Reductive Deconjugation of α-Bromo α,β-Unsaturated Esters Based on Redox Tautomerism of Diethyl Phosphonate

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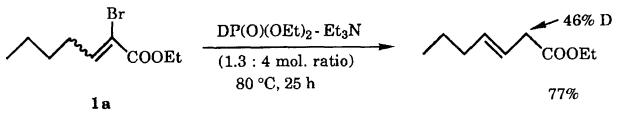
Synopsis. Reductive deconjugation of α-bromo α,β-unsaturated esters was performed by $DP(O)(OEt)_2$ or $P(OEt)_3$–H_2O in the presence of triethylamine from mechanistic viewpoint and was applied to the synthesis of a precursor of (±)-patulolide A.

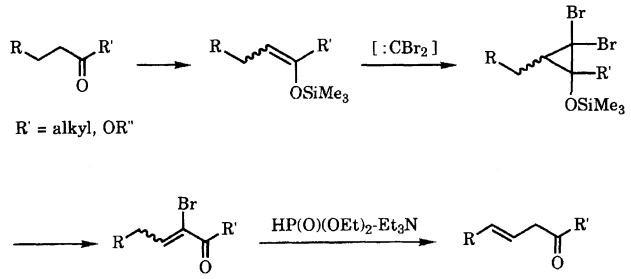
Redox tautomerism of dialkyl phosphonate (commercially named dialkyl phosphite) is of potential in reductive transformations.[1] A combination of dialkyl phosphonate and tertiary amine constitutes a versatile system for reduction of organic halides such as *gem*-dibromocyclopropanes and α-bromo α,β-unsaturated carbonyl compounds.[2] The latter is useful to introduce β,γ carbon–carbon double bond stereoselectively with one-carbon homologation because the α-bromo α,β-unsaturated carbonyl compounds are readily derived by the addition of dibromocarbene to silyl enol ethers or ketene alkyl silyl acetals (Scheme 1).

γ-Oxo or γ-hydroxy α,β-unsaturated carbonyl compounds are synthetically transformed from β,γ-unsaturated carbonyl ones. These processes are applied to the total syntheses of naturally occurring macrolides, recifeiolide[3] and pyrenophorin.[4] We herein report the behavior of diethyl phosphonate and triethyl phosphite in the reductive deconjugation.

A mixture of ethyl (*E*)- and (*Z*)-2-bromo-2-heptenoates (**1a**) was treated with $DP(O)(OEt)_2$ and triethylamine to give ethyl (*E*)-3-heptenoate in 77% yield with the regioselective deuterium incorporation at the 2-position (46%; 12% d_2, 68% d_1, 20% d_0 mixtures; Eq. 1). No deuterium incorporation was detected at the 4-position by ^1H NMR.



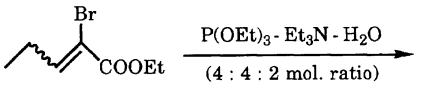
1a (1)



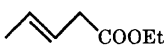
Scheme 1.

Reductive deconjugation is envisaged by involvement of the α-bromo β,γ-unsaturated ester **3**, which undergoes reduction with diethyl phosphonate and triethylamine (Scheme 2). The reduction of **3** is suggested to be faster than the reverse equilibrium to the α-bromo α,β-unsaturated ester **1** from the result shown in Eq. 1. The β,γ-unsaturated ester **2** is produced by kinetic protonation of the intermediary dienolate anion **4** at the 2-position with deuterium or proton derived from diethyl phosphonate or γ-proton of **1**. Ethyl bromophosphonate obtained is degraded with diethyl phosphonate and triethylamine.[1] The isomerization of the β,γ-unsaturated ester **2** to the corresponding α,β-unsaturated ester is found to be considerably slow under the conditions employed here.

