Straightforward Synthesis of Optically Pure Methyl (*S*)-2-Phthalimido-4-oxobutanoate and Some of Its Acetal and Thioacetal Derivatives

Patrick Meffre,* Philippe Durand, François Le Goffic
Laboratoire de Bioorganique et Biotechnologies, Associé au C.N.R.S., ENSCP, 11, rue Pierre et Marie Curie, F-75231 Paris 05, France
Fax +33(1)43260770
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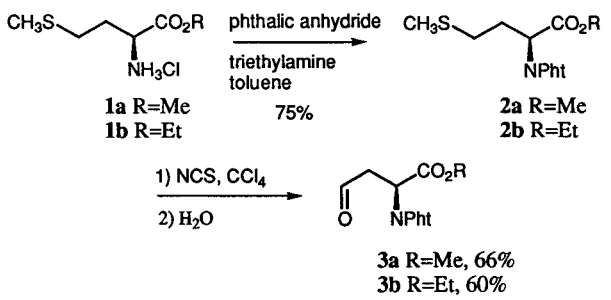
An improved procedure for the synthesis of optically pure methyl (*S*)-2-phthalimido-4-oxobutanoate **(3a)** and some of its acetal and thioacetal derivatives **4**, **5** and **7** from cheap commercially available L-methionine methyl ester hydrochloride **(1a)** is described.

Derivatives of (*S*)-2-amino-4-oxobutyric acid (aspartic acid β-semialdehyde) are interesting chiral intermediates for the synthesis of biologically relevant molecules of wide interest such as nicotinamine and analogues, iron chelating agents,[1] naturally occuring unusual α-amino acids,[2] serinephosphate peptide isosteres,[3] penicillin or cephalosporin analogues,[4] or some compounds used in enzyme studies.[5]

These compounds have been synthesized from expensive allylglycine via ozonolysis or oxidative cleavage,[1a,1b,5a,5b] from aspartic acid via reduction of the acid function on the side chain to give homoserine derivatives,[1c,2a,2b,3] from methionine via a homoserine derivative[2c] and subsequent oxidation to the aldehyde, or directly from expensive homoserine.[1d,1e,2d,2e,4,5c] Direct reduction of reactive aspartic acid derivatives also led to the aldehyde.[2f-h] Mostly, these strategies suffer from low yields due to the number of steps, or from expensive, impractical starting material or reagents.

Although the synthesis of ethyl ester **3b** has recently been described (64% yield)[6] from the corresponding methionine derivative **1b** using corrosive sulfuryl chloride as chlorinating agent and a "time consuming" hydrolysis, we report herein new and different results. We describe a reproducible, practical, high-yielding synthesis of optically pure title aldehyde **3a**, its thioacetal derivatives **4** and **5** and its acetal derivative **7** from commercially available L-methionine methyl ester hydrochloride **(1a)** by a two-step synthesis consisting of amino group protection giving phthalimido derivative **2a** followed by selective side-chain oxidation into aldehyde **3a** and its derivatives **4**, **5**, and **7**.

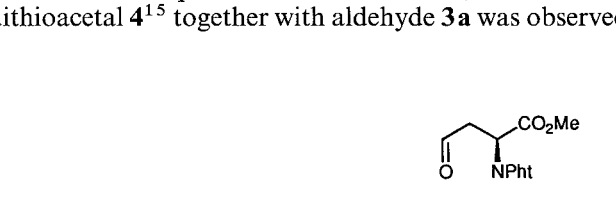


Scheme 1

We have previously shown that suitable S-substituted homocysteine thioether derivatives could be oxidized at the side chain in a regioselective way using a Pummerer-like reaction to form unusual α-amino acids.[7]

