In order to obtain the pure amines **3** and **4**, another approach must be taken.

Carbonyl compounds react with ferrocene under acidic conditions to form α-ferrocenylalkyl carbocations that can be deprotonated to form alkenes or scavenged by nucleophiles to yield α-ferrocenylalkyl derivatives[15,16,17]. We thus tried to convert (-)-menthol and (-)menthone to the aldehydes **27** and **30** or one of their derivatives. The conversion of the carboxylic acids **26** and **29** or the nitriles **25** and **28** to the aldehydes[18] appeared unattractive because of the low yields. Although (-)-menthone gives smoothly the oxirane **31** by reaction with sulfoxonium ylid[19], we found it impossible to rearrange it to the aldehydes **27** or **30**. However, we were successful in preparing the enol ether **15** by the Wittig reaction of (-)-menthone with methoxymethylene-triphenylphosphorane[14] (Scheme 2).The enol ether **15** reacts smoothly with ferrocene under acidic conditions to form carbocations **11** and **12**. These, on deprotonation, produce the alkene **16** (see scheme 1).

Reprotonation of the alkene leads to the carbocation **18**. Trapping of the carbocation with azide and reduction of the intermediate yields only one amine. According to its X-ray structure this amine is 1-{amino[(1S,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(S)-methyl}-ferrocene, i.e. compound **3**[14].

Based on this result, configurational assignments of all species in scheme 1 are possible. For the nomenclature of chiral α-ferrocenylalkyl carbocations, we follow earlier suggestions[11]. The remarkable stability of the α-ferrocenylalkyl carbocations[20] is due to a relatively high rotational barrier around the ferrocene-$C^{\oplus}$-bond (about 100 kJ/mol)[21]. Thus, even sterically crowded cations exist long enough to allow spectroscopic measurements and to obtain derivatives by nucleophilic substitution. However, upon longer storage in solution, they tend to form the thermodynamically more stable isomers that may exist in equilibrium with minor amounts of the less stable isomer[11]. The reaction of the enol ether **15** with ferrocene leads to a 90 : 10 mixture of the carbocations **11** and **12**. If the reaction mixture is treated immediately with azide ion, the amine **1** can be isolated after reduction of the intermediate azide **13**, due to its tendency to crystallize, in pure state. Amine **2**, which is formed in 10% yield only, does not crystallize. If the reaction mixture is left at room temperature for about 6 hours, the rearrangement to the thermodynamically more stable cation **12** is complete. Its scavenging by azide, followed by reduction, gives the pure amine **2**. The acidolysis of the alcohols **9** and **10** leads exclusively to the carbocations **11** and **12**, respectively, as seen by comparison of their NMR spectra; this indicates that **11** and **12** (and thus **1** and **2**) belong to the 'menthyl' series (with equatorial position of all substituents of the cyclohexane ring).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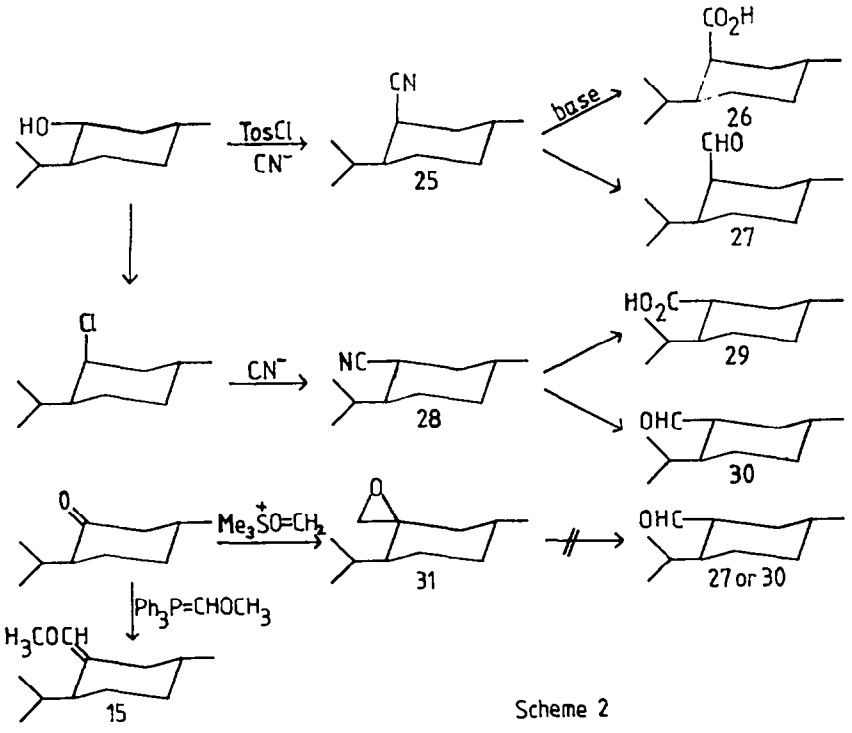
AlCl3
LiAlH4
FcCHO
H+
-H+
N3-
LiAlH4
FcH
H+
LiAlH4
LiAlH4
H+
H+
LiAlH4

