Supporting Information

O–N Intramolecular alkoxycarbonyl Migration of Typical Protective Groups in Hydroxyamino Acids

Mariusz Skwarczynski, Youhei Sohma, Mayo Noguchi, Tooru Kimura, Yoshio Hayashi^{},
and Yoshiaki Kiso^{*}*

Table of contents:

1. Figure 1S	S1
2. Spectroscopic data for compounds 1b-d , 2b-d , 5b and 6a,b .	S2-S5
3. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 1b .	S8-S9
4. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 1c .	S10-S11
5. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 1d .	S12-S13
6. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 2a .	S14-S15
7. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 2b .	S16-S17
8. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 2c .	S18-S19
9. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 2d .	S20-S21
10. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 5a .	S22-S23
11. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 5b .	S24-S25
12. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 6a .	S26-S27
13. Copy of ¹ H, ¹³ C NMR spectra and HPLC profile - 6b .	S28-S29

Figure 1S. HPLC profile of O–N intramolecular alkoxycarbonyl migration of the etoxycarbonyl group.

(2*R*,3*S*)-3-Amino-2-[(9H-fluoren-9-ylmethoxycarbonyl)oxy]-4-phenylbutanoic acid methyl ester, hydrochloride, 1b

The procedure described for **1a** using 9H-fluoren-9-ylmethoxycarbonyl chloride afforded **1b**:

¹H NMR (CD₃OD, 400 MHz): δ 7.83 (d, ³*J*(H,H) = 7.3 Hz, 2 H, CH), 7.68 (dd, ³*J*(H,H) = 0.5, 7.5 Hz, 2 H, CH) 7.44-7.29 (m, 7 H, CH), 7.16-7.14 (m, 2 H, CH), 4.89 (d, ³*J*(H,H) = 2.2 Hz, 1H, CH), 4.78, 4.75 (2dd, ²*J*(H,H) = 15.2 Hz, ³*J*(H,H) = 5.5, 5.7 Hz, 2 H, CH₂), 4.31 (bt, ³*J*(H,H) = 5.5 Hz, 1 H, CH), 4.00 (bt, ³*J*(H,H) = 7.0 Hz, 1 H, CH), 3.74 (s, 3 H, CH₃), 2.97, 2.84 (2dd, ²*J*(H,H) = 13.7 Hz, ³*J*(H,H) = 6.4, 9.3 Hz, 2 H, CH₂). ¹³C NMR (CD₃OD, 100 MHz): δ_c 168.6, 155.1, 144.7, 144.5, 142.9, 142.8, 135.6, 130.39, 130.37, 129.11, 129.05, 129.0, 128.3, 125.92, 125.90, 121.1, 73.4, 71.2, 53.94, 53.89, 48.2, 36.7. HRMS (FAB+): calcd. For C₂₆H₂₆NO₅ [*M*⁺+H]: 432.1811, found: 432.1815. Purity was higher than 99% (HPLC analysis at 230 nm).

(2*R*,3*S*)-3-Amino-2-[(2,2,2-trichloroethoxycarbonyl)oxy]-4-phenylbutanoic acid methyl ester, hydrochloride, 1c

The procedure described for **1a** using 2,2,2-trichloroethoxycarbonyl chloride afforded **1c**: ¹H NMR (CD₃OD, 400 MHz): δ 7.41-7.28 (m, 5 H, CH), 5.08 (d, ³*J*(H,H) = 2.4 Hz, 1H, CH), 5.00 (s, 2H, CH₂) 4.15 (ddd, ³*J*(H,H) = 2.4, 6.6, 9.1 Hz, 1 H, CH), 3.81 (s, 3 H, CH₃), 3.13, 3.04 (2dd, ²*J*(H,H) = 13.9 Hz, ³*J*(H,H) = 6.6, 9.1 Hz, 2 H, CH₂). ¹³C NMR (CD₃OD, 100 MHz): δ_c 168.1, 154.2, 135.6, 130.43, 130.42, 129.1, 95.6, 78.6, 74.4, 54.1, 53.9, 36.9. HRMS (FAB+): calcd. For C₁₄H₁₇NO₅ [*M*⁺+H]: 384.0172, found: 384.0177. Purity was higher than 99% (HPLC analysis at 230 nm).

