Synthesis of L-3,4-Didehydroproline: Favoured Orientation in the Key-Step Elimination Reaction

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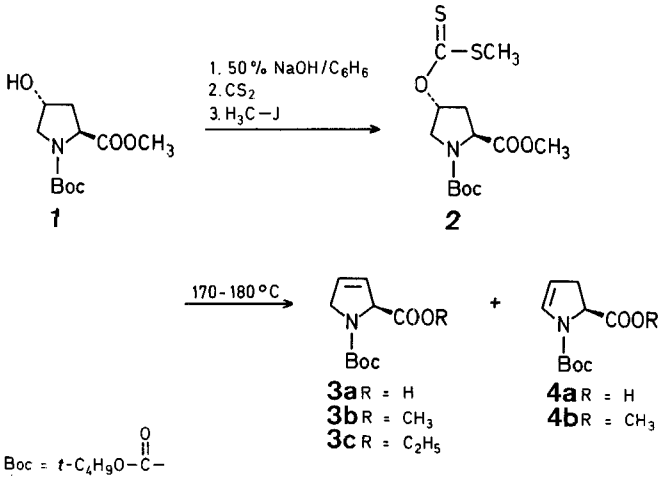
L-3,4-Didehydroproline is a very interesting compound in many respects. Its substitution for proline in peptide chains gives precursors of deuteriated or tritiated products[1-3]; labelled products allow structural study and radioimmunoassay analysis. The incorporation of 3,4-didehydroproline into biologically active peptides very seldom results in loss of activity[1,2,3,5], in fact in some cases the activity even increases, with reduced toxicity of the product[3,4].

The known syntheses[1,6] of 3,4-didehydroproline involve a resolution of the racemate obtained from 2-pyrrolecarboxylic acid and the access to large quantities of product remains tedious. In a previous paper[7], we reported the synthesis of *N*-Boc-L-3,4-didehydroproline **(3a)** starting from naturally occurring L-4-hydroxyproline; the key step of this synthesis was the Tchugaeff pyrolysis of the dithiocarbonate **2** from which elimination resulted mainly in Δ^3-olefin formation (Scheme **A**). In order to explain the observed selectivity and to obtain another access to **3** under milder conditions, new synthetic routes were investigated. The present work deals with new preparative methods leading to **3** starting from Boc-L-4-hydroxyproline methyl ester **(1)**, modified at the C-4 position, by thermal-*syn*-elimination and base-catalysed dehydrohalogenation.



Scheme A

The formation of olefins by thermal-*syn*-elimination starting from sulfoxides[8] and more recently from selenoxides[9] has been widely studied. Aryl sulfoxides and selenoxides were chosen as leaving groups in order to perform the eliminations at lower temperatures.

Sulfoxide **6** was obtained in two steps from **1** through sulfide **5** (Scheme **B**). Reaction using the triphenylphosphine/diethyl azodicarboxylate system, proposed for aryl alkyl ethers synthesis[10], was adapted for this purpose. Oxidation of **5** to **6**, which failed using hydrogen peroxide or sodium metaperiodate, was quantitatively performed by means of *m*-chloroperoxybenzoic acid. The use of excess *m*-chloroperoxybenzoic acid led to the formation of the sulfone **7** which remained unchanged under the thermolysis conditions. Thermolysis of crude **6** in refluxing toluene afforded mainly olefin **3b**, in addition to **4b**, with a good selectivity (Table).