Scheme 1

Table 1. ^{1}H-NMR spectra of ketones **6** and **23** and alkenes **16** and **17**, in $CDCl_3$ at 200 MHz (δ[ppm], J[Hz]).

compound	configuration	1	2 - 5	6 or 7	8 - 13	14, 14', 15
6	(1R,2S,5R)	4.22	4.83(m) 4.77(m) 4.50(m)	2.80 (dtr, J_1= 3.3, J_2=11.2)	1.90(m,1H) 1.74(m,3H) 1.34(m,2H) 0.90-1.20 (m,3H)	0.92(d,J=6.6) 0.90(d,J=6.6) 0.81(d,J=6.6)
23	(1S,2S,5R)	4.21	4.76(m) 4.46(m)	3.35(m)	2.04(m,2H) 1.76(m,3H) 1.52(m,1H) 1.33(m,1H) 1.03(m,1H) 0.80-0.95 (m,1H)	0.83(d,J=6.6) 0.89(d,J=6.8) 0.90(d,J=6.8)
16	E-(2S,5R)	4.12	4.17(m) 4.28(m)	5.89(s)	2.59(dd,1H, J_1= 3.6, J_2=12.8) 2.02(qua,1H, J = 6.6) 1.82(m,4H) 1.30(m,3H)	0.95(d,3H,J=6.6) 0.97(d,6H,J=6.4)
17[a]	Z-(2S,5R)	4.17	4.23(m, 3H) 4.73(m, 1H)	6.30(m)	-	-

a) Due to its instability, **17** could not be isolated in pure state. Assignment of the alkyl protons was therefore impossible.

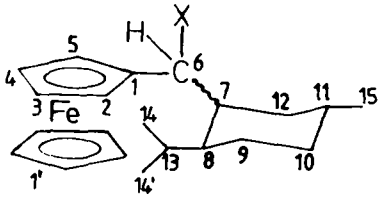


Scheme 2

Table 2. ^{1}H-NMR spectra of alcohols **9** and **10**, azides **13**, **14**, and **20**, and amines **1**, **2**, and **3**, in $CDCl_3$ at 200 MHz (δ[ppm], J[Hz]).