(2*R*,3*S*)-3-Amino-2-[(benzyloxycarbonyl)oxy]-4-phenylbutanoic acid methyl ester, hydrochloride, 1d

The procedure described for **1a** using benzyloxycarbonyl chloride afforded **1d**:

¹H NMR (CD₃OD, 400 MHz): δ 7.45-7.30 (m, 8 H, CH), 7.22-7.20 (m, 2 H, CH), 5.27 (s, 2H, CH₂), 4.97 (d, ³*J*(H,H) = 2.5 Hz, 1H, CH), 4.08 (ddd, ³*J*(H,H) = 2.5, 6.4, 9.2 Hz, 1 H, CH), 3.77 (s, 3 H, CH₃), 3.08, 2.97 (2dd, ²*J*(H,H) = 13.7 Hz, ³*J*(H,H) = 6.4, 9.2 Hz, 2 H, CH₂). ¹³C NMR (CD₃OD, 100 MHz): δ_c 168.7, 155.1, 136.5, 135.6, 130.40, 130.36, 130.0, 129.8, 129.6, 129.0, 73.5, 71.9, 54.0, 53.9, 36.7. HRMS (FAB+): calcd. For C₁₉H₂₂NO₅ [*M*⁺+H]: 344.1498, found: 344.1504. Purity was 97% (HPLC analysis at 230 nm).

(2*R*,3*S*)-3-[(9H-Fluoren-9-ylmethoxycarbonyl)amino]-2-hydroxy-4-phenylbutanoic acid methyl ester, 2b

The procedure described for **2a** using 9H-fluoren-9-ylmethoxycarbonyl chloride afforded **2b**:

¹H NMR (CD₃OD, 400 MHz): δ 7.78 (d, ³*J*(H,H) = 7.5 Hz, 2 H, CH), 7.60-7.56 (m, 2 H, CH), 7.39-7.35 (m, 2 H, CH), 7.32-7.16 (m, 7 H, CH), 4.24-4.10 (m, 5H, CH, CH₂), 3.65 (s, 3 H, CH₃), 2.94, 2.83 (2dd, ²*J*(H,H) = 13.5 Hz, ³*J*(H,H) = 7.1, 8.2 Hz, 2 H, CH₂). ¹³C NMR (CD₃OD, 100 MHz): δ_c 175.0, 158.2, 145.3, 142.6, 139.5, 130.5, 129.5, 128.8, 128.22, 128.20, 127.6, 126.3, 120.9, 72.3, 67.9, 56.9, 52.7, 48.4, 38.7. HRMS (FAB+): calcd. For C₂₆H₂₆NO₅ [*M*⁺+H]: 432.1811, found: 432.1818. Purity was higher than 97% (HPLC analysis at 230 nm).

(2*R*,3*S*)-2-Hydroxy-3-[(2,2,2-trichloroethoxycarbonyl)amino]-4-phenylbutanoic acid methyl ester, 2c

The procedure described for **2a** using 2,2,2-trichloroethoxycarbonyl chloride afforded **2c**:

¹H NMR (CD₃OD, 400 MHz): δ 7.29-7.17 (m, 5 H, CH), 4.69, 4.65 (2d, ²*J*(H,H) =

12.2 Hz, 2H, CH₂), 4.24 (ddd, ³*J*(H,H) = 2.4, 7.3, 8.4 Hz, 1 H, CH), 4.14 (d, ³*J*(H,H) = 2.4 Hz, 1H, CH), 3.67 (s, 3 H, CH₃), 2.96, 2.85 (2dd, ²*J*(H,H) = 13.5 Hz, ³*J*(H,H) = 7.1, 8.4 Hz, 2 H, CH₂). ¹³C NMR (CD₃OD, 100 MHz): δ_c 174.8, 156.3, 139.4, 130.5, 129.5, 127.6, 97.2, 75.4, 72.2, 57.2, 52.7, 38.6. HRMS (FAB+): calcd. For C₁₄H₁₇NO₅ [*M*⁺+H]: 384.0172, found: 384.0169. Purity was higher than 99% (HPLC analysis at 230 nm).

