Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4243–4247

TBSOTf-assisted three component coupling of epoxides, THF, and ylides derived from the phosphoniosilylation products of enones and α,β-unsaturated lactones

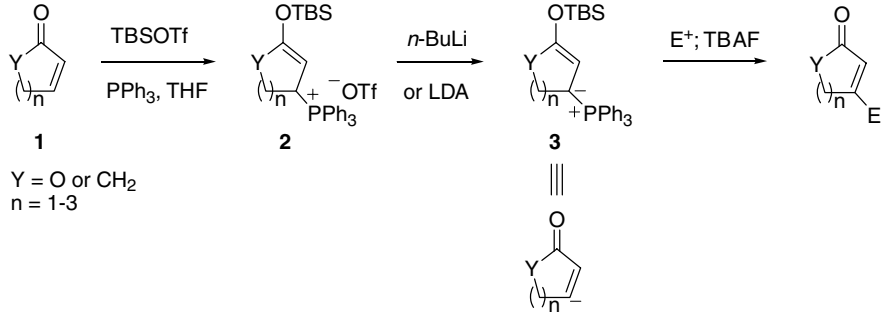
Jung Hyun Kim and Sun Ho Jung*

Department of Chemistry and Institute of Basic Science, Sungshin Women's University, Seoul 136-742, Republic of Korea

Received 14 February 2007; revised 5 April 2007; accepted 13 April 2007
Available online 19 April 2007

Abstract—Ylides **3**, derived from the phosphoniosilylation products of enones and α,β-unsaturated lactones, were reacted with epoxides **4** and TBSOTf in THF. Interestingly, the three component coupling products **5**–**8** were obtained after subsequent desilylation.

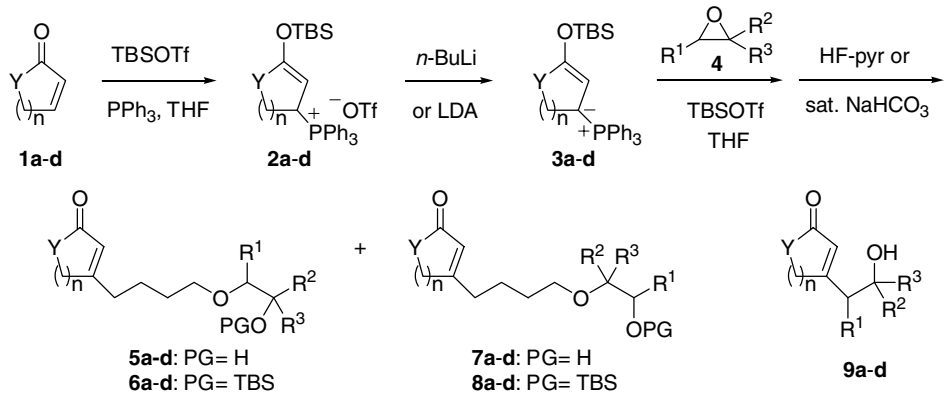
β-Functionalization of α,β-unsaturated carbonyl compounds can be effected by a variety of methods, which generally involve either the organometallic conjugate addition process[1] or the dipole reversal (at the β-position of enones) process.[2] It has been shown by Kozikowski,[3] Kim,[4] and Lee[5] that many useful functional groups can be efficiently introduced at the β-position of enones by a dipole reversal process utilizing the phosphoniosilylation reaction of enones with triphenylphosphine and *tert*-butyldimethylsilyl triflate (TBSOTf). In this process, ylides **3**, generated from phosphoniosilylation products **2** of enones by *n*-BuLi, serve as β-acylvinyl anion equivalents (Scheme 1, Y = CH_2). We have also been exploring the scope and application of this process, and recently we have demonstrated that such process can also be employed to α,β-unsaturated lactones and esters (Scheme 1, Y = O).[6] Ring-opening of epoxides, especially with carbon nucleophiles provides valuable routes to a wide variety of organic compounds.[7] However, to our best knowledge, there have been no reports on the ring-opening of epoxides with ylides derived from the phosphoniosilylation products of α,β-unsaturated carbonyl compounds. Thus, as an extension of studies on the development of new synthetic methods utilizing the phosphoniosilylation process we became interested in investigating the ring-opening reaction of epoxides with ylides **3** (Scheme 2). Herein, we wish to report very interesting and unusual results in these studies.