compound	configuration	1'	2 - 5	6	7	8-13	14,14',15	X
9	(1R,2S,5R,methyl R)	4.19	4.29(m) 4.17(m) 4.10(m)	4.74 (m)	2.25 (m)	1.75(m,1H) 1.67(m,2H) 1.43(m,1H) 1.31(m,1H) 1.16(m,1H) 0.76-1.01 (m,3H)	0.81(d, 6H; J= 6.8) 0.97(d, 3H;J= 7.0)	a
10	(1R,2S,5R,methyl S)	4.24	4.28(m) 4.17(m)	4.67 (m)	b	1.98(m,2H) 1.81(m,3H) 1.56(m,2H) 0.60-1.08 (m,3H)	0.88(d, J=6.8) 0.83(d, J=6.8) 0.81(d, J=6.6)	1.25
13	(1R,2S,5R,methyl R)	4.22	4.28(m) 4.17(m) 4.05(m)	4.78 (m)	2.12 (m)	1.63(m,3H) 1.28(m,3H) 0.65-1.05 (m,3H)	0.71(d, J=6.2) 0.84(d, J=6.8) 0.99(d, J=6.8)	-
14	(1R,2S,5R,methyl S)	4.21	4.04(m) 4.13(m) 4.18(m)	4.73 (d,J= 2.8)	2.06 (m)	1.60(m,3H) 1.26(m,3H) 0.71-1.01 (m,3H)	0.79(d, J=6.4) 0.83(d, J=6.8) 0.93(d, J=7.0)	-
20	(1S,2S,5R,methyl S)	4.20	4.03(m) 4.15(m) 4.28(m)	4.80 (m)	2.12 (m)	1.63(m,2H) 1.27(m,4H) 1.02(m,1H) 0.86(m,2H)	0.76(d, J=6,4) 0.84(d, J=6,8) 0.99(d, J=6.8)	-
1	(1R,2S,5R,methyl R)	4.14	4.23(m) 4.07(m)	c	2.16 (m)	1.65(m,2H) 1.26(m,4H) 0.80-1.00 (m,3H)	0.98(d, J=6.8) 0.83(d, J=7.0) 0.77(d, J=6.2)	1.54
2	(1R,2S,5R,methyl S)	4.16	4.10(m) 4.07(m)	c	2.14 (m)	1.71(m,2H) 1.54(m,4H 0.70-1.03 (m,3H)	0.91(d, J=7.0) 0.80(d, J=7.2) 0.79(d, J=6.4)	1.24
3	(1S,2S,5R,methyl S)	4.17	4.12(m) 4.25(m)	3.87 (d, J=6.4)	b	1.85(m,5H) 1.59(m,1H) 1.20(m,2H) 0.77(m,2H)	1.02(d, J=6.4) 0.94(d, J=6.6) 0.63(d, J=6.4)	1.56

a) Signal could not be detected due to overlap with alkyl moiety.
b) Signal not different from other alkyl signals.
c) Signal could not be detected due to overlap with ferrocene system.



The assignment of the configuration at the carbocationic centre is based on the behaviour of the cations towards bases. Cation **11** forms one alkene only, while cation **12** gives a mixture of two alkenes (about 1 : 1). Attempts to isolate the second alkene failed completely, it decomposes on chromatography, or on recrystallization. Only its NMR spectra could be obtained which suggest a Z-configuration for this compound. As deprotonation of the carbocations preferentially occurs in an "exo" mode[22], the E-alkene **16** should be formed from the sterically least crowded conformation of cation **11** and the Z-alkene **17** from the cation **12**. The fact that a mixture of **16** and **17** is obtained from cation **12**, is probably due to the instability of **17** which isomerizes and partly decomposes rapidly. Thus, the configuration of the cation **11** (and with it, the alcohol **9**, the azide **13** and the amine **1**) is shown to be (1R,2S,5R,methyl R), while cation **12** (and with it, alcohol **10**, azide **14** and amine **2**) is (1R,2S,5R,methyl S).

On the other hand the configuration of the 'neomenthyl' carbocation **18** and of the azide **20** must be (1S,2S,5R,methyl S), because of its relationship with amine **3**. If stored for a long period at room temperature (more than one week), a rearranged carbocation can be detected in solutions of **18**. Since this cation has a different ^{1}H-NMR pattern from that of **11**, **12**, and **18**, it must be the (1S,2S,5R,methyl R)-cation **19**. However, the rearrangement is so slow that decomposition of the cation solution occurs before its completion. Thus, amine **4** could not be obtained in pure state.

Table 3. ^{13}C-NMR spectra of alcohols **9** and **10**, azides **13**, **14**, and **20**, and amines **1**, **2**, and **3**, in $CDCl_3$ at 15.1 MHz.

compound	configuration	1'	1	2-5	6	7	8,11,13	9,10,12	14,14',15
9	(1R,2S,5R,methyl R)	68.34	93.25	69.33 67.69 67.23 67.05 66.02	[a]	45.76	43.22 35.16 26.35	33.55 32.65 24.42	22.81 21.55 15.58
10	(1R,2S,5R,methyl S)	68.28	90.91	69.83 68.19 67.69 67.40 66.11	[a]	44.18	43.68 35.02 26.67	34.46 32.35 24.18	22.75 21.34 15.28
13	(1R,2S,5R,methyl R)	68.96	89.86	67.79 67.27 67.07 65.71	63.37	46.94	43.63 34.94 26.56	33.83 32.47 24.09	22.66 21.43 15.45
14	(1R,2S,5R,methyl S)	68.91	86.26	67.61 67.49 67.22 67.02	63.74	44.53	43.01 35.04 26.61	34.72 32.29 23.92	22.60 21.22 15.14
20	(1S,2S,5R,methyl S)	68.75	91.99	68.10 67.90 66.41 65.10	67.51	62.92	49.65 41.80 38.68	35.76 29.66 26.74	24.72 22.52 22.26
1	(1R,2S,5R,methyl R)	68.31	95.01	67.40 66.61 66.14	49.98	46.49	43.54 35.28 26.32	33.14 32.65 24.41	22.75 21.55 15.52
2	(1R,2S,5R,methyl S)	68.25	91.82	67.68 67.25 66.67 66.35	49.89	45.24	43.33 34.87 26.41	34.37 32.53 24.13	22.75 21.29 15.25
3	(1S,2S,5R,methyl S)	68.13	97.00	68.89 67.19 66.38 65.35	49.48	49.28	42.45 37.68 29.83	35.66 26.85 24.89	22.54 22.22

