Tetrahedron Letters,Vol.28,No.20,pp 2243-2246,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

α-Alkylation of Acyclic Amino Acids with Self-Reproduction of the Center of Chirality. A new route to (S)-(+)-α-Alkylated Aspartic Acids.

Antoine FADEL* and Jacques SALAÜN

Laboratoire des Carbocycles, U.A. C.N.R.S. 478, Bâtiment 420, I.C.M.O,
Université de Paris-Sud, 91405 ORSAY CEDEX (France)

Summary : The amino acids 1a-d (alanine, phenylalanine, valine and methionine) are alkylated by ethyl bromoacetate, with inversion of configuration, to provide readily with high stereoselectivity the α-alkylated aspartic acids 9a-d through the chiral enolates 7a-d of the trans (2R,4S) oxazolidinones 6a-d, major products of cyclization of the imines 5a-d with benzoyl chloride.

Many optically active α-alkyl amino acids having the configuration found in the corresponding natural products are important enzyme inhibitors and present other interesting pharmaceutical activities[1]. We have previously shown that the amino acids 1 [2] could be alkylated [3] through the chiral enolates 3 derived from the cis 2-(t-butyl)oxazolidinones 2. We now report herein, that the alkylation of 1a-d with ethyl bromoacetate opens a convenient way to optically active α-alkylated aspartic acids.

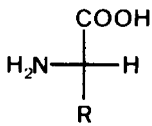
The sodium salts of the amino acids (S)-alanine 1a, (S)-phenylalanine 1b, (S)-valine 1c, and (S)-methionine 1d were first condensed with benzaldehyde to give the Schiff bases 5a-d respectively. Then 5a-d were cyclized by addition of benzoyl chloride at 0°C in CH_2Cl_2 and warming to room temperature with a modification [2] of the procedure previously reported[4] to provide a trans-cis mixture of phenyloxazolidinones 6. Comparison of the chemical shifts of the protons at C_2 and C_4 of cis and trans 2-(t-butyl)oxazolidinones 2 [2] with the corresponding protons of cis and trans 2-phenyloxazolidinones 6a-d, as well as the configuration of the product of alkylation 9a, led to consider a trans configuration for the major isomers of 6a-d [5,6]. (Trans/cis ratio : from 3:1 to 7.5:1, see scheme). The trans 2-phenyloxazolidinones 6a-d were separated by crystallization from a 1:3 mixture of methylene chloride and ether.

Upon treatment, with lithium hexamethyldisilazide (LHMDS [7], 1.1 equiv.) in THF à -78°C, the trans oxazolidinones 6a-d led to the enolates 7a-d, respectively. Then alkylation of 7a-d with 1.6 equiv. of ethyl bromoacetate (THF, -78°C, 1 h, warming to -10°C within 3 h, and work-up with AcOH at -50°C) followed by CH_2Cl_2 extraction provided stereospecifically the -enantiomeric- products 8a-d in high yields (85-95%) and high diastereoisomeric selectivity (above 95% ds, before crystallization [5,8]), comparable to those obtained from the lithium enolates of (t-butyl)-oxazolidinones [2], and imidazolidinones [9] or from the corresponding potassium enolates [4a].

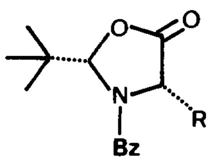
In every case the alkyl group entered the less shielded face of 7a-d, i.e. from the side opposite to the aryl group (R, Si face : ul approach) [10] implying the inversion of the original configuration (1 ⟶ 9). On the other hand, the alkylation of amino acids via the enolates 3 (from the cis oxazolidinone 2), occured too from the less shielded face but provided the products of retention of configuration (1 ⟶ 4) [2].

Finally, the α-alkylated aspartic acids 9a-d were generated from the oxazolidinones 8a-d upon simple acidic hydrolysis with 40% HBr at reflux for 3 h, and concentration followed by ion exchange (activated Dowex 50X.8.100) [2]. In this way 8a-d were converted into the (S)-(+)-α-alkylaspartic acids 9 [5,11] in 95% yield with high enantiomeric excess (ee > 95%) [12].

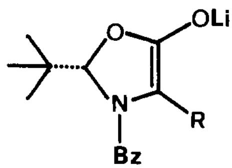
The α-methylation of aspartic acid 9a [13], via imidazolidinone , has been previously reported in 10 steps [14]. Much more readily this alkylation of the amino acids 1a-d with ethyl bromoacetate which involves the intermediacy of the trans N,O-heterocycles 6 prepared from inexpensive benzaldehyde [15], provided in three steps only α-substituted aspartic acids, with comparable reactivity and selectivity and milder cleavage conditions. While the α-benzylaspartic acid 9b (R = benzyl) has been already prepared in the racemic form [16], on the other hand 9c (R = isopropyl) and 9d (R = $CH_3SCH_2CH_2$-) were still unknown.