Scheme 1.

Keywords: Phosphoniosilylation; Epoxide opening; Three component coupling; Enones; α,β-Unsaturated lactones.
* Corresponding author. Tel./fax: +82 2 920 7192; e-mail: shjung@sungshin.ac.kr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.067



For **1-3** & **5-9**, **a**: Y = O, n = 2; **b**: Y = CH_2, n = 2; **c**: Y = CH_2, n = 1; **d**: Y = CH_2, n = 3

For **4-9**, **p**: R^1=R^2= H; R^3= CH_2Ph; **q**: R^1=R^2= H; R^3= CH_2CH_3; **r**: R^2=H, R^1= R^3= $(CH_2)_4$; **s**: R^1=R^2= H; R^3= Ph; **t**: R^1= H, R^2= R^3= CH_3

Scheme 2.

At the outset, we envisaged that it might be possible for ylides **3** to attack epoxides **4** to give alcohols **9**, considering the nature of epoxides as good electrophiles and an addition of Lewis acid would facilitate the epoxide ring-opening process. To test these notions we examined the epoxide ring-opening reaction using ylide **3a** derived from 5,6-dihydro-2*H*-pyran-2-one **1a** and (2,3-epoxypropyl)benzene **4p** as model substrates (Scheme 2). Initially this epoxide opening process was attempted in the absence of Lewis acid. When ylide **3a** was reacted with epoxide **4p** in tetrahydrofuran (THF) at −78 °C and the reaction mixture was subsequently treated with tetrabutylammonium fluoride (TBAF) in the same reaction vessel, no epoxide opening reaction was observed. Therefore, the use of Lewis acid was considered to promote the reaction. For this purpose TBSOTf was selected as the choice of Lewis acids to avoid complication of silyl group scrambling. When ylide **3a** was reacted with **4p** in the presence of TBSOTf in THF at −78 °C, and the resulting intermediate was then treated with HF–pyridine at −78 °C to rt in the same reaction vessel, an epoxide opening product was obtained in reasonable yield together with some unidentifiable products. However, spectroscopic analysis indicated that the product was not alcohol **9ap**. To our surprise, the structure of this product turned out to be **5ap**, a three

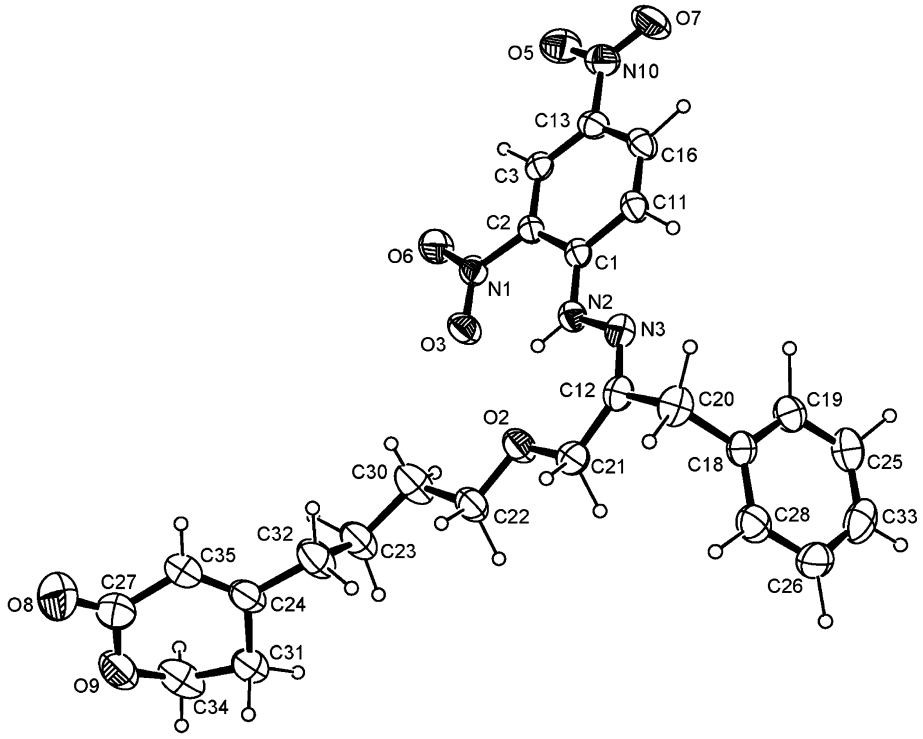
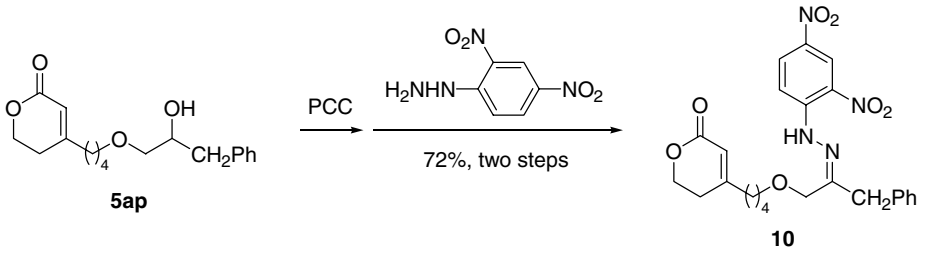