Triethyl phosphite induces reduction or reductive phosphonation of *gem*-dibromocyclopropanes in cooperation with triethylamine depending on the amount of water, in which diethyl phosphonate should be generated in situ by hydrolysis of triethyl phosphite.[5] This combination of triethyl phosphite, triethylamine, and water (4 : 4 : 2 mol. ratio) was as effective as the above-mentioned system for reductive deconjugation of ethyl 2-bromo-2-pentenoate (**1b**) leading to the stereoselective formation of ethyl (*E*)-3-pentenoate (**2b**) in 96% yield (Eq. 2). The higher reaction temperature in a sealed tube was required for the better conversion. Phosphonation was not observed in this case, indicating no formation of a carbene-like intermediate via removal of bromide from the α-bromo β,γ-unsaturated enolate anion as reported in the reductive phosphonation.[5]



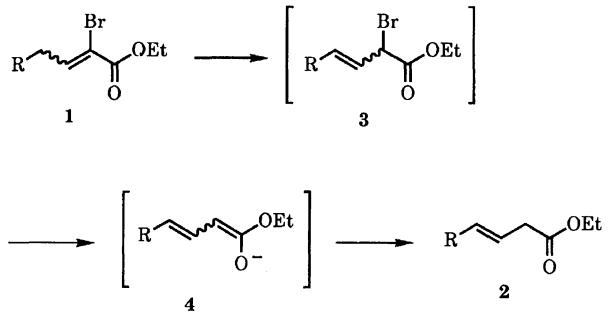
1b



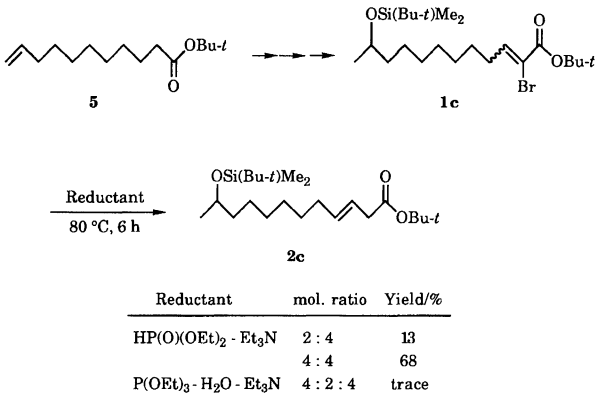
(2)

2b 80 °C, 6 h: 27%
120 °C, 8 h (sealed tube): 96%

Treatment of the α-bromo α,β-unsaturated ester **1c** with diethyl phosphonate and triethylamine gave the (*E*)-β,γ-unsaturated ester **2c** (Scheme 3). The decrease in the amount of diethyl phosphonate lowered the yield. The reductant consisting of triethyl phosphite, triethylamine, and water was not valid. The ester **2c** is considered to be a precursor for the preparation of (±)-patulolide A.[6] The starting compound is *t*-butyl 10-undecenoate (**5**), which was reduced to the hydroxy ester



Scheme 2.



Reductant	mol. ratio	Yield/%
$HP(O)(OEt)_2$ - Et_3N	2 : 4	13
	4 : 4	68
$P(OEt)_3$ - H_2O - Et_3N	4 : 2 : 4	trace

Scheme 3.

with $NaBH_4$ followed by protection with *t*-butyldimethylsilyl chloride. The ketene alkyl silyl acetal was obtained by use of $^-N(SiMe_3)_2$ as a base. Addition of dibromocarbene generated from bromoform and KOBu-*t* gave the ester **1c** via ring opening.

Some considerations have been described on reductive deconjugation with diethyl phosphonate or triethyl phosphite, which is synthetically of high potential including total synthesis of naturally occurring compounds.

Experimental

$DP(O)(OEt)_2$ was prepared by treatment of sodium diethyl phosphonate with D_2O. The α-bromo β,γ-unsaturated esters **1a,b** were prepared as described in our previous paper.[4]