1a R = CH_3
b = benzyl
c = isopropyl
d = $CH_3SCH_2CH_2$-

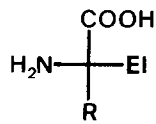


2

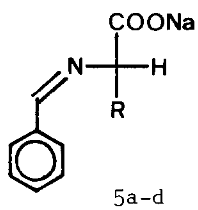


3

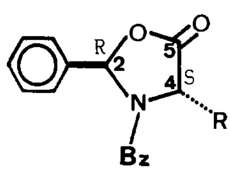
Bz = C_6H_5CO



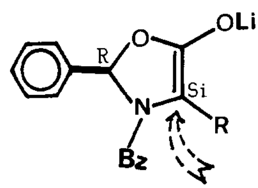
4



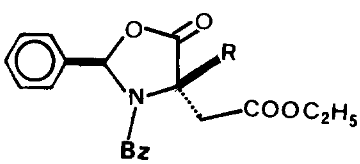
5a-d



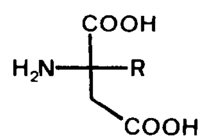
	Trans/cis	Y%
6a	7.5:1	94
b	3 :1	88
c	4.5:1	92
d	4 :1	93



(R)-7a-d
ul-approach



8a-d ds > 95%
(85-94%)



(S)-(+)-9a-d
(94-95%)

References

1) Amino Acids, Peptides and Proteins the Chemical Society : London 1979, vol. 10, p. 11.

2) D. Seebach and A. Fadel, Helv. Chim. Acta, 68, 1243 (1985).

3) See for α-alkylated amino acids : a) R. Naef, D. Seebach, Helv. Chim. Acta, 68, 135 (1985); D. Seebach, J.D. Aebi, R. Naef, Th. Weber, Helv. Chim. Acta, 68, 144 (1985) and references cited therein ; b) U. Schöllkopf, Pure Appl. Chem. 55, 1799 (1983) ; U. Schöllkopf, Topics Curr. Chem. 109, 65 (1983).

4) a) S. Karady, J.S. Amato, L.M. Weinstock, Tetrahedron Lett. 25, 4337 (1984) ; b) cf. also R.G. Hiskey, J.M. Jung, J. Am. Chem. Soc., 85, 578 (1963).

5) Satisfactory spectral and analytical data were obtained on all new compounds.

6) 6a : mp = 164.8°C ; $[\alpha]_D^{20}$ = +225.0° (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1803, 1660 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) : 7.7-6.9 (m, 10 arom. H), 6.76 (s, H-C(2)), 4.86 (q, J = 6.5 Hz, H-C(4)), 1.5 (d, J = 6.5 Hz, CH_3-C(4)). ^{13}C-NMR ($CDCl_3$) : 172.56 (s, C(5)), 170.48 (s, CON), [12 arom. C : 136.50 (s), 135.27 (s), 131.41 (d), 130.04 (d), 128.83 (4d), 127.04 (2d), 126.64 (2d)], 90.44 (d, C(2)), 52.91 (d, C(4)), 17.71 (q, CH_3).

6b : mp = 184.3°C ; $[\alpha]_D^{20}$ = +385.2° (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1802, 1655 cm^{-1} ; ^{1}H-NMR($CDCl_3$): 7.6-6.7 (m, 15 arom. H), 5,83 (s, H-C(2)), 5.2 (m, H-C(4)), 3.4 (AB, br, J = 13.5 Hz, CH_2 benzyl); ^{13}C-NMR ($CDCl_3$) : 171.35 (s, C(5)), 169.33 (s, CON), [18 arom. C : 136.19 (s), 135,29 (s), 130.88 (s), 129.93 (2d), 128,93 (2d), 128.59 (4d), 127.79 (4d), 126.71 (4d)], 91.29 (d, C(2)), 57.78 (br.d, C(4)), 34.92 (br.t. CH_2 benzyl).