Figure 1. X-ray crystal structure of **10**.



Scheme 3.

component coupling product, which was unambiguously confirmed by X-ray crystallographic analysis of a crystalline derivative **10** (Fig. 1).[8] Compound **10** was prepared in 72% overall yield by oxidation with PCC followed by treatment with 2,4-dinitrophenylhydrazine (Scheme 3). It is believed that THF is involved in the formation of product **5ap** via its concomitant ring opening in the ring opening reaction of epoxide **4p** with ylide **3a** (vide infra). This result is related closely to the three component coupling reported by Yamamoto.[9]

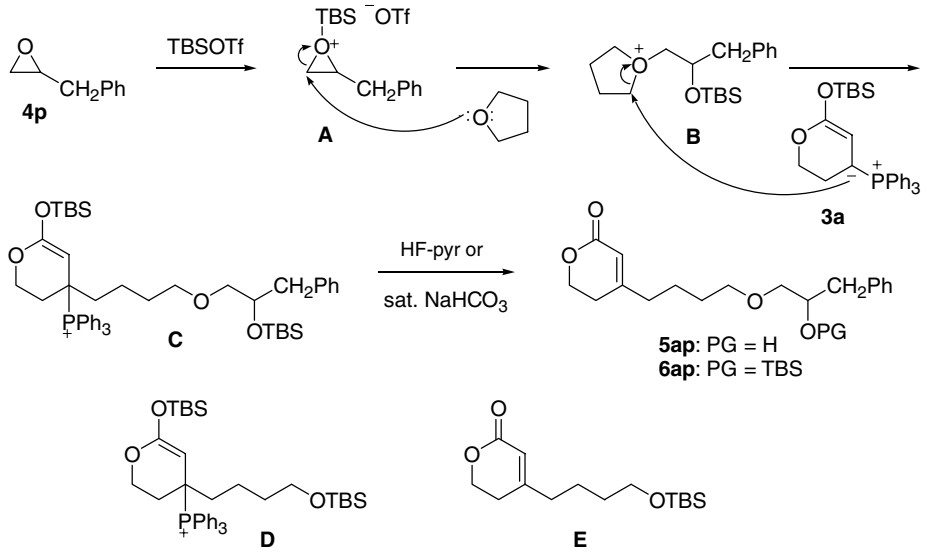
To assure that this butyloxy group incorporation is general, with a variety of α,β-unsaturated carbonyl compounds and epoxides we have examined this four-step one pot process, that is, (1) phosphoniosilylation with Ph_3P and TBSOTf, (2) ylide formation with *n*-BuLi or LDA, (3) epoxide opening reaction and (4) desilylation, varying α,β-unsaturated carbonyl compounds and epoxides (Scheme 2). We found that the reaction process is quite general as the reaction of ylide **3a** and epoxide **4p** in the presence of TBSOTf in THF resulted in butyloxy group incorporated product **5ap**. The results are shown in Table 1. It is noteworthy that the formation of products, alcohols or their TBS ethers, could be controlled by the choice of a desilylating agent. Upon treating the epoxide opening reaction mixtures with HF–pyridine at −78 °C to rt, alcohols **5a–d** or **7a–d** were obtained as products. When saturated sodium bicarbonate solution was used as a desilylating agent, products were TBS ethers **6a–d** or **8a–d**. It is also of value to mention that this butyloxy group incorporated epoxide opening process proceeds with a high regioselectivity. With epoxides **4p–r** consisting of primary and secondary carbons, regioisomers **5a–d** or **6a–d** were obtained as exclusive products (entries 1–3, 5–7, 10–12, and 15–17), while the other regioisomers **7a–d** or **8a–d** were produced selectively with epoxides such as styrene oxide **4s** and 1,2-epoxy-2-methylpropane **4t** (entries 4, 8, 9, 13, and 14). The regioselectivities observed in this process are well compared to those observed in typical Lewis acid-assisted ring opening reactions of epoxides.