



Title	Effective Synthesis of Optically Active TrifluoromethyldiazirinyI Homophenylalanine and Aroylalanine Derivatives with the Friedel-Crafts Reaction in Triflic Acid
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3 Effective Synthesis of Photoreactive Homophenylalanine and Aroylalanine

4

5 Effective Synthesis of Optically Active Trifluoromethyldiazirinyl

6 Homophenylalanine and Aroylalanine Derivatives with Friedel-Crafts

7 Reactions in Triflic Acid.

8

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26

1 Abstract
2 Effective Friedel-Crafts reactions with
3 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirine and optically active
4 *N*-TFA-Asp(Cl)-OMe in triflic acid afforded homophenylalanine derivatives
5 effectively without loss of the optical purity.

6

7

8 Key words:

9 diazirine; photoaffinity labeling; Friedel-Crafts reaction; triflic acid;

10

11

1 Introduction

2 Photoaffinity labeling is a useful biochemical method in the
3 investigations of structural and functional relationships between small
4 biologically active compounds and biomolecules, such as enzymes, RNA, and
5 DNA.¹⁾ Various photophores, such as phenyldiazirine, arylazide and
6 benzophenone, have been developed as the photophores. It would be ideal
7 because we can furnish photolabeling groups with minimum structural
8 alteration. It has been also established that
9 (3-trifluoromethyl)phenyldiaziriny function can be selectively activated
10 without giving damages to peptides and proteins by irradiating at 350nm.²⁾
11 But it usually requires not only steps of manipulations to introduce
12 photophores into the target molecules, but also independent construction of
13 the (3-trifluoromethyl)phenyldiaziriny groups. These encouraged us in
14 establishing effective protocol to furnish the
15 (3-trifluoromethyl)phenyldiaziriny photophore.³⁾ It was expected that amino
16 acid derivatives carrying photolabeling group would become powerful tool in
17 the mechanistic investigations of biologically active peptides, and in
18 studying their metabolic pathways.

19 We focused on developing the (3-trifluoromethyl)diaziriny photophore
20 into homophenylalanine (hPhe), since interesting biological behaviors have
21 been discovered by replacing a phenylalanine in biological peptides with
22 hPhe^{4, 5)} and also reported as a starting material for pharmaceutical
23 products such as benazepril and enalapril, both of which inhibit angiotensin
24 converting enzyme (ACE)^{6, 7)} Efficient synthesis of photoactivatable optically
25 pure hPhe is important. Although several synthetic protocols for optically
26 active hPhe have been reported with various methodologies including
27 enzymatic resolution,⁸⁾ Suzuki-coupling,⁹⁾ diastereoselective Michael
28 addition¹⁰⁾ and catalytic asymmetric hydrogenation¹¹⁾, these required the

1 special reagents or precursors. It might not be suitable to apply those for
2 preparation of diazirinylated hPhe because some conditions might decline
3 the diazine function. In this paper, we would like to report an effective
4 method providing optically active diazirinyl hPhe with featuring
5 Friedel-Crafts (F-C) reactions with
6 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirin **1**¹²⁾ and β -acid chloride
7 of aspartic acid **2**¹³⁾ as key steps.

8

9 Results and Discussion

10 We chose β -acid chloride form of *N*-trifluoromethyl (*S*)-aspartic acid
11 α -methyl ester **2** as the electrophilic precursor. When we first attempted the
12 reaction between **1** and **2** at room temperature employing aluminium
13 chloride as the activator, however, the desired reaction did not proceed and
14 both **1** and **2** were recovered in CH₂Cl₂ or CH₃NO₂. (Fig.1, Run 1 and 2) The
15 reflux conditions led decomposition of **2**. (Fig.1, Run 3 and 4) Although F-C
16 reactions between *N*-aspartic anhydride derivatives and aromatics have
17 been reported,¹⁴⁻¹⁹⁾ the aromatics had to be employed excess amounts as the
18 solvents. It would be preferable if we could use stoichiometric amounts of
19 aromatics in the process by taking account of not only operational feasibility
20 as well as economic matters. The reaction did not proceed by employing
21 titanium chloride, which had been effective for formylation²⁰⁾ as the activator
22 in CH₂Cl₂ or neat conditions. (Fig.1, Run 5 and 6) It was found that the
23 desired reaction smoothly proceeded at 0 °C to give the adduct **3** and **4** in
24 over 87% by employing stoichiometric amounts of **1**, when
25 trifluoromethanesulfonic acid (TfOH) was employed as the solvent. The
26 suspension at the initial stage became clear solution upon the onset of the
27 reaction. The regioisomer **3** and **4** were readily separated by silica gel column
28 chromatography. The NOESY spectrum of major product **3** gave the