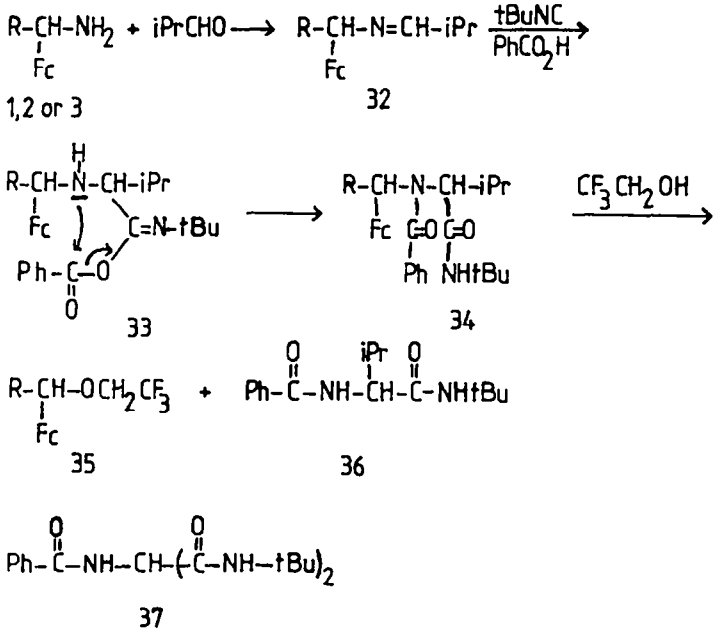
a) Signals not different from ferrocene signals

Table 4. ^{1}H-NMR spectra of carbocations **11**, **12**, and **18**, in D-trifluoroacetic acid, at 200 MHz (δ[ppm],J[Hz]).

compound	configuration	1'	3,4	2,5	6	7	8-13	14,14',15
11	(1R,2S,5R,methyl R)	5.05	6.37 (m)	5.11(m) 4.55(m)	7.63(d, J=6.4)	2.22 (m)	0.85-2.15 (m)	0.95(d,6H, J=6.0) 0.72(d,3H, J=6.8)
12	(1R,2S,5R,methyl S)	5.15	6.30 (m)	4.98(m) 4.47(m)	7.08(d, J=10.8)	2.42 (m)	0.95-2.30 (m)	1.11(d,3H, J=6.6) 1.03(d,6H, J=6.2)
18	(1S,2S,5R,methyl S)	5.17	6.37 (m)	5.09(m) 4.55(m)	7.67(m)	2.06 (d,J= 14.2)	0.70-2.25 (m)	1.12(d,3H, J=5.0) 0.91(d,6H, J=1.6)

Table 5. ^{13}C-NMR spectra of carbocations **11**, **12**, and **18**, in D-trifluoroacetic acid, at 15.1 MHz.

compound	1'	1	3,4	2,5	6	7	8	11	12	9,10,13	14,14',15
11	82.07	104.86	95.08 95.22	78.75 81.78	147.77	48.16	51.90	35.37	46.56	35.02 30.85 25.81	22.29 21.80 16.63
12	81.04	105.35	95.65 94.80	79.70 78.79	143.47	49.89	55.89	35.49	43.83	33.20 28.96 25.18	22.22 21.52 15.40
18	80.96	106.43	95.77 94.83	79.99 78.76	141.16	43.86	52.82	36.69	42.75	30.97 28.43 26.12	21.90 21.52 20.96