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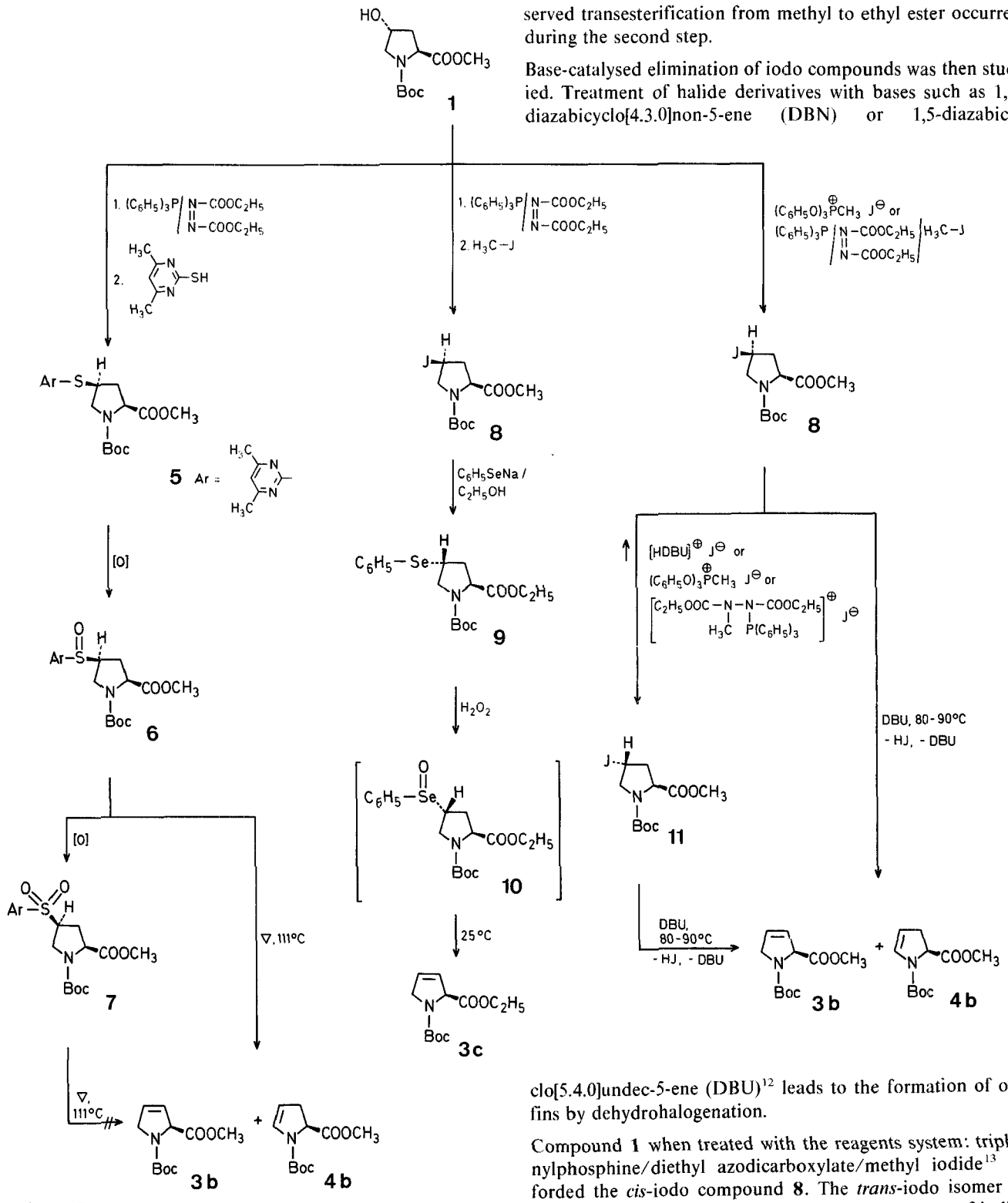

Scheme B

In the synthesis through seleno compounds, all reactions were carried out in the same reaction vessel, without isolation of any intermediates (Scheme **B**). Selenophenol was not commercially available and unpleasent to manipulate. For these reasons selenide **9** was prepared unlike the sulfide analog; compound **9** was obtained in two steps starting from **1** through iodide **8** *(vide infra)*; compound **8** was then reacted with sodium phenylselenide[11] in boiling ethanol to give **9**, which was directly oxidised by hydrogen peroxide to yield selenoxide **10**. Compound **10** underwent elimination at room temperature to afford exclusively the Δ^3-olefin **3c**. The observed transesterification from methyl to ethyl ester occurred during the second step.

Base-catalysed elimination of iodo compounds was then studied. Treatment of halide derivatives with bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[12] leads to the formation of olefins by dehydrohalogenation.

Compound **1** when treated with the reagents system: triphenylphosphine/diethyl azodicarboxylate/methyl iodide[13] afforded the *cis*-iodo compound **8**. The *trans*-iodo isomer **11** was obtained by isomerisation of **8** in the presence of iodide ion (Scheme **B**). Use of excess reagents, higher temperature, and longer reaction time in the preceding procedure gave a mixture of **11** and **8**. Use of methyltriphenoxyphosphonium iodide[14] furnished an alternative route to **11**. Both isomers were easily separated by chromatography. Eliminations of both iodides were carried out in toluene, in the presence of DBU. Elimination of hydrogen iodide from **8** gave mainly the Δ^3-olefin **3b**, whereas elimination from **11** afforded both olefins **3b** and **4b** in almost equal amounts (Table). At room temperature more than 90% of DBU hydroiodide precipitated in toluene; the tertiary base was thus readily recovered. It was verified that isomerisation of both iodides occurred very

slowly under the conditions of elimination, and did not significantly influence the olefin distribution resulting from each isomer. We have additionally checked that isomerisation of both olefins does not occur at 80–90 °C in toluene solution, in presence of DBU and DBU hydroiodide.