1 correlation signals between C₂ OCH₃ and C₃ H, which disclosed the
2 substitution pattern. In the case of mainor product **4**, NOESY correlation
3 was obtained C₄ OCH₃ and both C₃ and C₅ H. (*R*)-**2** was also reacted with **1**
4 in the same condition to afford (*R*)-**3** and **4** in good yield. (Fig.1, Run 7)
5 Notably the higher temperature afforded complexed mixture because the
6 decomposition of **1** and **2**. (Fig.1, Run 8) These results were consistent with
7 the report that diazirinyl *N-N* double bond was easily decomposed in the
8 presence of Lewis acid over 25 °C.²¹⁾ Unfortunately,
9 3-phenyl-3-(3-trifluoromethyl)-3*H*-diazirine, which has no activating
10 methoxy substituent on benzene ring, did not react with (*S*)- or (*R*)- **2** in
11 TfOH at 0°C. Higher temperature decomposed the diazirinyl ring at higher
12 temperatures. We have already reported that the
13 3-phenyl-3-(3-trifluoromethyl)-3*H*-diazirine easily reacted with
14 dichloromethyl methyl ether to give formylation product in TfOH.²²⁾ These
15 results indicated that the reactivity of both acyl donor and acyl acceptor also
16 plays a critical role. Furthermore, trifluoromethyldiazirinyl moiety plays
17 slightly as the electron withdrawing group for nucleophilic substitution of
18 aromatic compounds.²³⁾

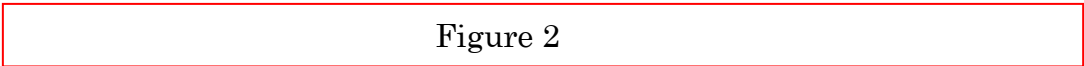
19
20  Figure.1
21

22 As the adduct **3** and **4** in hand, the newly introduced carbonyl group
23 was then reduced to a hPhe derivative. It has already been reported that the
24 diazirinyl *N-N* double bond was labiel under H₂-Pd/C conditions.²⁴⁾ We found
25 selective reduction of benzylic carbonyl to methylene could be performed
26 with triethylsilane / TFA system to give **5** in good yield.²⁵⁾ No decomposition
27 of the diazirinyl ring was observed during the reduction. Finally
28 deprotections of (*S*)- and (*R*)- **5** were performed using an alkaline condition to

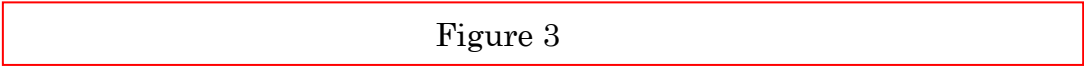
1 afford diazirinyl hPhe **6** in good yield (90%). However, the conditions
2 decomposed to result complex mixture when aroyl derivative **3** was employed.
3 Deprotection of **3** could be achieved by treating with 6N HCl in acetic acid at
4 80 °C, affording **7** (Scheme 1).