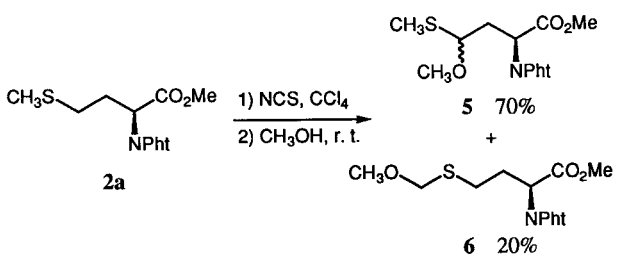
The phthaloyl moiety was chosen as an amino protecting group in **2a** to avoid any internal amine participation[8] and this protection was performed using a standard procedure.[9]

The second step is a Pummerer-like reaction using *N*-chlorosuccinimide (NCS)[7,10] in carbon tetrachloride. α-Chlorination was chosen because of its regioselectivity towards branched-chain carbons compared to methyl groups.[11] Transient chlorinated derivatives (mixture of isomers)[6,7,11c] were then hydrolyzed as described in the experimental section (nitrogen bubbling into aqueous acidic medium) into aldehyde **3a** in good yield (Scheme 1). Hydrolysis using $HgCl_2$, $CdCO_3$, H_2O;[12] NCS, $AgNO_3$, acetonitrile;[13] or $CuCl_2$. $2H_2O$, CuO, H_2O, acetone[14] led to lower yields. However, when the hydrolysis was performed in aqueous alkaline medium, formation of dithioacetal **4**[15] together with aldehyde **3a** was observed.

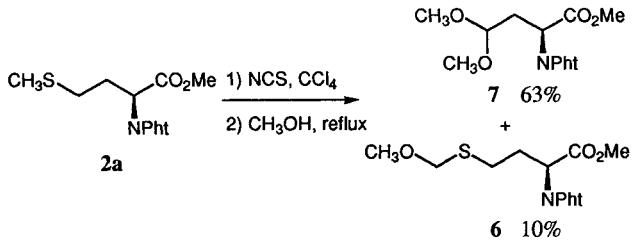


Scheme 2

Moreover, methanolysis at room temperature of the mixture of transient chlorinated derivatives afforded hemithioacetal **5** (1.3:1 mixture of diastereoisomers) and isomer **6** in 70 and 20% yield, respectively, based on **2a** after silica gel column chromatography (Scheme 3). Unlike the results of Dehmlow et al.[6] methanolysis at reflux of the mixture of the transient chlorinated derivatives furnished directly the dimethoxy acetal **7** in 63% yield based on **2a** together with a small amount of **6** (10% yield based on **2a**) (Scheme 4).



Scheme 3



Scheme 4

The enantiomeric purity of **3a** was checked by Jones oxidation[16] to α-methyl *N*-phthaloyl-L-aspartate, its esterification into dimethyl *N*-phthaloyl-L-aspartate and comparison with literature data.[17]

For direct comparison with ethyl ester **2b** and **3b** already described in the literature by Dehmlow et al.,[6] we performed the same sequence as shown in Scheme 1 starting with commercially available L-methionine ethyl ester hydrochloride **(1b)**. Ethyl ester **2b** was obtained in 75% yield as a colorless oil: $[\alpha]_D^{20} = -29.4°$ ($c = 1.09$, $CHCl_3$) {Lit.[6] $[\alpha]_D^{24} = -16.3°$ ($c = 0.98$, $CHCl_3$)}. Ethyl ester **3b** was obtained in 60% yield as a colorless oil: $[\alpha]_D^{20} = -26.2°$ ($c = 1.07$, $CHCl_3$) {Lit.[6] $[\alpha]_D^{24} = -7.94°$ ($c = 0.46$, $CHCl_3$)}. Therefore, compounds obtained as described in the literature[6] seem to be partially racemized.

In conclusion, the procedures described herein allow the easy and efficient synthesis of optically pure aldehyde **3a** and hemithio- and dimethoxy acetal derivatives **5** and **7**, respectively, using cheap and easily handled reagents. Synthetic uses of such intermediates are under investigation in our laboratory.