Examination of Table shows that, in all cases, the Δ^3-olefin **3** was the major product, independant of the type of elimination and of the configuration of the starting material.

Thermal *syn*-elimination and dehydrohalogenation gave high selectivity (entries 1, 2, 4) while selenoxide elimination at room temperature even proved to be specific. However, dehydrohalogenation appeared less regioselective since the *trans*-iodide **11** afforded both olefins in almost equal amounts (entry 5). It should be noted that base-catalysed elimination resulted in partial loss of chirality (entries 4, 5).

In conclusion, these various methods provided good access to L-3,4-didehydroproline, especially the one-pot synthesis through seleno compounds which gave the highest overall yield under the mildest conditions.

The unexpected and predominant orientation of the elimination gave the Δ^3-olefin as major product in all cases. Our results suggested that this orientation was mainly dependent on a stability gain arising from the formation of two sp^2 carbons at C-3 and C-4 in all cases. Dehydrohalogenation catalysed by hindered bases also appeared sensitive to the stereochemistry of the starting material. The Δ^4-olefin of the enamine type provided a good starting material for other synthetic projects which are currently being studied.

Table. Preparation of Olefins **3** and **4**

Substrate	Configuration	Elimination Temperature	Products Total Yield [%][a]	Ratio of 3 : 4		$[\alpha]_D^{20}$ of **3** (*c*, CH_3OH)
4	2*S*,4*R*	170–180 °C	69	93 : 7		—
6	2*S*,4*S*	111 °C	67	87 : 13	**3b:**	−232° (0.99)
10	2*S*,4*R*	25 °C	87[b]	100 : 0	**3c:**	−234° (1.28)
8	2*S*,4*S*	80–90 °C	93	87 : 13	**3b:**	−207° (1.56)
11	2*S*,4*R*	80–90 °C	93	54 : 46	**3b:**	−217° (1.54)

[a] Yield of product isolated from elimination step.
[b] Overall yield from **1**.

^{1}H-N.M.R. spectra were recorded on a Cameca 250 MHz spectrometer in $CDCl_3$ with TMS as internal standard. N.M.R. data indicated the presence of two conformers with respect to the N—CO bond[16] for each proline derivative. I.R. spectra were recorded on a Perkin-Elmer 457 spectrometer. Optical rotations were measured with a Perkin-Elmer automatic polarimeter in a 10 cm cell path in methanol. Microanalyses were obtained from the "service central d'analyse du CNRS". T.L.C. analyses were performed on Kieselgel G-precoated plates and developed by spraying with (A): 1. 6 normal hydrochloric acid; 2. ninhydrin in ethanol; 3. heating, or (B): 1% potassium permanganate in 1 normal sulfuric acid for unsaturated products. Preparative column chromatography was conducted with Kieselgel 60 (Merck), eluting with ethyl acetate/hexane mixtures as for T.L.C.

(4*S*)-*N*-Boc-4-[2-(4,6-dimethylpyrimidyl)-thio]-L-proline Methyl Ester (5):

Compound **1** (0.981 g, 4 mmol) and triphenylphosphine (2.1 g, 8 mmol) are dissolved in dry tetrahydrofuran (25 ml) and the solution is cooled to 0 °C. Diethyl azodicarboxylate (1.4 g, 8 mmol) in tetrahydrofuran (5 ml), then 4,6-dimethyl-2-mercaptopyrimidine (1.49 g, 10 mmol) without solvent, are added. After 1 h of stirring at 0 °C, T.L.C. (40/60) shows complete disappearance of **1**. Solvent is evaporated under vacuum and the residue chromatographed with the same eluent as for T.L.C. to give **5** as colorless crystals; yield: 1.397 g (95%); m.p. 98–99 °C (from ethyl acetate/hexane); $[\alpha]_D^{20}$: −66° (*c* 0.67).

$C_{17}H_{25}N_3SO_4$	calc.	C 55.57	H 6.86	N 11.43	S 8.73
(367.5)	found	55.71	6.93	11.55	8.61

^{1}H-N.M.R. ($CDCl_3$): δ = 1.43, 1.47 (2s, 9H); 2.07, 2.09 (2m, 1H, H-3'); 2.39 (s, 6H); 2.86 (m, 1H, H-3); 3.40, 3.43 (2m, 1H, H-5'); 3.76 (s, 3H); 4.14, 4.22 (2m, 1H, H-5); 4.18–4.31 (br m, 1H, H-4); 4.36, 4.43 (2m, 1H, H-2); 6.72 ppm (s, 1H).