(2*R*,3*S*)-3-[(Benzyloxycarbonyl)amino]-2-hydroxy-4-phenylbutanoic acid methyl ester, 2d

The procedure described for **2a** using benzyloxycarbonyl chloride afforded **2d**:

¹H NMR (CD₃OD, 400 MHz): δ 7.33-7.17 (m, 10 H, CH), 5.01, 4.97 (2d, ²*J*(H,H) = 12.8 Hz, 2H, CH₂), 4.21 (dt, ³*J*(H,H) = 2.2, 7.9 Hz, 1 H, CH), 4.11 (d, ³*J*(H,H) = 2.2 Hz, 1H, CH), 3.62 (s, 3 H, CH₃), 2.93, 2.83 (2dd, ²*J*(H,H) = 13.5 Hz, ³*J*(H,H) = 7.5, 8.0 Hz, 2 H, CH₂). ¹³C NMR (CD₃OD, 100 MHz): δ_c 175.0, 158.2, 139.5, 138.4, 130.4, 129.5, 129.4, 128.9, 128.6, 127.6, 72.2, 67.4, 56.9, 52.6, 38.8. HRMS (FAB+): calcd. For C₁₉H₂₂NO₅ [*M*⁺+H]: 344.1498, found: 344.1504. Purity was 97% (HPLC analysis at 230 nm).

***O*-Ethoxycarbonyl-L-serine benzyl ester, hydrochloride, 5b**

The procedure described for **5a** using *N*-(tert-butoxycarbonyl)-L-serine benzyl ester afforded **5b**:

¹H NMR (CD₃OD, 400 MHz): δ 7.43-7.33 (m, 5H, CH), 5.35, 5.29 (2d, ²*J*(H,H) = 12.1 Hz, 2 H, CH₂), 4.63, 4.55 (2dd, ²*J*(H,H) = 12.3 Hz, ³*J*(H,H) = 3.1, 4.4 Hz, 2 H, CH₂), 4.51 (dd, ³*J*(H,H) = 3.1, 4.4 Hz, 1H, CH), 4.18 (q, ³*J*(H,H) = 7.1, Hz, 2 H, CH₂), 1.27 (t, ³*J*(H,H) = 7.1 Hz, 3 H, CH₃). ¹³C NMR (CD₃OD, 100 MHz): δ_c 167.7, 155.7, 136.3, 129.8, 129.74, 129.72, 69.6, 66.0, 65.6, 53.6, 14.5. HRMS (FAB+): calcd. For

$C_{13}H_{18}NO_5$ [$M^+ + H$]: 268.1185, found: 2268.1190. Purity was higher than 99% (HPLC analysis at 230 nm).

***N*-Ethoxycarbonyl-L-threonine benzyl ester, 6a**

Compound **6a** prepared from **5a** via the O–N alkoxy carbonyl migration reaction according to the procedure described in the main text:

1H NMR (CD_3OD , 400 MHz): δ 7.39–7.29 (m, 5H, CH), 5.19 (s, 2 H, CH_2), 4.28 (dq, $^3J(H,H) = 3.1, 6.4$ Hz, 1 H, CH), 4.21 (d, $^3J(H,H) = 3.1$ Hz, 1 H, CH), 4.10 (q, $^3J(H,H) = 7.1$ Hz, 2 H, CH_2), 1.24 (t, $^3J(H,H) = 7.1$ Hz, 3 H, CH_3), 1.19 (d, $^3J(H,H) = 6.4$ Hz, 3 H, CH_3). ^{13}C NMR (CD_3OD , 100 MHz): δ_c 172.5, 159.3, 137.3, 129.6, 129.3, 129.2, 68.5, 68.0, 62.3, 61.3, 20.4, 15.0. HRMS (FAB+): calcd. For $C_{14}H_{20}NO_5$ [$M^+ + H$]: 282.1341, found: 282.1348. Purity was higher than 99% (HPLC analysis at 230 nm).

