Tin-Free, Radical-Mediated γ-Alkylations of α,β-Unsaturated Esters via O-*tert*-Alkyl Dienol Ethers

Jin Young Lee, Sunggak Kim*

Center for Molecular Design & Synthesis and Department of Chemistry, School of Molecular Science (BK-21), Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea
Fax +82(42)8698370; E-mail: skim@kaist.ac.kr

Received 19 September 2007

Abstract: Tin-free, radical-mediated γ-alkylation of α,β-unsaturated esters is accomplished by radical addition and β-fragmentation of O-*tert*-alkyl dienol ethers and subsequent iodine atom transfer process.

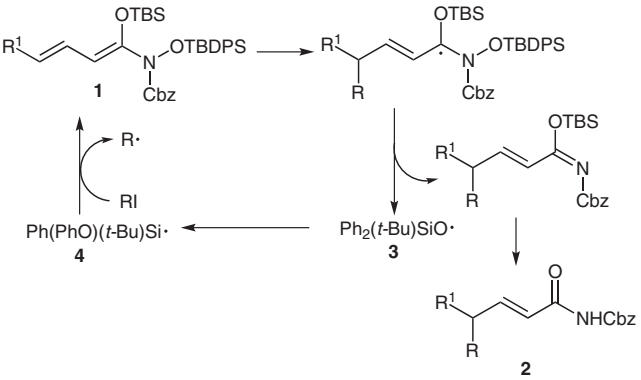
Key words: alkylation, carboxylic ester, fragmentation, radicals, tin-free

Reaction of an enolate anion of an α,β-unsaturated carbonyl compound with an alkylating agent generally affords an α-alkylation product as a major product.[1] Thus, the γ-alkylation of α,β-unsaturated carbonyl compounds has been a very challenging problem in synthetic organic chemistry. Several methods to effect the γ-alkylation of α,β-unsaturated carbonyl compounds have been developed over the years and include the use of γ-arylsulfonyl group as a regiospecific control group,[2] copper dienolates,[3] and zinc bromide catalyzed alkylation of O-silylated dienolates.[4,5] However, those methods have limitations, depending critically on the nature of alkylation agents and dienolates.

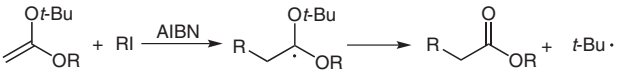
Previously, we reported a radical-mediated γ-functionalization approach based on the addition of an alkyl radical to diene ketene O,N-acetal **1** followed by the cleavage of N–O bond to afford γ-alkylated carboxylic imide **2** after aqueous workup (Scheme 1).[6,7] In this approach, the radical rearrangement of silyloxy radical **3** into silyl radical **4** was utilized to achieve tin-free conditions.[8,9]

During our studies on the radical alkylation using ketene enol ethers, Roberts reported a similar approach involving radical addition–fragmentation approach using O-*tert*-alkyl enol ethers as shown in Scheme 2.[10] In our continued effort to develop a tin-free approach to achieve γ-alkylation of α,β-unsaturated carboxylic esters, we have studied the radical reaction of silyl dienol ethers **5** derived from α,β-unsaturated esters.

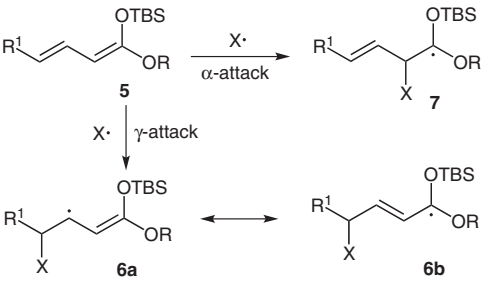
Our approach is based on three factors. First, our idea to accomplish the γ-alkylation relies on the stability of radical intermediates derived from α- and γ-attack of the alkyl radical onto silyl dienol ether **5**. It is evident that intermediate **6** should be more stable than intermediate **7** due to the allylic nature of **6** (Scheme 3). Second, one of the key



Scheme 1 Radical-mediated γ-functionalization of α,β-unsaturated carboxylic amides