5
6  Scheme 1

7
8 The enantiopurities of compounds **6** and **7** were determined with chiral
9 HPLC (CHIROBIOTIC T, Astec)²⁶⁾ which revealed these were >98% ee to
10 prove no racemization during the synthesis. (Fig. 2)

11
12  Figure 2

13
14 Photolysis properties of diazirinyl compounds were examined with
15 black light (15W). We have already demonstrated that the concentration of
16 diazirinyl compound was to be set less than 1 mM to minimize the
17 isomerization to the diazo compound.²⁷⁾ Maximum absorptions at 360 nm for
18 **6** and **7** were decreased upon irradiation times (Fig.3). The half-life of **6** and **7**
19 was determined to be 8.5 and 3.2 min, respectively based on the intensity at
20 360 nm. We concluded the values are fast enough for photoaffinity labeling.

21
22  Figure 3

23
24 In these studies we have developed effective synthesis of photoreactive
25 and enantiomerically pure hPhe and 2-methoxybenzoylalanine from
26 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirin and (*S*) and (*R*)
27 aspartic acid derivative as the effective photolabeling probe without
28 racemization. The key F·C reaction proceeded by employing

1 trifluoromethanesulfonic acid as the solvent. The following silane promoted
2 reduction took place the transformation the benzylic carbonyl to methylene.
3 The results will be contributed to the studies in structure-activity
4 relationships for the side chain of aromatic α -amino acids.

5

6 Experimental

7 General methods. Optical rotation values were measured by a JASCO
8 DIP-370 polarimeter. IR spectra were measured by a JASCO FTIR-4100. ^1H -,
9 ^{13}C - and ^{19}F - NMR spectra were measured by a JEOL ECA 500 spectrometer.
10 In the ^1H -NMR spectra, the chemical shifts are expressed in ppm downfield
11 from the signal for tetramethylsilane used as an internal standard. Splitting
12 patterns are designated as s (singlet), d (doublet), t (triplet), and m
13 (multiplet). In the ^{13}C -NMR spectra, the ^{13}C chemical shifts of the solvents
14 were used as the internal standard ($^{13}\text{CDCl}_3$ 77.0ppm; or $^{13}\text{CD}_3\text{OD}$, 49.5ppm).
15 In the ^{19}F -NMR spectra, the chemical shifts are reported with default
16 values without correction. MS spectra were obtained with a Hitachi
17 NanoFrontier LD mass spectrometer. Chiral HPLCs were performed with
18 CHIROBIOTIC T (Astec) 4.6 x 250 mm, eluted with 10% EtOH – H₂O; flow
19 rate 1.0 ml/min; UV detection at 210 nm.

20

21 (*S*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)
22 phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((*S*)-**3**) and (*S*)-methyl
23 4-(4-methoxy-2-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-4-oxo-
24 2-(2,2,2-trifluoroacetamido)butanoate ((*S*)-**4**)

25 Compound **1**¹²) (24.7 mg, 0.11 mmol) and (*S*)- **2**¹³) (29.0 mg, 0.11 mmol)
26 were dissolved in TfOH (0.25 ml, 2.9 mmol) at 0 °C. The yellow reaction
27 mixture was stirred for two hours at the same temperature, then poured into
28 cold water and AcOEt (30 : 30 ml). The organic layer was washed with

1 aqueous 1M HCl, saturated NaHCO₃, 1N HCl and saturated NaCl, then
2 dried over MgSO₄, and filtered. The filtrate was concentrated, the residue
3 was subjected to silica chromatography (AcOEt : n-hexane = 1 : 5) to afford
4 pure (*S*)-**3** (34.4 mg, 71%) and (*S*)-**4** (13.6 mg, 28%) as a pale yellow oil.