***N*-Ethoxycarbonyl-L-serine benzyl ester, 6b**

Compound **6b** prepared from **5b** via the O–N alkoxy carbonyl migration reaction according to the procedure described in the main text:

1H NMR (CD_3OD , 400 MHz): δ 7.39–7.29 (m, 5H, CH), 5.19 (s, 2 H, CH_2), 4.32 (t, $^3J(H,H) = 4.5$ Hz, 1H, CH), 4.09 (q, $^3J(H,H) = 7.1$, Hz, 2 H, CH_2), 3.88, 3.81 (2dd, $^2J(H,H) = 11.2$ Hz, $^3J(H,H) = 4.2, 5.0$ Hz, 2 H, CH_2), 1.23 (t, $^3J(H,H) = 7.1$ Hz, 3 H, CH_3). ^{13}C NMR (CD_3OD , 100 MHz): δ_c 172.2, 158.9, 137.3, 129.6, 129.3, 129.1, 68.0, 63.0, 62.2, 57.9, 15.0. HRMS (FAB+): calcd. For $C_{13}H_{18}NO_5$ [$M^+ + H$]: 268.1185, found: 268.1193. Purity was 98% (HPLC analysis at 230 nm).

FILE 1 SVS 1 SEQ 43
CH.1<D> C.S 1.25 ATT 7 OFFS 15 05/28/05 15:32

D-7500 INTEGRATOR REPORT

ANALYZED: 05/28/05 15:32 REPORTED: 06/01/05 16:12
SYSTEM : 1
METHOD : 56.20X OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 43

FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AR/H1% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	18.00	27741	636100	99.733	BB
2	24.11	549	1700	0.267	BB
TOTAL					
		28290	637800	100.000	
PEAK REJ :

FILE 1 SYS 1 SEQ 20
CH1<D> C.S 1.25 ATT 8 OFFS 5 07/05/03 14:14

D-7500 INTEGRATOR REPORT

ANALYZED: 07/05/03 14:14 REPORTED: 05/31/05 15:52
SYSTEM : 1
METHOD : 58.00PURE OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 20
FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AB/HI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	24.59	821	5042	0.234	BB
2	25.82	165048	2148281	98.577	BB
3	34.51	870	4083	0.189	BB
TOTAL			166339	2155416	100.000
PEAK REJ :		0

FILE 1 SYS 1 SEQ 46
CH.1<D> C.S 1.25 ATT 7 OFFS 15 06/01/05 17:35

(RAW) STORAGE NO. 56 WRITTEN

D-7500 INTEGRATOR REPORT

ANALYZED: 06/01/05 17:35 REPORTED: 06/01/05 18:20
SYSTEM : 1
METHOD : 54 00N-TROC OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 46

FILE : 1 (06/18/05 19:03) MODULE T-PROC : PUMP= 1 , DETECTOR= 1
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	RC
1	22.04	35154	956343	100.000	BB
TOTAL			956343	100.000	
PEAK REJ :

FILE 1 SYS 1 SEQ 44
CH.1<D> C.S 1.25 ATT 8 OFFS 10 06/02/05 15:16

D-7500 INTEGRATOR REPORT

ANALYZED: 06/02/05 15:16 REPORTED: 06/02/05 16:06
SYSTEM : 1
METHOD : 52.10 OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 44
FILE : 1 (05/18/05 19:03) MODULE T-PRG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : $\emptyset$

NO.	RT	HEIGHT	AREA	CONC	BC
1	21.14	661	20642	1.241	BV
2	21.76	54342	1612500	96.910	VB
3	39.88	778	30778	1.850	BB
TOTAL		55781	1663920	100.000	
PEAK REJ :		$\emptyset$

FILE 1 SYS 1 SEQ 47
CH.1<D> C.S 1.25 ATT 8 OFFS 5 05/31/05 18:21

D-7500 INTEGRATOR REPORT

ANALYZED: 05/31/05 18:21 REPORTED: 06/01/05 16:16
SYSTEM : 1
METHOD : 11.0X OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 47

FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	20.73	815	11604	0.460	BB
2	21.49	170183	2509098	99.540	BB
TOTAL		170998	2520702	100.000	
PEAK REJ :		0

D-7500 INTEGRATOR REPORT

ANALYZED: 04/28/05 11:46 REPORTED: 06/01/05 16:03
SYSTEM : 1
METHOD : 109.00x OPERATOR:
CHANNEL : 1 <DIGITAL> SEQ : 27
FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1 , DETECTOR= 1
CALC-METHOD: AR/HK <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	23.78	10557	153781	1.357	BV
2	24.12	8091	129043	1.139	VB
3	31.74	1016892	11049607	97.504	BB
TOTAL					
PEAK DET.	1035540	11332431	100.000