All solvents and reagents were used as purchased. CCl_4 was stored over 4 Å molecular sieves before use. L-Methionine esters **1a, b** are commercially available from Aldrich or are easily synthesized following literature procedures.[18] Purifications by flash column chromatography were performed using silica gel 60 0.04–0.063 mm (230–400 mesh) (Merck ref 9385), and TLC using silica gel 60F254, layer thickness 0.2 mm on aluminum sheets.

Mps were determined on a Mettler FP 62 apparatus and are corrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1 cm cell. IR spectra were obtained using a Nicolet 205 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane.

Compounds **2a**, **3a** and **5** gave C,H,N,O analysis ± 0.30%.

Methyl (*S*)-2-Phthalimido-4-methylthiobutanoate (2a); General Procedure:

In a 2 L round-bottomed flask fitted with a Dean-Stark apparatus, reflux condenser, and a drying tube containing calcium chloride were placed L-methionine methyl ester hydrochloride **(1a)** (50 g, 0.25 mol), phthalic anhydride (37.1 g, 0.25 mol, 1 equiv), triethylamine (100 mL, 0.72 mol, 2.9 equiv) and toluene (1 L). This mixture was magnetically stirred and heated under reflux until the calculated amount (ca. 4.5 mL) of water had separated. The reaction mixture was allowed to cool to r.t. and triethylamine hydrochloride was filtered off. The filtrate was washed with aq HCl (1 N), then with water to neutrality. The organic layer was dried ($MgSO_4$), filtered, and evaporated under vacuum leaving an oil (54.6 g, 75%). Crystallisation occured after efficient vacuum drying and storage overnight at −20 °C. Mp 40–41 °C; $[\alpha]_D^{20} = -41.6°$ ($c = 1.49$, $CHCl_3$) {Lit.[19] mp 33–34 °C; $[\alpha]_D^{20} = -46.2°$ ($c = 1$, $CHCl_3$)}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3S), 2.4–2.6 (m, 4 H, CH_2CH_2), 3.69 (s, 3 H, CO_2CH_3), 5.1 (m, 1 H, CH), 7.6–7.9 (m, 4 H, Pht).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.2 (CH_3S), 28.0, 30.7 (CH_2CH_2), 50.7 (CHN), 52.8 (CH_3O), 123.5, 131.7, 134.2 (C_{arom}), 167.5, 169.5 (CO).

MS (DCI, NH_3): *m/z* 294 $(M + H)^+$, 311 $(M + NH_4)^+$.

Ethyl Ester **2b**:

Identically obtained in 75% yield as a colorless oil. $[\alpha]_D^{20} = -29.4°$ ($c = 1.09$, $CHCl_3$) {Lit.[6] $[\alpha]_D^{24} = -16.3°$ ($c = 0.98$, $CHCl_3$)}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, $J = 7.1$ Hz, 3 H, CH_3), 2.08 (s, 3 H, CH_3S), 2.4–2.6 (m, 4 H, CH_2CH_2), 4.20 (q, $J = 7.1$ Hz, 2 H, OCH_2), 5.07 (m, 1 H, CH), 7.6–7.9 (m, 4 H, Pht).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.0 (CH_3), 15.2 (CH_3S), 28.0, 30.8 (CH_2CH_2), 50.9 (CHN), 61.8 (CH_2O), 123.5, 131.7, 134.1 (C_{arom}), 167.5, 168.9 (CO).

Methyl (*S*)-2-Phthalimido-4-oxobutanoate (3a); General Procedure:

This reaction must be performed under a well ventilated hood. In a 250 mL two-necked round-bottomed flask fitted with a gas inlet and a drying tube containing calcium chloride were placed methylthiobutanoate **2a** (5.86 g, 20 mmol) and CCl_4 (60 mL). The mixture was magnetically stirred under a nitrogen atmosphere at r.t. and *N*-chlorosuccinimide (2.8 g, 21 mmol, 1.05 equiv) was added in one portion. The reaction mixture was then stirred for 2 h. The supernatant succinimide formed during the reaction was filtered through sintered glass with suction into a three-necked 250 mL round-bottomed flask and rinsed with CCl_4 (40 mL). This flask was equipped with a gas inlet (needle) so that nitrogen could bubble into the solution and the gas outlet was connected (via a cold water condenser) to a flask containing a hypochlorite solution to scavenge the sulfur byproducts. Water (120 mL) was then added and nitrogen was gently bubbled through the solution overnight at r.t. The phases were separated and the aqueous (acidic) phase was extracted with CH_2Cl_2 (50 mL). The organic phases were combined and added to 120 mL aq HCl (1 N). Stirring under nitrogen bubbling was repeated once again for 4 h. The phases were separated and the organic phase was washed with sat. aq $NaHCO_3$ (100 mL), then with water and dried (Na_2SO_4). Evaporation of the solvent left 5.7 g of crude product. Flash chromatography (silica gel; cyclohexane–EtOAc, 3:1 then 1:1) gave aldehyde **3a** (3.45 g, 66%) as a white solid after efficient vacuum drying and storage overnight at −20 °C. Mp 64–68 °C. $[\alpha]_D^{20} = -50.5°$ ($c = 1.17$, $CHCl_3$).[20]

^1H NMR (200 MHz, $CDCl_3$): δ = 3.26 (ddd, $J = 0.8$, 7.7, 18.4 Hz, 1 H, C*H*CHO), 3.55 (ddd, $J = 0.8$, 6, 18.4 Hz, 1 H, C*H*CHO), 3.74 (s, 3 H, CO_2CH_3), 5.51 (dd, $J = 6$, 7.7 Hz, 1 H, CHN), 7.7–7.9 (m, 4 H, Pht), 9.75 (t, $J = 0.8$ Hz, 1 H, CHO).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 42.8 (CH_2), 45.9 (CHN), 53.1 (CO_2CH_3), 123.6, 131.5, 134.3 (C_{arom}), 167.1, 168.8 (CO), 197.4 (CHO).

MS (DCI, NH_3): *m/z* 262 $(M + H)^+$, 279 $(M + NH_4)^+$.

IR (neat): ν = 1720, 1750, 1780, 2720, 2820 cm^{-1}.

Ethyl Ester **3b**:

Identically obtained in 60% yield based on **2b** as a colorless oil. $[\alpha]_D^{20} = -26.2°$ ($c = 1.07$, $CHCl_3$) {Lit.[6] $[\alpha]_D^{24} = -7.94°$ ($c = 0.46$, $CHCl_3$)}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.20 (t, $J = 7.2$ Hz, 3 H, CH_3), 3.24 (ddd, $J = 0.9$, 7.8, 18.4 Hz, 1 H, C*H*CHO), 3.52 (ddd, $J = 0.9$, 6, 18.4 Hz, 1 H, C*H*CHO), 4.19 (q, $J = 7.2$ Hz, 2 H, OCH_2), 5.46 (dd, $J = 6$, 7.8 Hz, 1 H, CHN), 7.7–7.9 (m, 4 H, Pht), 9.75 (t, $J = 0.9$ Hz, 1 H, CHO).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.9 (CH_3), 42.7 (CH_2CO), 46.1 (CHN), 62.3 (CO_2CH_2), 123.5, 131.5, 134.2 (C_{arom}), 167.1, 168.2 (CO), 197.5 (CHO).

MS (DCI, NH_3): *m/z* = 276 $(M + H)^+$, 293 $(M + NH_4)^+$.