Scheme 3

The three amines **1**, **2**, and **3** have been tested for their ability to induce new chirality in the synthesis of a model compound for peptides by four component condensation (4CC) (Scheme 3). Thus, 2-methylpropanal and the amine have been condensed to the azomethine **32** which is subsequently treated with 2-isocyano-2-methylpropane and benzoic acid. The solvent of choice for many 4CC reactions is 2,2,2-trifluoroethanol[23]. During the course of the reaction, the ferrocenylalkyl residue is removed by acidolysis, the trifluoroethyl ether **35** is formed. Thus, the optical rotation of the valine derivative **36** is directly indicative for the inducing ability of the amine. In 2,2,2-trifluoroethanol as solvent, the formation of malonamide derivative **37** is completely suppressed[11,24]. For comparison, the results obtained with 1-ferrocenyl-2-methylpropyl amine **38**, the standard amine used in most cases, are included in table 6.

Table 6. Four component condensations of the amines **1**, **2**, **3**, and **38**.

amine	chemical yield(%)	$[\alpha]_D^{20}$(of **36**)[a]	e.e.(%)[b]	configuration of **36**
1	46	-39	64	S
2	59	- 3.1	5	S
3	48	+ 3.0	5	R
(S)-(+)-**38**	52	-24.0	39	S

a) c = 1, in $CHCl_3$/acetic acid 1:1 b) e.e. = enantiomeric excess

The results indicate a remarkable difference between the amines **2** and **3** on the one hand (whose induction is negligible) and the amine **1** on the other, which gives even better results than the amine **38** and is therefore particularly well-suited for stereoselective peptide syntheses by 4CC.

Experimental

^{1}H-NMR spectra have been obtained with Jeol PMX 60 and Bruker WP 200 instruments, ^{13}C-NMR spectra with a Jeol FX 60 instrument. IR spectra have been measured with a Perkin-Elmer 157 and optical rotations with a Roussel Jouan Digital 71 instrument. Mass spectra have been obtained with a Varian CH 5 instrument.

The preparation of the acid chlorides[12] **5** and **24**, the chlorides[12] **7** and **8** and the enol ether[14] **15** has already been described. The synthesis of the ketones **6** and **23** follows known procedures[25], as well as the reduction of the ketones to the alcohols **9** and **10**, and **21** and **22**, respectively[11].

From acid chloride **24**, a mixture of 'menthyl' ketone **6** and 'neomenthyl' ketone **23** is obtained which is separated by chromatography (silica gel, dichloromethane), **6**: R_f = 0.5, **23**: R_f = 0.7.

1-{Oxo[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-methyl}-ferrocene 6
Yield (from **5**): 80%, from **24**: 55%. $[\alpha]_D^{20}$ = - 32.7 (c = 0.3, benzene). M.p. 93° C. MS: 352 (M^+, 100%). $C_{21}H_{28}FeO$ (352.30) calc. C 71.59 H 8.01, found C 71.79 H 8.22.

1-{Oxo[(1S,2S,5R)-2-isopropyl-5-methylcyclohexyl]-methyl}-ferrocene 23.
Yield (from **24**): 25%. $[\alpha]_D^{20}$ = - 11.4 (c = 1, benzene). M.p. 101° C. MS: 352 (M^+, 100%). $C_{21}H_{28}FeO$ (352.30) calc. C 71.59 H 8.01, found C 71.76 H 8.26.

The reduction of ketone **6** leads to a mixture of alcohols **9** and **10** which can be separated by chromatography (silica gel, dichloromethane), **9**: R_f = 0.6, **10**: R_f = 0.4.

Reduction of ketone **23** leads to a mixture of alcohols **21** and **22** (about 1 : 1), which could not be separated. $[\alpha]_D^{20}$ = + 5.3 (c = 1, benzene).

1-{Hydroxy[(1R,2S,5S)-2-isopropyl-5-methylcyclohexyl]-(R)-methyl}-ferrocene 9.
Yield: 72%. $[\alpha]_D^{20}$ = - 6.8 (c = 0.5, benzene). M.p. 92 - 93° C. MS: 354 (M^+, 96%) 215 (100%). $C_{21}H_{30}FeO$ (354.30) calc. C 71.19 H 8.53, found C 71.35 H 8.43.