5 (*S*)- **3**: [α]_D +77° (c 1.0, CHCl₃); IR (film) cm⁻¹ : 3330, 1720, 1675, 1610;
6 ¹H-NMR (CDCl₃) δ : 7.79 (1H, d, *J* = 8.0 Hz), 7.54 (1H, brd, *J* = 8.0 Hz), 6.80
7 (1H, d, *J* = 8.0 Hz), 6.66 (1H, s), 4.89-4.86 (1H, m), 3.91 (3H, s), 3.78 (1H, dd,
8 *J* = 19.2, 4.3 Hz), 3.73 (3H, s), 3.57 (1H, dd, *J* = 18.9, 4.0 Hz); ¹³C-NMR
9 (CDCl₃) δ : 197.34, 170.12, 159.47, 156.91 (q, ²*J*_{CF} = 37.6 Hz), 136.06, 131.46 ,
10 126.42, 121.77 (q, ¹*J*_{CF} = 274.7 Hz), 118.80, 115.63 (q, ¹*J*_{CF} = 287.9 Hz), 109.63,
11 55.85, 53.15, 48.92, 45.29, 28.45 (q, ²*J*_{CF} = 40.4 Hz); ¹⁹F-NMR (CDCl₃) δ :
12 -63.18, -74.34; ESI-MS *m/z*: 442 (M+H)⁺, ESI-HRMS: calcd. for C₁₆H₁₄F₆N₄O₅
13 (M+H)⁺, 442.0832; found, *m/z* 442.0826.

14 (*S*)- **4**: [α]_D +57° (c 1.0, CHCl₃); IR (film) cm⁻¹ : 3330, 1725, 1690, 1610;
15 ¹H-NMR (CDCl₃) δ : 7.82 (1H, d, *J* = 8.6 Hz), 7.63 (1H, brd, *J* = 7.4 Hz), 7.19
16 (1H, s), 7.02 (1H, d, *J* = 8.6 Hz), 4.97-4.94 (1H, m), 3.91 (3H, s), 3.86-3.82 (4H,
17 m), 3.56 (1H, dd, *J* = 18.3, 3.4 Hz); ¹³C-NMR (CDCl₃) δ : 196.22, 169.70,
18 163.71, 157.05 (q, ²*J*_{CF} = 38.0 Hz), 132.51, 130.09, 129.53, 121.62 (q, ¹*J*_{CF} =
19 275.1 Hz), 117.60, 115.56 (q, ¹*J*_{CF} = 287.5 Hz), 115.20, 55.87, 53.25, 48.71,
20 40.81, 29.22 (q, ²*J*_{CF} = 40.0 Hz); ¹⁹F-NMR (CDCl₃) δ : -66.75, -72.86; ESI-MS
21 *m/z*: 442 (M+H)⁺, ESI-HRMS: calcd. for C₁₆H₁₄F₆N₄O₅ (M+H)⁺, 442.0832;
22 found, *m/z* 442.0828.

23

24 (*R*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)
25 phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((*R*)-**3**) and (*R*)-methyl
26 4-(4-methoxy-2-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-4-oxo-
27 2-(2,2,2-trifluoroacetamido)butanoate ((*R*)-**4**)

28 The same treatment of **1** (24.7 mg, 0.11 mmol) and (*R*)- **2** (29.0 mg, 0.11

1 mmol) as described in above gave (*R*)-**3** (33.0 mg, 68%) and (*R*)-**4** (9.2 mg,
2 19%) as yellow oil. The ¹H-, ¹³C- NMR and IR of these samples were identical
3 to these record for (*S*)-**3** and **4**.

4 (*R*)-**3** [α]_D -76° (c 1.0, CHCl₃); (*R*)-**4**: [α]_D -58° (c 1.0, CHCl₃)

5

6 (*S*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)

7 phenyl)-2-(2,2,2-trifluoroacetamido)butanoate ((*S*)-**5**)

8 To a solution of (*S*)-**3** (169 mg, 0.38 mmol) in TFA (1.5 ml, 20 mmol),
9 Et₃SiH (0.30 ml, 1.9 mmol) was added dropwise. The reaction mixture was
10 stirred for two hours, and partitioned with AcOEt (80 ml). The organic layer
11 was washed with saturated NaHCO₃, 1N HCl and saturated NaCl, then
12 dried over MgSO₄ and filtered. After the filtrate was concentrated, the
13 residue was subjected to silica chromatography (AcOEt : n-hexane = 1 : 10) to
14 afford a colorless amorphous mass (115 mg, 76%).