Methyl (*S*)-2-Phthalimido-4,4-(dimethylthio)butanoate (4):
This reaction must be performed under a well ventilated hood. Chlorination was performed using the same quantity and protocol as described for the synthesis of **3a**. After filtration of the succinimide, sat. aq $NaHCO_3$ (20 mL) was added and the mixture was stirred overnight at r.t. The phases were separated and the organic phase was washed with sat. aq $NaHCO_3$ (60 mL) and water (60 mL), and dried ($MgSO_4$). After evaporation of the solvent, flash chromatography (silica gel; cyclohexane–EtOAc, 3:1 then 1:1) gave dithioacetal **4** (1.73 g, 26%) and aldehyde **3a** (1.83 g, 35%). TLC (cyclohexane–EtOAc, 3:1): **4**, $R_f = 0.4$; **3a**, $R_f = 0.15$. **4**, $[\alpha]_D^{20} = -39.4°$ ($c = 1$, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.08$, 2.11 (2 s, 6H, CH_3S), 2.55–2.8 (m, 2H, CH_2), 3.68 (dd, $J = 6.4$, 8.5 Hz, 1H, SCHS), 3.74 (s, 3H, CO_2CH_3), 5.37 (dd, $J = 5.5$, 8.9 Hz, 1H, CHN), 7.7–7.9 (m, 4H, Pht).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 12.1$, 12.9 (CH_3S), 33.6 (CH_2), 50.1, 51.2, 52.9 (CO_2CH_3, CHN, SCHS), 123.6, 131.7, 134.2 (C_{arom}), 167.4, 169.3 (CO).

MS (DCI, NH_3): $m/z = 292$ $(M-CH_3SH+H)^+$, 309 $(M-CH_3SH+NH_4)^+$, 357 $(M+NH_4)^+$.

Methyl (*S*)-2-Phthalimido-4-methylthio-4-methoxybutanoate (5) and Methyl (*S*)-2-Phthalimido-4-methoxymethylthiobutanoate (6):
This reaction must be performed under a well ventilated hood. Chlorination was performed using the same quantity and protocol as described for the synthesis of **3a**. After filtration of the succinimide, MeOH (100 mL) was added and the mixture was stirred overnight at r.t. $NaHCO_3$ (3.38 g, 40 mmol, 2 equiv) was then added followed by water (150 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The organic phases were combined, washed with water (40 mL) and dried (Na_2SO_4). Evaporation of the solvent under vacuum left a crude oil (quantitative yield) which was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 4:1 then 2:1). Hemithioacetal **5** (4.57 g, 71%) was obtained as a clear oil (1.3:1 mixture of diastereomers) followed by **6** (1.26 g, 20%; 90% purity, contaminated with small amounts of **4**, **7** and **5**). TLC (cyclohexane–EtOAc, 4:1): **5**, $R_f = 0.25$; **6**, $R_f = 0.2$.

Compound **5**:

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.00$, 2.02 (2 s, 3H, CH_3S), 2.5–2.9 (m, 2H, CH_2), 3.23, 3.33 (2 s, 3H, CH_3O), 3.74 (s, 3H, CO_2CH_3), 4.18, 4.42 (2 dd, $J = 3.9$, 9.8 and 5.9, 7.6 Hz, 1H, SCHO), 5.1–5.3 (m, 1H, CHN), 7.7–7.9 (m, 4H, NPht).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 9.1$, 9.2 (CH_3S), 34.6, 34.9 (CH_2), 49.3, 49.7, 52.8, 55.5 (OCH_3, CHN), 82.5, 84.5 (SCHO), 123.4, 123.5, 131.7, 131.8, 134.1, 134.2 (C_{arom}), 139.4, 167.4 (CO).

MS (DCI, NH_3): $m/z = 341$ $(M+NH_4)^+$, 309 $(M-CH_3OH+NH_4)^+$, 293 $(M-CH_3SH+NH_4)^+$, 292 $(M-CH_3OH+H)^+$, 276 $(M-CH_3SH+H)^+$.

Compound **6**:

$[\alpha]_D^{20} = -31.8°$ ($c = 1.32$, $CHCl_3$) {Lit.[7] $[\alpha]_D^{20} = -31°$ ($c = 4.9$, $CHCl_3$)}.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.5$–2.8 (m, 4H, CH_2CH_2), 3.31 (s, 3H, CH_3O), 3.73 (s, 3H, CO_2CH_3), 4.60 (s, 2H, SCH_2O), 5.0–5.3 (m, 1H, CHN), 7.7–7.9 (m, 4H, NPht).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 27.6$, 28.9 (CH_2CH_2), 50.8, 52.7, 55.6 (CHN, OCH_3, CO_2CH_3), 75.3 (OCH_2S), 123.5, 131.7, 134.2 (C_{arom}), 167.5, 169.4 (CO).