1-{Hydroxy[(1R,2S,5S)-2-isopropyl-5-methylcyclohexyl]-(S)-methyl}-ferrocene 10. Yield: 16%. $[\alpha]_D^{20}$ = - 80.0 (c = 0.5, benzene). M.p. 95 - 97° C. MS: 354 (M^+, 93%) 215 (100%). $C_{21}H_{30}FeO$ (354.30) calc. C 71.19 H 8.53, found C 71.27 H 8.63.

The Grignard reaction[12] of the chlorides **7** and **8** with ferrocenecarboxaldehyde follows standard procedures and leads to 36% of **9** and 24% of **10**, separated as above.

The solutions of the carbocations **11**, **12**, **18** and **19** for NMR spectroscopy have been prepared by dissolving about 200 mg of the alcohols **9**, **10**, or the mixture of **21** and **22**, or the alkene **16** in 1.5 ml of deuterated trifluoroacetic acid. For cations **11** and **12**, enol ether **15** (100 mg) and ferrocene (100 mg) may be dissolved together in 1.5 ml of D-trifluoroacetic acid.

Carbocations **11** and **12** from enol ether **15**:

Following a known procedure[16], 0.1 mol (18.2 g) of **15** and 0.1 mol (18.6 g) of ferrocene are dissolved under nitrogen in 100 g of trichloroacetic acid and 15 ml of dichloromethane. The mixture is cooled to - 10° C and under stirring, 0.2 mol (15.0 ml) of fluorosulfonic acid are added dropwise. Stirring is continued for 35 minutes at - 10° C. The solution then contains a 9 : 1 mixture of the carbocations **11** and **12**. If stirring is continued under nitrogen for 6 h at room temperature, the solution contains exclusively carbocation **12**.

Deprotonation of the carbocations **11** and **12**:

The solutions are neutralized slowly with 30% aqueous sodium hydroxide in such a manner not to rise the temperature above 40° C. From **11**, alkene **16** is isolated exclusively and purified as described[14]. Yield: 75%. $[\alpha]_D^{20}$ = - 128.7 (c = 1, benzene). M.p. 53° C (from hexane).

From **12**, a mixture of the alkenes **16** and **17** is obtained (about 1 : 1). Due to its instability, **17** could not be isolated in pure state. Preparation and properties of amine **3** from alkene **16** via cation **18** and azide **20** have been described already[14].

Scavenging of the cations **11** and **12** with lithium azide follows published methods[11,14]. For the reduction to the amines, purification of the azides **13** and **14** is not necessary. For analytical purposes, they may be purified by chromatography (silica gel, hexane).

1-{Azido[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(R)-methyl}-ferrocene 13. Yield: 75%. $[\alpha]_D^{20}$ = + 31.3 (c = 0.5, benzene). M.p. 98° C (from hexane). MS: 379 (M^+, 82%) 121 (100%). IR: 2095 (vs) (KBr). $C_{21}H_{29}FeN_3$ (379.34) calc. C 66.49 H 7.71 N 11.08, found C 66.71 H 7.83 N 10.94.

1-{Azido[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(S)-methyl}-ferrocene 14. Yield: 72%. $[\alpha]_D^{20}$ = - 94.2 (c = 1.5, benzene). Oil. MS: 379 (M^+, 84%) 121 (100%). IR: 2090 (vs) (film). $C_{21}H_{29}FeN_3$ (379.34) calc. C 66.49 H 7.71 N 11.08, found C 66.45 H 7.48 N 11.05.

The reduction of the azides with $LiAlH_4$ is as standard procedure already described[11,14].

1-{Amino[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(R)-methyl}-ferrocene 1. Yield: 70% (from **13**). $[\alpha]_D^{20}$ = - 41.1 (c = 0.5, benzene). M.p. 83° C (from hexane). MS: 351 (M^+, 13%) 214 (100%). $C_{21}H_{31}FeN$ (353.34) calc. C 71.39 H 8.84 N 3.96, found C 71.27 H 8.95 N 3.88.

1-{Amino[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]-(S)-methyl}-ferrocene 2. Yield 89% (from **14**). $[\alpha]_D^{20}$ = - 59.1 (c = 1.5, benzene). Oil. MS: 351 (M^+, 18%) 214 (100%). $C_{21}H_{31}FeN$ (353.34) calc. C 71.39 H 8.84 N 3.96, found C 71.24 H 8.80 N 3.82.