Reductive Deconjugation of Ethyl 2-Bromo-2-heptenoate with $DP(O)(OEt)_2$ and Triethylamine. A solution of ethyl 2-bromo-2-heptenoate (**1a**, 0.235 g, 1.0 mmol), $DP(O)(OEt)_2$(0.181 g, 1.3 mmol), and triethylamine (0.405 g, 4.0 mmol) was heated at 80 °C for 25 h. White precipitate was formed as the reaction proceeded. The precipitate was filtered off and washed with ether (10 ml). The filtrate and ethereal solution were combined and concentrated. The isolated α-deuterio β,γ-unsaturated ester (77%) was identified by comparison of the spectral data with those of ethyl (*E*)-3-heptenoate.[4] The stereoselectivity was checked by IR and ^{13}C NMR spectra. IR (neat) 1740, 1160, 964 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=0.91 (t, 3H, J=6.0 Hz), 1.31 (t, 3H, J=7.4 Hz), 1.5—1.7 (m, 2H), 1.7—2.2 (m, 2H), 2.7—3.0 (m, 0.92H), 4.02 (q, 2H, J=7.4 Hz), 5.3—5.6 (m, 2H); ^{13}C NMR ($CDCl_3$, 23 MHz) δ=13.6, 14.3, 22.4, 34.7, 38.3, 60.5, 122.0, 134.6, 172.2. MS m/z 156 (M^+, 12% d_2, 68% d_1, 20% d_0).

Reductive Deconjugation of Ethyl 2-Bromo-2-pentenoate with Triethyl Phosphite, Triethylamine, and Water. A solution of ethyl 2-bromo-2-pentenoate (**1b**, 0.207 g, 1.0 mmol), triethyl phosphite (0.664 g, 4.0 mmol), triethylamine (0.405 g, 4.0 mmol), and water (0.036 g, 2.0 mmol) was heated at 120 °C for 8 h in a glass sealed tube. White precipitate was formed as the reaction proceeded. The precipitate was filtered off and washed with ether (10 ml). The filtrate and ethereal solution were combined and concentrated. ^1H NMR analysis showed the formation of ethyl (*E*)-3-pentenoate (**2b**)[4] with 1,1,2,2-tetrachloroethane as an internal standard.

Synthesis of the β,γ-Unsaturated Ester 2c. *t*-Butyl 10-oxoundecanoate (5.12 g, 20.0 mmol) prepared from *t*-butyl 10-undecenoate (**5**)[3] was dropwise added to $NaBH_4$ (0.378 g, 10.0 mmol) in ethanol (60 ml) over 15 min. The mixture was stirred at room temperature for 1 h. A few drops of acetic acid were added to the resultant mixture, which was extracted with ether (3×50 ml). The aqueous solution was adjusted to pH 2 with 3 M HCl (1 M=1 mol dm^{-3}) and extracted with ether (3×10 ml). The combined ethereal solution was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue eluting with hexane–AcOEt (10 : 1 v/v) gave *t*-butyl 10-hydroxyundecanoate in 90% yield (4.64 g). R_f=0.27. IR (neat) 3420, 1734, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.18 (d, 3H, J=6.2 Hz), 1.2—1.7 (m, 14H), 1.44 (s, 9H), 2.19 (t, 2H, J=7.3 Hz), 3.7—3.9 (m, 1H); CIMS m/z 259 (M^++1); High-resolution CIMS. Found: m/z 259.229. Calcd for $C_{15}H_{31}O_3$: M, 259.230. Thus obtained hydroxy ester (2.58 g, 10.0 mmol) was treated with *t*-butyldimethylsilyl chloride (1.81 g, 12.0 mmol) and imidazole (2.45 g, 36.0 mmol) in DMF (6 ml). The mixture was stirred at room temperature for 40 h. Ether (30 ml) was added to the resultant mixture, which was washed with saturated aqueous $CuSO_4$ solution, water, saturated aqueous $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and concentrated. Flash chromatography of the residue eluting with hexane–AcOEt (10 : 1 v/v) gave *t*-butyl 10-(*t*-butyldimethylsiloxy)-undecanoate in 95% yield (3.53 g). R_f=0.67. IR (neat) 1734, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=0.03 (s, 6H), 0.91 (s, 9H), 1.10 (d, 3H, J=6.0 Hz), 1.2—1.6 (m, 14H), 1.43 (s, 9H), 2.19 (t, 2H, J=7.3 Hz), 3.6—3.8 (m, 1H). CIMS m/z 373 (M^++1). Anal. ($C_{21}H_{44}O_3Si$) C, H, N. Buthyllithium in hexane (1.6 M, 2.0 mmol) was concentrated in vacuo and ether (5 ml) was added at −78 °C. Hexamethyldisilazane (0.323 g, 2.0 mmol) was added slowly and then the mixture was warmed to 0 °C. Stirring was continued at 0 °C for 30 min. *t*-Butyl 10-(*t*-butyldimethylsiloxy)undecanoate (0.744 g, 2.0 mmol) was added dropwise over 30 min at −78 °C. The mixture was kept at −78 °C for 2 h with stirring. Trimethylsilyl chloride (0.217 g, 2.0 mmol) and triethylamine (0.020 g, 0.2 mmol) were added at a time. After stirring at the same temperature for 20 min, the reaction temperature was raised to room temperature. The mixture was kept for 2 h with stirring and concentrated in vacuo. After addition of ether (5×2 ml), the supernatant solution was collected and concentrated. To the mixture of thus obtained crude ketene silyl acetal and potassium *t*-butoxide (0.224 g, 2.0 mmol) in hexane (2 ml) and toluene (1.4 ml) was added bromoform