(4*S*)-*N*-Boc-4-[2-(4,6-dimethylpyrimidyl)-sulfoxyl]-L-proline Methyl Ester (6):

Compound **5** is oxidised with *m*-chloroperoxybenzoic acid (1 equiv) in dichloromethane at 0 °C according to Ref.[17]. Crude **6** containing traces of sulfone **7** is used directly for the next step. An analytical sample of **6** is obtained by chromatography (60/40) as colourless crystals; m.p. 126–127 °C (from ether); $[\alpha]_D^{20}$: −7.5 (*c*, 0.67).

$C_{17}H_{25}N_3SO_5$	calc.	C 53.25	H 6.57	N 10.96	S 8.36
(383.5)	found	53.06	6.59	10.87	8.06

I.R. (CCl_4): ν = 1742 (ester); 1705 (urethane); 1060, 1077 cm^{-1} (sulfoxide).

^{1}H-N.M.R. ($CDCl_3$): 2 conformers + 2 isomers at the S-atom: δ = 1.39, 1.41, 1.43, 1.47 (4s, 9H); 2.5–2.8 (br m, 2H, H-3 + H-3'); 2.58 (s, 6H); 3.7–4.1 (br m, 3H, H-4 + H-5 + H-5'); 3.75, 3.76 (2s, 3H); 4.3–4.5 (br m, 1H, H-2); 7.16 ppm (s, $1H_{arom}$).

Thermolysis of Sulfoxide 6:

Crude **6**, obtained from **5** (1.102 g, 3 mmol) as described above, is dissolved in toluene (15 ml) and refluxed for 2–3 h until T.L.C. (60/40) shows complete disappearance of **6**. Evaporation of the solvent and chromatography (25/75) gives **4b** and **3b** as colourless oils.

3b: yield: 0.396 g (58%); $[\alpha]_D^{20}$: −232° (*c* 0.99).

$C_{11}H_{17}NO_4$	calc.	C 58.14	H 7.54	N 6.16
(227.3)	found	57.99	7.57	6.13

I.R. (neat): ν = 3090 (vinyl CH); 1759 + 1744 (shoulder) (ester); 1705 (urethane); 1623, 770, 685 cm^{-1} (double bond).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.43, 1.48 (2s, 9H); 3.72, 3.73 (2s, 3H); 4.2–4.3 (m, 2H, H-5 + H-5'); 4.95, 5.01 (2m, 1H, H-2); 5.71, 5.75 (2m, 1H, H-3); 5.96, 6.02 ppm (2m, 1H, H-4).

4b: yield: 0.059 g (9%); $[\alpha]_D^{20}$: −108° (*c* 0.71).

$C_{11}H_{17}NO_4$	calc.	C 58.14	H 7.54	N 6.16
(227.3)	found	57.71	7.40	6.33

I.R. (neat): ν = 3120 (vinyl CH); 1759 + 1744 (shoulder) (ester); 1705 (urethane); 1623, 763, 703 cm^{-1} (double bond).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.44, 1.49 (2s, 9H); 2.7 (m, 1H, H-3'); 3.1 (m, 1H, H-3); 3.76 (s, 3H); 4.59, 4.66 (2m, 1H, H-2); 4.91, 4.95 (2m, 1H, H-4); 6.52, 6.65 ppm (2m, 1H, H-5).

One-Pot Conversion of 8 to 3c through Selenoxide 10:

Iodide **8** is obtained as described below starting from **1** (0.589 g, 2.4 mmol). Tetrahydrofuran is evaporated under vacuum below 30 °C and dry ethanol (10 ml) is added. An ethanol solution of sodium phenylselenide[11] (1.1 eq.) is introduced and the resulting mixture is refluxed until the starting material is completely consumed (T.L.C. 25/75); then tetrahydrofuran (5 ml) is added, the pale yellow solution is cooled in an ice bath, and 30% hydrogen peroxide (10 eq.) is added dropwise within 10 min under stirring below 20 °C. The mixture turns brown and is stirred at room temperature until T.L.C. (25/75) shows complete disappearance of the selenoxide **10** (~1.5 h). Potassium permanganate spraying indicates the presence of a single unsaturated product which is extracted with ether (2 × 50 ml), washed with aqueous sodium hydrogen carbonate (2 × 15 ml), then with water (2 × 15 ml), until neutral, and dried with magnesium sulfate. Silica gel chromatography (25/75) of crude product affords **3c** as a colourless oil; yield: 0.504 g (87%); $[\alpha]_D^{20}$: −234° (*c* 1.28).