Four component condensations:

The amine (**1**, **2**, **3** or **38**) (10 mmol) and 2-methylpropanal (1.1 g, 15 mmol) are dissolved in CCl_4 (15ml) and stirred with 5 g of molecular sieve (4 Å) for 1 h. TLC indicates complete formation of azomethine **32**. After filtering and evaporating of the solvent and excess aldehyde, the residue is dissolved in 10 ml of 2,2,2-trifluoroethanol. Benzoic acid (1.83 g, 15 mmol) and 2-isocyano-2-methylpropane (0.83 g, 10 mmol) are added and the mixture is stirred at room temperature for 4 hours. Hexane (100 ml) is added and the precipitated valine derivative **36** is isolated by filtration. (S)-**36** has an optical rotation $[\alpha]_D^{20}$ = - 61.4 (c = 1, $CHCl_3$/acetic acid 1 : 1)[26]. Yields are reported in table 6.

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References

1. D. Enders and R.W. Hoffmann, Chem. i. u. Z., 1985, **19**, 177; see also: J. Dugundji, R. Kopp, D. Marquarding and I. Ugi, Top. Curr. Chem., 1978, **75**, 165.
2. T. Hayashi and M. Kumada, Acc. Chem. Res., 1982, **15**, 395.
3. K.B. Sharpless and T.R. Verhoeven, Aldrichimica Acta, 1979, **12**, 63.
4. D. Enders, 'Selectivity - A Goal for Synthetic Efficiency', W. Bartmann and B.M. Trost, Eds., Verlag Chemie, Weinheim 1984.
5. D. Seebach, A.K. Beck, M. Schiess, L. Widler, and A. Wonnacott, Pure Appl. Chem., 1983, **55**, 1807.
6. K. Yamamoto, J. Wakatsuki, and R. Sugimoto, Bull. Chem. Soc. Jpn., 1980, **53**, 1132.
7. I. Ugi, 'The Peptides', Vol II. E. Gross and J. Meienhofer, Eds., Academic Press: New York 1980.
8. I. Ugi, D. Marquarding, and R. Urban, 'Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins', Vol. VI, B. Weinstein, Ed., Marcel Dekker: New York 1982.
9. K. Schlögl and M. Fried, Monatsh. Chem., 1964, **95**, 558.
10. G. Eberle, I. Lagerlund, I. Ugi, and R. Urban, Tetrahedron, 1978, **34**, 977.
11. R. Herrmann, G. Hübener, F. Siglmüller, and I. Ugi, Liebigs Ann. Chem., **1986**, 251.
12. J.G. Smith and G.F. Wright, J. Org. Chem., 1952, **17**, 1116.
13. G.Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch, and I. Ugi, Angew. Chem., 1970, **82**, 77; Angew. Chem. Int. Ed. Engl., 1970, **9**, 64.
14. A. Gieren, C.P. Kaerlein, T. Hübner, R. Herrmann, F. Siglmüller, and I. Ugi, Tetrahedron, 1986, **42**, 427.
15. R. Herrmann and I. Ugi, Angew. Chem., 1979, **91**, 1023; Angew. Chem. Int. Ed. Engl., 1979, **18**, 956.
16. R. Herrmann and I. Ugi, Tetrahedron, 1981, **37**, 1001.
17. B. Misterkiewicz, J. Organomet. Chem., 1982, **224**, 43.
18. H.C. Brown and C.P. Garg, J. Am. Chem. Soc., 1964, **86**, 1085.
19. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 1965, **87**, 1353.
20. W.E. Watts, J. Organomet. Chem. Libr., 1979, **7**, 399.
21. T.D. Turbitt and W.E. Watts, J. Chem. Soc., Perkin Trans. 2, **1974**, 177.
22. C.A. Bunton, W. Crawford, N. Cully and W.E. Watts, J. Chem. Soc., Perkin Trans. 1, **1980**, 2213.
23. R. Obrecht and I. Ugi, unpublished results.
24. A. Gieren, B. Dederer, G. George, D. Marquarding, and I. Ugi, Tetrahedron Lett., **1977**, 1503.
25. G. Gokel and I. Ugi, J. Chem. Educ., 1972, **49**, 294.
26. D. Marquarding, P. Hoffmann, H. Heitzer, and I. Ugi, J. Am. Chem. Soc., 1970, **92**, 1969.