15 [α]_D +65° (c 1.0, CHCl₃); IR (film) cm⁻¹ : 3320, 1720, 1610; ¹H-NMR
16 (CDCl₃) δ : 7.11 (1H, d, *J* = 7.4 Hz), 7.04 (1H, d, *J* = 7.4 Hz), 6.74 (1H, brd, *J* =
17 6.9 Hz), 6.57 (1H, s), 4.64-4.62 (1H, m), 3.81 (1H, s), 3.68 (1H, s), 2.64 (2H, t,
18 *J* = 7.7 Hz), 2.25-2.22 (1H, m), 2.10-2.03 (1H, m); ¹³C-NMR (CDCl₃) δ : 171.00,
19 157.40, 156.74 (q, ²*J*_{CF} = 37.2 Hz), 130.41, 130.21, 128.69, 122.07 (q, ¹*J*_{CF} =
20 274.3 Hz), 118.90, 115.63 (q, ¹*J*_{CF} = 287.5 Hz), 108.12, 55.24, 52.65, 52.18,
21 31.03, 28.37 (q, ²*J*_{CF} = 40.0 Hz), 25.32; ¹⁹F-NMR (CDCl₃) δ : -66.54, -75.28.
22 ESI-MS *m/z*: 400 (M-N₂+H)⁺, ESI-HRMS: calcd. for C₁₆H₁₆F₆NO₄ (M-N₂+H)⁺,
23 400.0978; found, *m/z* 400.0989.

24

25 (*R*)- Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)

26 phenyl)-2-(2,2,2-trifluoroacetamido)butanoate ((*R*)-**5**)

27 The same treatment of (*R*)-**3** (168 mg, 0.38 mmol) as described in above
28 gave (*R*)-**5** (121 mg, 80%) as yellow oil. The ¹H-, ¹³C- NMR and IR of these

1 samples were identical to these record for (*S*)-5.

2 $[\alpha]_D -65^\circ$ (c 1.0, CHCl₃).

3

4 (*S*)-2-amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)
5 phenyl)butanoic acid ((*S*)-6)

6 To a solution of (*S*)-4 (26.4 mg, 60 μmol) in MeOH (6.0 ml), 1N NaOH
7 (0.50 ml) was added at room temperature. After stirring for 1 hour, silica gel
8 (2 g) was added. The resulting mixture was then evaporated. The residue
9 was subjected to silica chromatography (CH₂Cl₂ : MeOH : H₂O : acetic acid =
10 10 : 2 : 0.25 : 0.05) to afford a colorless solid (17.3 mg, 91%).

11 $[\alpha]_D -15^\circ$ (c 2.0, MeOH); IR (film) cm⁻¹ : 2950, 1680; ¹H-NMR (CD₃OD) δ:
12 7.22 (1H, d, *J* = 7.4 Hz), 6.79 (1H, d, *J* = 7.4 Hz), 6.68 (1H, s), 4.33 (1H, q, *J* =
13 4.8 Hz), 3.82 (3H, s), 2.73 (2H, t, *J* = 7.4 Hz), 2.27-2.18 (1H, m), 2.07-2.01 (1H,
14 m); ¹³C-NMR (CD₃OD) δ: 173.82, 159.24, 132.56, 131.76, 129.42, 123.65 (q,
15 ¹*J*_{CF} = 273.5 Hz), 119.90, 109.14, 55.92, 53.69, 31.64, 29.57 (q, ²*J*_{CF} = 40.4 Hz),
16 27.44; ¹⁹F -NMR (CD₃OD) δ: -66.38; ESI-MS *m/z*: 318 (M+H)⁺, ESI-HRMS:
17 calcd. for C₁₃H₁₅F₃N₃O₃ (M+H)⁺, 318.1060; found, *m/z* 318.1067; chiral HPLC
18 *t*_R = 13.2 min

19

20 (*R*)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)
21 phenyl)butanoic acid ((*R*)-6)