[10] This process works well with epoxides **4p–r** in both cyclohexenone **1b** and cyclopentenone **1c** series (entries 5–7 and 10–12), in which products were obtained in good to excellent yields (for alcohols 73–91%, for TBS ethers 60–98%). Ylide **3a** derived from lactone **1a** reacted smoothly with the same epoxides to give products in moderate to good yields (entries 1–3, for alcohols 49–61%, for TBS ethers 43–59%). With styrene oxide **4s** and 1,2-epoxy-2-methylpropane **4t** (entries 4, 8, 9, 13, and 14), the yields of products **7a–d** or **8a–d** (vide supra) were moderate (for alcohols 30–54%, for TBS ethers 24–49%). Lower yields in these cases might be in part due to a rearrangement of the epoxides to carbonyl compounds. In the case of cycloheptenone **1d** (entries 15–17), the yields of products were relatively low (for alcohols 23–51%, for TBS ethers 20–43%). When acyclic variants of α,β-unsaturated carbonyls such as 3-buten-2-one, trans-3-nonen-2-one, and methyl acrylate were tried, either no significant amounts or poor yields of products were obtained. Either lower reactivity of ylides or decomposition of epoxides and ylides might be responsible for the unsuccessful outcomes in acyclic derivatives.

Table 1. β-Butyloxy group incorporated epoxide opening of enones and α,β-unsaturated lactones in THF[11]

Entry	Starting material	Epoxide	Product[a,b]	Yield[c,d] (%)
1	**1a**	**4p**	**5ap** (**6ap**)	49 (45)
2	**1a**	**4q**	**5aq** (**6aq**)	61 (43)
3	**1a**	**4r**	**5ar** (**6ar**)	53 (59)
4	**1a**	**4s**	**7as** (**8as**)	40 (43)
5	**1b**	**4p**	**5bp** (**6bp**)	91 (98)
6	**1b**	**4q**	**5bq** (**6bq**)	81 (88)
7	**1b**	**4r**	**5br** (**6br**)	87 (65)
8	**1b**	**4s**	**7bs** (**8bs**)	54 (41)
9	**1b**	**4t**	**7bt** (**8bt**)	31 (24)
10	**1c**	**4p**	**5cp** (**6cp**)	77 (71)
11	**1c**	**4q**	**5cq** (**6cq**)	78 (83)
12	**1c**	**4r**	**5cr** (**6cr**)	73 (60)
13	**1c**	**4s**	**7cs** (**8cs**)	36 (49)
14	**1c**	**4t**	**7ct** (**8ct**)	30[e] (31)
15	**1d**	**4p**	**5dp** (**6dp**)	51 (43)
16	**1d**	**4q**	**5dq** (**6dq**)	41 (37)
17	**1d**	**4r**	**5dr** (**6dr**)	23 (20)

[a] Products when HF–pyridine was used in the desilylation step.
[b] Products in parentheses refer to products when saturated $NaHCO_3$ solution was used in the desilylation step.
[c] Overall isolated yields of alcohols.
[d] Yields in parentheses refer to overall isolated yields of TBS ethers.
[e] Tetrabutylammonium fluoride (1 M in THF) was used in the desilylation step.