6c : mp = 178.1°C ; $[\alpha]_D^{20}$ = +221.8° (c = 1, $CHCl_3$) ; IR ($CHCl_3$), 1800, 1655 cm^{-1}, ^{1}H-NMR ($CDCl_3$): 7.9-6.7 (m, 10 arom. H), 6.62 (s, H-C(2)), 4.92 (d, J = 3 Hz, H-C(4)), 2.70 and 1.78 (AB, br, H_2-C-C(4)), 1.17 (d, J = 7.5 Hz, CH_3). 1.08 (d, J = 7.5 Hz, CH_3) ; ^{13}C-NMR ($CDCl_3$) : 170.29 (s, C(5)), 169.97 (s, CON), [12 arom. C : 136.73 (s), 135.44 (s), 131.15 (d), 129.88 (d), 128.69 (4d), 126.88 (2d), 126.75 (2d)], 91.39 (d, C(2)), 60.80 (br.d, C(4)), 30.64 (br.d), 17.86 (q), 16.79 (br.q).

6d : mp = 157.0°C ; $[\alpha]_D^{20}$ = +280.4°C (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1796, 1655 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) : 7.57-6.88 (m, 10 arom. H), 6.74 (s, H C(2)), 5.00 (t, J = 4.8 Hz, H-C(4)), 2.85-2.20 (m, $2CH_2$), 2.07 (s, CH_3-S-) ; ^{13}C-NMR ($CDCl_3$) : 172.06 (s, C(5)), 170.6 (s, CON), [12 arom. C : 136.7 (s), 135.1 (s), 131.31 (d), 129.98 (d), 128.74 (d), 126.91 (d), 126.76 (d)], 91.18 (d, C(2)), 55.22 (d, C(4)), 28.66 (2t), 14.89 (q).

7) To improve the formation of enolates 7, lithium diisopropylamide (LDA) and lithium diethylamide (LDEA) must be used in the cases of 6d and 6c respectively.

8) 8a : mp = 109.4°C, $[\alpha]_D^{20}$ = +220.1° (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1800, 1725, 1650 cm^{-1}, ^{1}H-NMR ($CDCl_3$) : 7.70 - 6.76 (m, 10 arom. H), 6.69 (s, H-C(2)), 4.24 (q, J = 7.25 Hz, CH_2 ester), 3.51 (AB, J = 18 Hz, CH_2-C(4)), 2.01 (s, CH_3-C(4)), 1.32 (t, J = 7.25 Hz, CH_3 ester) ; ^{13}C-NMR ($CDCl_3$): 174.08 (s, COO), 170.93 (s, C(5)), 169.13 (s, CON), [12 arom. C : 136.10 (s), 135.87 (s), 129.89 (d), 129.69 (d), 128.47 (2d), 128.37 (2d), 127.20 (2d), 125.91 (2d)], 91.21 (d, C(2)), 61.29 (t), 60.42 (s, C(4)), 38.96 (t), 24.28 (q), 14.10 (q).

8b : mp = 183.0°C ; $[\alpha]_D^{20}$ = +69.6° (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1800, 1730, 1650 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) : 7.60-7.32 (m, sh, 5 arom. H), 7.32-6.76 (m, 8 arom. H), 6.67 (d.d, J = 7 and J = 7.3 Hz, 2 arom. H), 6.51 (s, H-C(2)), 5.55 (d, J = 7 Hz, 2 arom. H), 4.27 (q, J = 7 Hz, CH_2 ester), 3.61 (AB, J = 17.5 Hz, H_2C-COO), 3.71 (AB, J = 13.5 Hz, CH_2 benzyl), 1.35 (t, J = 7 Hz, CH_3 ester) ; ^{13}C-NMR ($CDCl_3$) : 173.08 (s, COO), 170.87 (s, C(5)), 169.82 (s, CON), [18 arom. C : 136,43 (s), 135.20 (s), 134.50 (s), 130.88 (2d), 129.38 (d), 129.16 (2d), 128.97 (d) ; 128.22 (2d), 127.86

(2d, s), 127.72 (2d), 125.28 (2d)], 91.65 (d, C(2)), 66.23 (s, C(4)), 61.42 (t), 42.32 (t), 39.08 (t), 14.14 (q).

8c : mp = 82.5°C ; $[\alpha]^{20}$ = +166.1° (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1795, 1730, 1652 cm^{-1} ; ^1H NMR ($CDCl_3$) : 7.36-7.05 (m, 10 arom. H), 6.79 (s, H-C(2), 4.24 (q, J = 7 Hz, CH_2 ester), 3.55 (AB, J = 18 Hz, CH_2-C(4)), 2.75 (sept., J = 7 Hz, CH isopropyl, 1.34 (t, J = 7 Hz, CH_3 ester), 1.27 (d, J = 7 Hz, CH_3), 1.23 (d, J = 7 Hz, CH_3) ; ^{13}C-NMR ($CDCl_3$) : 172.39 (s, COO), 171.64 (s, (C5)), 170.66 (s, CON), [12 arom. C : 136.46 (s), 135.65 (s), 129.84 (2d), 129.55 (2d), 128.48 (2d), 128.34 (2d), 127.55 (2d), 126,11(2d)], 90.52 (d, C(2)), 67.67 (s, C(4)), 61.33 (t), 36.00 (t), 35.46 (d), 18.73 (q), 18.27 (q), 14.11 (q).