22 The same treatment of (*R*)-4 (26.0 mg, 60 μmol) as described in above
23 gave (*R*)-6 (16.8 mg, 90%) as yellow oil. The ¹H-, ¹³C- NMR and IR of these
24 samples were identical to these record for (*S*)-6

25 $[\alpha]_D +15^\circ$ (c 2.0, MeOH); chiral HPLC *t*_R = 17.0 min

26

27 (*S*)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)
28 phenyl)-4-oxobutanoic acid ((*S*)-7)

1 To a stirred solution of (*S*)-**3** (31.6 mg, 72 μ mol) in acetic acid (12 ml),
2 concentrated HCl (12 ml) was added. The reaction mixture was stirred for 12
3 hours at 50°C, then concentrated. The residue was subjected to silica
4 chromatography (CH₂Cl₂ : MeOH : H₂O : acetic acid = 10 : 2 : 0.25 : 0.05) to
5 afford a colorless solid (22.3 mg, 94%).

6 $[\alpha]_D -14^\circ$ (c 2.0, MeOH); IR (film) cm⁻¹ : 2940, 1670, 1610; ¹H-NMR
7 (CD₃OD) δ : 7.87 (1H, d, *J* = 8.0 Hz), 6.95 (1H, d, *J* = 8.6 Hz), 6.81 (1H, s),
8 3.99-3.97 (4H, m), 3.72 (1H, d, *J* = 19.5 Hz), 3.55 (1H, d, *J* = 19.5 Hz) ;
9 ¹³C-NMR (CD₃OD) δ : 199.11, 179.04, 160.88, 136.24, 132.52, 128.79, 123.34
10 (q, ¹*J*_{CF} = 273.9 Hz), 119.74, 111.08, 56.54, 51.84, 29.54 (q, ²*J*_{CF} = 40.4 Hz),
11 23.2; ¹⁹F -NMR (CD₃OD) δ : -66.83; ESI-MS *m/z*: 332 (M+H)⁺, ESI-HRMS:
12 calcd. for C₁₃H₁₃F₃N₃O₄ (M+H)⁺, 332.0853; found, *m/z* 332.0866; chiral HPLC
13 *t*_R = 10.2 min.

14
15 (*R*)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)
16 phenyl)-4-oxobutanoic acid ((*R*)-**7**)

17 The same treatment of (*R*)-**4** (31.8 mg, 72 μ mol) as described in above
18 gave (*R*)-**7** (21.0 mg, 88%) as yellow oil. The ¹H-, ¹³C- NMR and IR of these
19 samples were identical to these record for (*S*)-**6**

20 $[\alpha]_D +14^\circ$ (c 2.0, MeOH); chiral HPLC *t*_R = 15.0 min

21
22 Photolysis of the diazirinyl compounds in methanol

23 Methanolic solution of (*S*)- **6** or **7** (0.5 mM) was placed in a quartz
24 cuvette. After replacing the inner atmosphere with nitrogen, photolysis was
25 carried out with 15 W black-light (UVP Inc., San Gabriel, California, USA) at
26 a distance 2 cm from the surface of light source.

27
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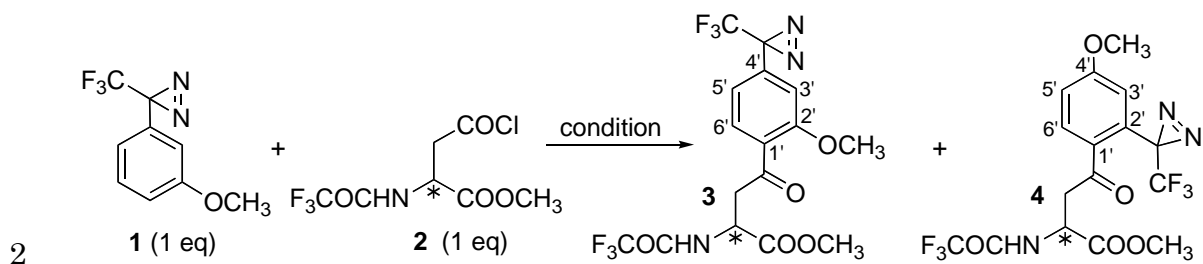
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- 28