MS (DCI, NH_3): $m/z = 341$ $(M+NH_4)^+$, 324 $(M+H)^+$.

Methyl (*S*)-2-Phthalimido-4,4-dimethoxybutanoate (7):
This reaction must be performed under a well ventilated hood. Chlorination was performed using the same quantity and protocol as described for the synthesis of **3a**. After filtration of the succinimide, MeOH (100 mL) was added and the mixture was refluxed under stirring for 36 h, after which TLC and NMR analysis showed a significant presence of **5**. TLC (cyclohexane–EtOAc, 3:1): **5**, $R_f = 0.3$; **7**, $R_f = 0.2$. $NaHCO_3$ (3.38 g, 40 mmol, 2 equiv) was then added followed by water (200 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The organic phases were combined, washed with water (40 mL) and dried (Na_2SO_4). Evaporation of the solvent under vacuum left a crude oil which was dissolved in MeOH (100 mL) and refluxed overnight in the presence of a catalytic amount of concentrated H_2SO_4 (4 drops). Addition of $NaHCO_3$ (1 g) followed by the same workup as before led to a clear crude oil (6 g, quantitative yield). Flash chromatography (silica gel; cyclohexane–EtOAc, 3:1) gave **7** (3.24 g, 53%) as an oil. Also recovered, a 1:1 mixture of **6** and **7** (1.3 g, 20%).[21] TLC (cyclohexane–EtOAc, 3:1): **6**, $R_f = 0.25$; **7** $R_f = 0.2$.

Compound **7**, $[\alpha]_D^{20} = -19.5°$ ($c = 1.5$, $CHCl_3$) {Lit.[7] $[\alpha]_D^{20} = -20°$ ($c = 9$, $CHCl_3$)}.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.35$–2.65 (m, 2H, CH_2), 3.21, 3.28 (2 s, 6H, CH_3O), 3.72 (s, 3H, CO_2CH_3), 4.41 (t, $J = 5.7$ Hz, 1H, OCHO), 5.01 (dd, $J = 4.9$, 9.6 Hz, 1H, CHN), 7.6–7.9 (m, 4H, Pht).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 31.8$ (CH_2), 48.5, 52.8, 53.0, 53.2 (CHN, OCH_3, CO_2CH_3), 102.0 (OCHO), 123.4, 131.7, 134.1 (C_{arom}), 167.3, 169.4 (CO).

MS (DCI, NH_3): $m/z = 325$ $(M+NH_4)^+$, 308 $(M+H)^+$, 293 $(M-CH_3OH+NH_4)^+$, 276 $(M-CH_3OH+H)^+$.

α-Methyl *N*-Phthaloyl-L-aspartate (8) and Dimethyl *N*-Phthaloyl-L-aspartate (9):
Compound **8** was synthesized from **3a** (Jones oxidation) on a 1 mmol scale (97% yield) as described in the literature:[16] $[\alpha]_D^{20} = -59.5°$ ($c = 0.605$, $CHCl_3$) {Lit.[17] $[\alpha]_D^{20} = -47.3°$ ($c = 0.595$, $CHCl_3$)}. Esterification (MeOH, cat. H_2SO_4, r.t. overnight, 82% based on **3a**) yielded **9**: $[\alpha]_D^{20} = -53.6°$ ($c = 1.4$, $CHCl_3$) {Lit.[17] $[\alpha]_D^{20} = -44.6°$ ($c = 1.427$, $CHCl_3$}. The ^{1}H and ^{13}C NMR spectra were consistent with literature data and showed a purity > 95%.

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(21) Refluxing pure isolated **5** in acidic methanol (MeOH, cat. H_2SO_4) allowed the formation of dimethoxy acetal **7** in only 36% isolated yield based on **2a**.