FILE 1 SVS 1 SEQ 45
CH.1<D> C.S 1.25 .AII 8 OFFS 10 06/03/05 15:26

D-7500 INTEGRATOR REPORT

ANALYZED: 06/03/05 15:26 REPORTED: 06/03/05 16:12
SYSTEM : 1
METHOD : 110.00% OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 45
FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AB/EI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	27.53	227351	3395836	99.517	BB
2	39.87	737	16466	0.483	BB
TOTAL		228088	3412302	100.000	
PEAK REJ :		0

FILE 1 SVS 1 SEQ 26
CH.1<D> C.S 1.25 ATT 9 OFFS 0 05/12/05 11:19

D-7500 INTEGRATOR REPORT

ANALYZED: 05/12/05 11:19 REPORTED: 06/01/05 16:20
SYSTEM : 1
METHOD : MSMK37-2 OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 26
FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	20.52	2094	25134	1.838	BB
2	26.54	128935	1326196	96.985	BB
3	30.20	1229	16087	1.176	BB
TOTAL			132258	1367417	100.000

NEAR NET

FILE 1 SVS 1 SEQ 44
CH.1<D> C.S 1.25 ATT 7 OFFS 15 06/06/05 16:18

D-7500 INTEGRATOR REPORT

ANALYZED: 06/06/05 16:18 REPORTED: 06/06/05 17:03
SYSTEM : 1
METHOD : 121.20 OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 44
FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AREA/HEIGHT COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	18.28	47762	1353231	100.000	BB
TOTAL		47762	1353231	100.000	
PEAK REJ :		0

FILE 1 SYS 1 SEQ 44
CH.1<D> C.S 1.25 ATT 7 OFFS 15 08/07/05 15:52

D-7500 INTEGRATOR REPORT

ANALYZED: 08/07/05 15:52 REPORTED: 08/07/05 16:37
SYSTEM : 1
METHOD : 124.20 OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 44

FILE : 1 (08/18/05 19:03) MODULE T-PROG : PUMP= 1 , DETECTOR= 1
CALC-METHOD: AB/H% <AREA> COMPONENT IBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	17.69	42600	1174680	100.000	BB
TOTAL			42600	1174680	100.000

PEAK REJ : 0

FILE 1 SYS 1 SEQ 44
CH.1<D> C.S 1.25 ATT 8 OFFS 10 06/08/05 15:55

D-7500 INTEGRATOR REPORT

ANALYZED: 06/08/05 15:55 REPORTED: 06/08/05 16:40
SYSTEM : 1
METHOD : 125.0X OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 44

FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1 , DETECTOR= 1
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	22.43	154655	2186354	100.000	BB
TOTAL					
		154655	2186354	100.000	
PEAK REJ :		0			

FILE 1 SYS 1 SEQ 44
CH.1<D> C.S 1.25 ATT 8 OFFS 10 06/08/05 15:55

D-7500 INTEGRATOR REPORT

ANALYZED: 06/08/05 15:55 REPORTED: 06/08/05 16:40
SYSTEM : 1
METHOD : 125.0X OPERATOR: MARIUS
CHANNEL : 1<DIGITAL> SEQ : 44

FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1 , DETECTOR= 1
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	22.43	154655	2186354	100.000	BB
TOTAL		154655	2186354	100.000	

PEAK REJ : 0

FILE 1 SVS 1 SEQ 44
CH.1<D> C.S 1.25 ATT 8 OFFS 5 05/27/05 15:58

D-7500 INTEGRATOR REPORT

ANALYZED: 05/27/05 15:58 REPORTED: 06/01/05 16:08
SYSTEM : 1
METHOD : 126.0X OPERATOR: MARIUS
CHANNEL : 1 <DIGITAL> SEQ : 44

FILE : 1 (05/18/05 19:03) MODULE T-PROG : PUMP= 1, DETECTOR= 1
CALC-METHOD: AB/HIX <AREA> COMPONENT IBL : 0

NO.	RT	HEIGHT	AREA	CONC	BC
1	17.68	9897	14579	1.439	BB
2	21.18	9890	98215	98.215	BB
3	24.08	673	3593	0.346	BB
TOTAL		99360	1013069	100.000	
PEAK REJ :		0