1 Figure legends
2
3 Figure 1
4 Friedel-Crafts reactions with diazirinyl compound **1** and optically pure
5 aspartic acid derivative **2**.
6
7
8 Scheme 1
9 Synthesis of optically pure diazirinyl homophenylalanine derivatives.
10 Reagents and conditions: (a) Triethylsilane, trifluoroacetic acid, (*S*)- 76%,
11 (*R*)- 80%; (b) NaOH, MeOH, (*S*)- 91%, (*R*)- 90%; (c) 6N HCl, acetic acid, 80 °C,
12 (*S*)- 94%, (*R*)- 88%.
13
14
15
16 Figure 2
17 Chiral HPLC chromatogram of synthetic diazirinyl (*S*)- or (*R*)- **6** and (*S*)- or
18 (*R*)- **7** with chiral HPLC.
19 Condition; CHIROBIOTIC T (Astec) 4.6 x 250 mm, eluted with 10% EtOH –
20 H₂O; flow rate 1.0 ml/min; UV detection at 210 nm.
21
22
23 Figure 3
24 Photolysis of the 0.5 mM of (*S*)-**6** (a) and (*S*)-**7** (b) in methanol with 15 W
25 black light.
26 The photolysis reaction mixture, at the times (in min), was indicated with
27 numbers.
28

1 Figure 1



entry	catalyst	solvent	temperature	time (h)	yield
1	AlCl ₃	CH ₂ Cl ₂	rt	12h	0 ^a
2	AlCl ₃	CH ₃ NO ₂	rt	12h	0 ^a
3	AlCl ₃	CH ₂ Cl ₂	reflux	12h	0 ^b
4	AlCl ₃	CH ₃ NO ₂	reflux	12h	0 ^b
5	TiCl ₄	CH ₂ Cl ₂	50° C	3h	0 ^b
6	TiCl ₄		0° C	2h	0 ^a
7	TfOH		0° C	2h	(<i>S</i>)- 71 (3), 28 (4) (<i>R</i>)- 68 (3), 19 (4)
8	TfOH		50° C	2h	0 ^b

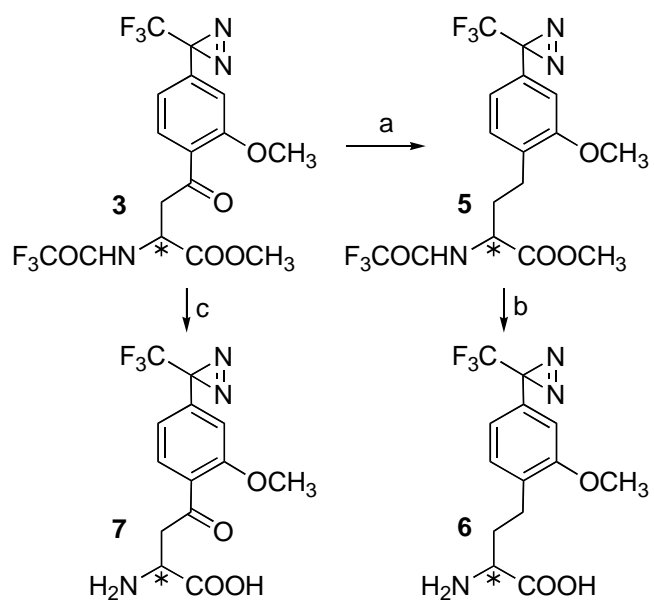
3 ^a no reaction occurred, ^b the starting material 1 was decomposed.