(0.303 g, 1.2 mmol) over 30 min at −20 °C. Stirring was continued at −20 °C for 15 min and at room temperature for 1 h. Water (10 ml) was added to the mixture, which was extracted with ether (3×20 ml). The combined ethereal solution was washed with brine, dried over $MgSO_4$, and concentrated. After recovery of *t*-butyl 10-(*t*-butyldimethylsiloxy)undecanoate by distillation, flash chromatography of the residue eluting with hexane–benzene (1 : 5 v/v) gave **1c** in 32% yield (0.300 g). R_f=0.58. IR (neat) 1728, 1628, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.04 (s, 6H), 0.88 (s, 9H), 1.11 (d, 3H, J=6.0 Hz), 1.2—1.6 (m, 12H), 1.51 (s, 9H), 2.30 (q, 2H, J=7.3 Hz), 3.7—3.9 (m, 1H), 7.16 (t, 1H, J=7.3 Hz); CIMS m/z 463 (M^++1); High-resolution CIMS. Found: m/z 463.224. Calcd for $C_{22}H_{44}O_3SiBr$: M, 463.224. The ester **1c** (23.2 mg, 0.05 mmol) was treated with diethyl phosphonate (27.6 mg, 0.2 mmol) and triethylamine (20.2 mg, 0.2 mmol) at 80 °C for 6 h. The precipitate was filtered off and washed with ether (5 ml). After concentration of the combined organic layer in vacuo, flash chromatography eluting with hexane–acetone (2 : 1 v/v) gave the ester **2c** in 68% yield (13.1 mg). R_f=0.58. IR (neat) 1738, 1150, 968 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.04 (s, 6H), 0.88 (s, 9H), 1.11 (d, 3H, J=6.0 Hz), 1.2—1.4 (m, 10H), 1.44 (s, 9H), 1.5—1.6 (m, 2H), 2.92 (d, 2H, J=5.4 Hz), 3.7—3.9 (m, 1H), 5.4—5.6 (m, 2H); ^1H NMR (benzene-d_6, 270 MHz) δ=0.13 (s, 6H), 1.05 (s, 9H), 1.16 (d, 3H, J=6.0 Hz), 1.2—1.6 (m, 10H), 1.42 (s, 9H), 1.9—2.1 (m, 2H), 2.95 (dd, 2H, J=7.0, 1.4 Hz), 3.7—3.9 (m, 1H), 5.48 (ddt, 1H, J=15.7, 7.2, 1.4 Hz), 5.70 (ddt, 1H, J=15.7, 7.0, 1.4 Hz); ^{13}C NMR (benzene-d_6, 68 MHz) δ=−4.0, −3.7, 14.7, 18.8, 24.6, 26.6, 28.7, 30.1, 30.3, 33.3, 40.1, 40.6, 69.3, 80.2, 123.6, 134.6, 171.2; CIMS m/z 385 (M^++1); High-resolution CIMS. Found: m/z 385.314. Calcd for $C_{22}H_{45}O_3Si$: M, 385.314.

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