8d : mp = 126.6°C ; $[\alpha]^{20}$ = +137.3° (c = 1, $CHCl_3$) ; IR ($CHCl_3$) : 1795, 1730, 1655 cm^{-1} ; ^1H NMR ($CDCl_3$) : 7.40 - 6.85 (m, 10 arom. H), 6.76 (s, H C(2)), 4.25 (q, J = 7.2 Hz, CH_2 ester), 3.46 (AB, J = 18 Hz, H_2C-C(4)), 2.97 - 2.45 (m, $2CH_2$), 2.17 (s, CH_3-S-), 1.32 (t, J = 7.2 Hz, CH_3 ester) ; ^{13}C-NMR ($CDCl_3$) : 171.20 (s, COO), 170.89 (s, C(5)), 170.00 (s, CON), [12 arom. C : 136.50 (s), 135.68 (s), 130.04 (d), 129.79 (d), 128.49 (4d), 127.49 (2d), 125.96 (2d)], 91.14 (d, C(2)), 63.83 (s, C(4)), 61.45 (t), 37.70 (t), 37.32 (t), 28.79 (t), 15.75 (q), 14.04 (q).

9) D. Seebach, M. Boes, R. Naef, W.B. Schweizer, J. Am. Chem. Soc. 105, 5390 (1983).

10) D. Seebach, V. Prelog, Angew. Chem. Int. Ed. Engl. 21, 654 (1982).

11) 9a : mp = 248.0° Dec. $[\alpha]^{20}$ = +52.83° (c = 0.60, H_2O) (Lit.[14] mp = 245-248° Dec. $[\alpha]_D$ = +53.3°(c= 0.67, H_2O) ; IR (KBr) : 3400, 3140, 1592 cm^{-1} ; ^1H-NMR (D_2O) (HOD, 4.8 ppm) : 2.74 (AB, J = 17 Hz, CH_2), 1.48 (s, CH_3).

9b : mp = 235° Dec. $[\alpha]^{20}$ = +50.88° (c = 0.8, H_2O) ; IR (KBr) : 3400 br, 3140 br, 1605 br cm^{-1} ; ^1H-NMR (D_2O) (HOD, 4.8 ppm) : 7.47-7.31 (m, 3 arom. H), 7.31-7.15 (m, 2 arom. H), 3.11 (AB, J = 14 Hz, CH_2 benzyl), 2.84 (AB, J = 18 Hz, H_2C-COO).

9c : mp = 190°. $[\alpha]^{20}$ = +55.38° (c = 0.86, H_2O) ; IR (KBr) : 2430, 3160, 1605 cm^{-1} ; ^1H-NMR (D_2O) (HOD, 4.8 ppm) : 2.76 (AB, J = 17 Hz, CH_2), 2.05 (sept, J = 7 Hz, CH), 0.99 (d, J = 7 Hz, CH_3), 0.98 (d, J = 7 Hz, CH_3).

9d : mp = 122°. $[\alpha]^{20}$ = +40.57° (c = 0.8, H_2O) ; IR (KBr) : 3400, 3120, 1605 cm^{-1} ; ^1H-NMR (D_2O) (HOD, 4.8 ppm) : 2.76 (AB, J = 18 Hz, CH_2COO), 3.00-1.90 (m, $2CH_2$), 2.12 (s, CH_3).

12) The enantiomeric excesses were determined by comparison with lit. (9a)[14] while for the unknown amino acids (9b-d) their optical rotations were not significantly improved after several recrystallizations.

13) S. Terashima, K. Achiwa, S.-I. Yamada, Chem. Pharm. Bull. 14, 572 (1966) ; 14, 1138 (1966).

14) J.D. Aebi, D. Seebach, Helv. Chim. Acta, 68, 1507 (1985) and references cited therein.

15) Comparatively to very expensive pivalaldehyde used to prepare 2.

16) B. Kuebel, P. Gruber, R. Hurnans and W. Steglich, Chem. Ber. 112, 128 (1979).

(Received in France 18 February 1987)