$C_{12}H_{19}NO_4$	calc.	C 59.73	H 7.94	N 5.80
(241.3)	found	59.79	7.88	5.63

I.R. (neat): ν = 3090 (vinyl CH); 1758 + 1745 (shoulder) (ester); 1708 (urethane); 1623, 770, 685 cm^{-1} (double bond).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.26$, 1.28 (2t, 3H, $J = 7.1$ Hz); 1.44, 1.48 (2s, 9H); 4.1–4.3 (m, 2H, H-5 + H-5′); 4.19 (q, 2H, $J = 7.1$ Hz); 4.94, 5.01 (2m, 1H, H-2); 5.71, 5.76 (2m, 1H, H-3); 5.94, 6.00 ppm (2m, 1H, H-4).

(4*S*)-*N*-Boc-4-iodo-L-proline Methyl Ester (8):

Compound **8** is prepared by the published method[13] with modifications in order to avoid isomerisation of **8** to **11**. To **1** (1.226 g, 5 mmol) and triphenylphosphine (1.574 g, 6 mmol) in dry tetrahydrofuran (15 ml) cooled at 0 °C and stirred under an inert atmosphere, is added diethyl azodicarboxylate (1.045 g, 6 mmol) in tetrahydrofuran (5 ml) followed by methyl iodide (0.852 g, 6 mmol) in tetrahydrofuran (5 ml). After addition, stirring is continued at room temperature. Starting material consumption and iodo isomer appearance are monitored by T.L.C. (25/75). The solvent is evaporated under vacuum below 30 °C and the residue chromatographed (25/75) to give traces of the isomer **11** and product **8** as colourless crystals; yield: 1.598 g (90%); m.p. 63–64 °C (from ether/hexane); $[\alpha]_D^{20}$: −22° (*c* 1.04).

$C_{11}H_{18}JNO_4$	calc.	C 37.20	H 5.11	N 3.94	J 35.73
(355.2)	found	37.45	5.10	3.83	35.71

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.41$, 1.46 (2s, 9H); 2.32, 2.35 (2m, 1H, H-3′); 2.87, 2.89 (2m, 1H, H-3); 3.6–3.7 (m, 1H, H-5′); 3.76 (s, 3H); 4.0–4.2 (m, 2H, H-4 + H-5); 4.24, 4.31 ppm (2m, 1H, H-2).

(4*R*)-*N*-Boc-4-iodo-L-proline Methyl Ester (11):

The same procedure as for **8** is used except that **1** (1.226 g, 5 mmol) and the reagent system (10 mmol) are reacted at room temperature and that stirring is continued for 22 h. Column chromatography (25/75) allows the separation of both isomers to give compound **8** [yield: 0.544 g (30%)] and **11** as a colourless oil; yield: 1.065 g (60%); $[\alpha]_D^{25}$: −56° (*c* 0.78).

$C_{11}H_{18}JNO_4$	calc.	C 37.20	H 5.11	N 3.94	J 35.73
(355.2)	found	37.53	5.21	3.82	35.97

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.42$, 1.47 (2s, 9H); 2.41 (m, 1H, H-3′); 2.58 (m, 1H, H-3); 3.72, 3.80 (2m, 1H, H-5′); 3.74 (s, 3H); 3.96, 3.98 (2m, 1H, H-5); 4.3–4.5 ppm (m, 2H, H-2 + H-4).

Using an alternative procedure adapted from Ref.[15], compound **1** (0.491 g, 2 mmol) and methyltriphenoxyphosphonium iodide[14] in hexamethylphosphoric triamide (10 ml) are stirred at room temperature for 23 h and at 50–60 °C for 2 h. Work up by chromatography as above gives **8** [yield: 0.185 g (26%)] and **11** [yield: 0.476 g (67%)].

Dehydrohalogenation of 8 or 11 to 3b and 4b:

A 0.1 molar solution of compound **8** or **11** (0.356 g, 1 mmol) in toluene and 1,5-diazabicyclo[5.4.0]undec-5-ene (1.1 eq) are heated at 80–90 °C for 8 h. The mixture is then allowed to stand at room temperature in order to complete precipitation of the DBU hydroiodide. The precipitate is filtered, the solvent evaporated, and the olefins **3b** and **4b** separated as described above; yield: 0.184 g (81%) and 0.027 g (12%) from **8**, 0.114 g (50%) and 0.098 g (43%) from **11**, respectively.

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