4

1

2 Scheme 1

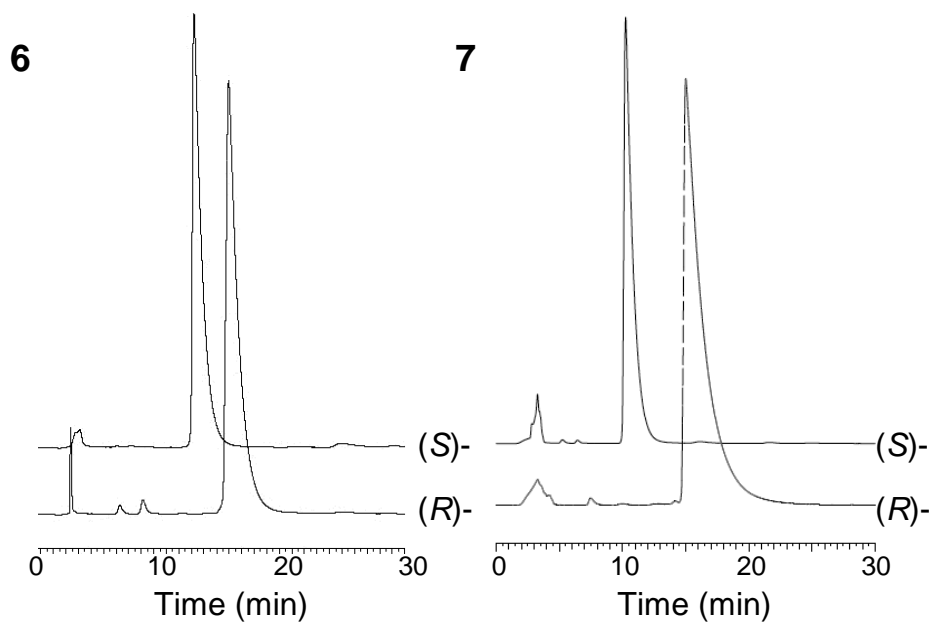
3



4

5

1 Figure 2

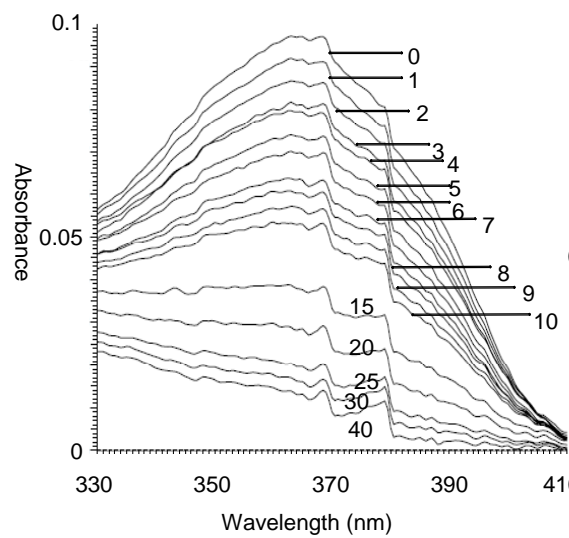


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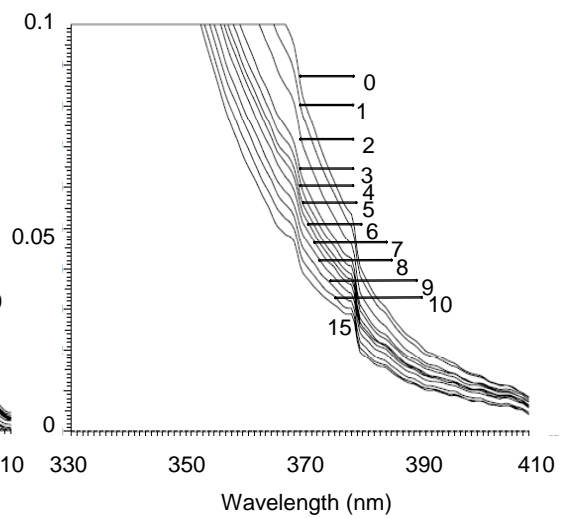
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1 Figure 3

2 (a)



(b)



3