Although far from being predicted, the formation of products **5** and **6** seems to be explainable by a mechanism as described by the hypothetical sequence of Scheme 4. At the beginning, the cyclic oxonium ion **A** would be generated from epoxide **4p** and TBSOTf. The nucleophilic attack of the THF oxygen to the oxonium ion **A** would form another oxonium ion **B**, which would immediately be attacked by ylide **3a**. The subse-



Scheme 4.

quent desilylation of the resulting three component coupling intermediate **C** would complete the formation of **5ap** or **6ap**. One might think of another possibility that TBSOTf-assisted ring opening of THF by ylide **3a** occur first and thus formed intermediate **D** then open the epoxide ring with the aid of TBSOTf. If the reaction proceeds along this mechanism, **D** should be formed as an intermediate. However, the formation of **D** was precluded by no detection of compound **E** or its alcohol when the reaction was interrupted and the mixture was subsequently desilylated. The same result was observed when a control experiment, that is, the reaction of ylide **3a** and TBSOTf in THF in the absence of the epoxide **4p**, was carried out. These results exclude the possibility of the latter mechanism.

In summary, ylides derived from the phosphoniosilylation products of enones and α,β-unsaturated lactones, react with THF and epoxides in the presence of TBSOTf to give three component coupling products. The results illustrate an unusual example that a reaction solvent, THF participates in the three component coupling reaction. Further research is now in progress to understand the effect of solvents and Lewis acids on this process.

Acknowledgments

This work was supported by a grant from the Sungshin Women's University in 2006. We thank Dr. Joo Hwan Cha at the Korea Institute of Science and Technology for the X-ray structure determination.

References and notes

1. (a) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley-Interscience: New York, 1980; (b) Taylor, R. J. K. *Organocopper Reagents*; Oxford University Press: Oxford, 1994.
2. (a) Taylor, R. J. K. *Synthesis* **1985**, 364; (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; (c) Hulce, M. *Org. React.* **1990**, *38*, 225; (d) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
3. (a) Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400; (b) Kozikowski, A. P.; Jung, S. H. *Tetrahedron Lett.* **1986**, *27*, 3227.
4. (a) Kim, S.; Lee, P. H. *Tetrahedron Lett.* **1988**, *29*, 5413; (b) Kim, S.; Lee, P. H.; Kim, S. S. *Bull. Korean Chem. Soc.* **1989**, *10*, 218; (c) Kim, S.; Kim, Y. G.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 2043; (d) Kim, S.; Park, J. H.; Kim, Y. G.; Lee, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1188; (e) Kim, S.; Lee, B. S.; Park, J. H. *Bull. Korean Chem. Soc.* **1993**, *14*, 654.
5. (a) Lee, P. H.; Kim, S. *Bull. Korean Chem. Soc.* **1992**, *13*, 580; (b) Lee, P. H.; Cho, M.; Han, I.-S.; Kim, S. *Tetrahedron Lett.* **1999**, *40*, 6975.
6. (a) Jung, S. H.; Kim, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 365; (b) Jung, S. H.; Kim, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1375; (c) Jung, S. H.; Kim, J. H.; Kim, H. J. *Bull. Korean Chem. Soc.* **2004**, *25*, 136; (d) Kim, J. H.; Jung, S. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1729.
7. For reviews, see: (a) Klunder, J. M.; Posner, G. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 223–226; (b) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 262–266; (c) Garrat, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 277–280; (d) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437; (e) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149; (f) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp 1309–1326.
8. Crystallographic data for **10**, as a CIF file, have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 635861. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge

CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

9. For an example of participation of THF in the three component coupling, see: Saito, S.; Yamazaki, S.; Shiozawa, M.; Yamamoto, H. *Synlett* **1999**, 581.
10. For an analysis of the regioselectivity of epoxide ring opening in terms of hard-soft acid-base (HSAB) theory, see: (a) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1980**, *58*, 302; For a good review on the selectivity in reactions of epoxide, see: (b) Kirk, D. N. *Chem. Ind.* **1973**, 109; For recent examples of the regioselectivity of epoxide opening, see: (c) Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2007**, *63*, 469; and Helliwell, M.; Thomas, E. J.; Vickers, C. *ARKIVOC* **2007**, 209.
11. The following experimental procedure is illustrative (Table 1, entry 6): To a solution of triphenylphosphine (302 mg, 1.14 mmol) in tetrahydrofuran (3.0 mL) was added TBSOTf (262 μL, 1.14 mmol) and 2-cyclohexen-1-one (100 μL, 1.04 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was cooled to −78 °C and *n*-butyllithium (933 μL of 1.34 M solution in hexanes, 1.25 mmol) was added dropwise to give a dark brown-colored solution. After the mixture being stirred for 1 h, 1,2-epoxybutane (179 μL, 2.08 mmol) and TBSOTf (478 μL, 2.08 mmol) was added quickly. The reaction mixture was stirred for 1 h and HF–pyridine (92.4 μL, 3.50 mmol) was added. After being warmed to room temperature, the reaction mixture was stirred for 1 h. The usual extractive work-up and flash column chromatography (hexane:EtOAc = 1:2–1:3) gave 3-[4-(2-hydroxybutoxy)-butyl]-cyclohex-2-enone **5bq** (204 mg, 81%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91 (s, 1H), 3.79–3.67 (m, 1H), 3.58–3.43 (m, 3H), 3.28 (dd, $J = 8.3$, 9.3 Hz, 1H), 2.42–2.31 (m, 4H), 2.28 (br, 2H), 2.07–1.98 (m, 2H), 1.62 (br, 4H), 1.57–1.43 (m, 2H), 0.99 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.3, 166.5, 126.0, 75.1, 71.9, 71.1, 38.0, 37.6, 29.9, 29.5, 26.4, 23.8, 22.9, 10.2. IR (neat) 3446, 3026, 2932, 2871, 1656, 1619, 1456, 1427, 1374, 1350, 1321, 1256, 1195, 1113, 967, 885 cm^{-1}. MS (*m*/*z*, relative intensity) 240 (M^+, 0.4), 222 (0.4), 151 (15), 123 (100), 109 (12), 73 (5.0). Similarly, except for the use of satd $NaHCO_3$ in place of HF–pyridine in the desilylation step, 3-{4-[2-(*tert*-butyldimethylsilanyloxy)-butoxy]-butyl}-cyclohex-2-enone **6bq** was obtained (323 mg, 88%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.90 (s, 1H), 3.73–3.60 (m, 1H), 3.45 (br, 2H), 3.33 (dd, $J = 2.7$, 5.6 Hz, 2H), 2.42–2.31 (m, 4H), 2.28 (br, 2H), 2.01 (t, $J = 6.4$ Hz, 2H), 1.60 (br, 4H), 1.61–1.38 (m, 2H), 0.95 (t, $J = 6.8$ Hz, 3H), 0.91 (s, 9H), 0.081 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.2, 166.6, 126.0, 75.5, 72.9, 71.1, 38.1, 37.6, 29.9, 29.6, 27.7, 26.3, 26.1, 23.9, 23.0, 10.1, −4.14, −4.47. IR (neat) 2956, 2928, 2854, 1680, 1656, 1623, 1460, 1378, 1252, 1113, 832, 775 cm^{-1}. MS (*m*/*z*, relative intensity) 354 (M^+, 0.2), 297 (100), 187 (2.3), 151 (76), 123 (14), 115 (38), 109 (15).