Scheme 2 Radical addition–fragmentation of O-*tert*-alkyl enol ethers

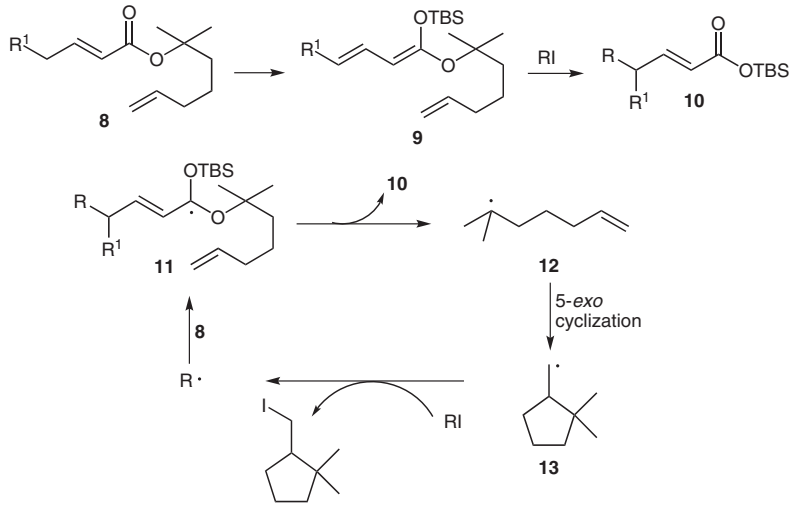


Scheme 3 Radical approach to the γ-alkylation of α,β-unsaturated carboxylic ester.

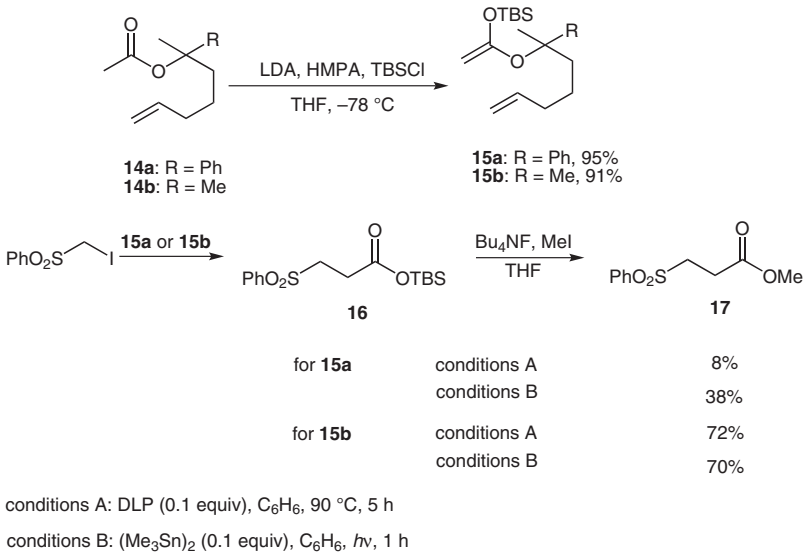
features in this approach is a facile β-fragmentation of intermediate **11** to yield alkylation product **10** along with liberation of *tert*-alkyl radical **12**. Finally, to achieve the tin-free conditions, Curran's iodine-atom-transfer process was employed.[11] A noteworthy feature in this approach is to generate reactive primary alkyl radical **13** by a radical cyclization of *tert*-alkyl radical **12** for an efficient iodine-atom transfer (Scheme 4).

In order to test our rationale, we initially prepared **15a** from **14a** to facilitate the β-fragmentation process by generation of a very stable *tert*-benzylic radical. Radical reaction of **15a** with iodomethyl phenyl sulfone in refluxing

SYNLETT 2008, No. 1, pp 0049–0054
Advanced online publication: 03.12.2007
DOI: 10.1055/s-2007-992385; Art ID: U08507ST



Scheme 4 Radical approach for the γ-alkylation of **8** via **9**



Scheme 5 Radical alkylation of ketene enol ether **15**. Conditions A: DLP (0.1 equiv), C_6H_6, 90 °C, 5 h. Conditions B: $(Me_3Sn)_2$ (0.1 equiv), C_6H_6, *h*ν, 1 h.

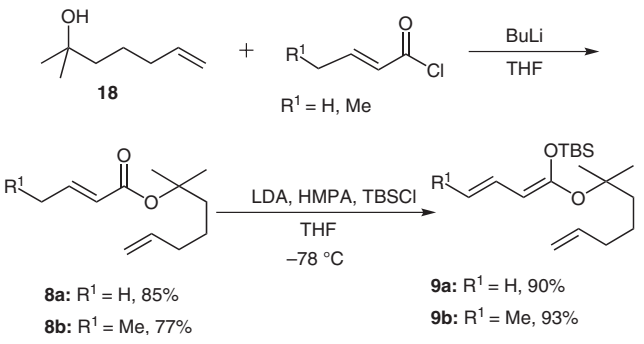
benzene using lauroyl peroxide (DLP) for five hours afforded the desired product in a very low yield (8%).

The yield was improved to some extent by performing the reaction in benzene using a catalytic amount of hexamethylditin (0.1 equiv) under irradiation (300 nm) for one hour. It appeared that the low yield resulted from instability of **15a** under thermally and photochemically initiated conditions. To increase the stability of ketene enol ether **15**, we introduced a methyl group instead of the phenyl group in **15a**. When the reaction was repeated with **15b** under the similar conditions, **17** was isolated in 72% and 70% yield, respectively (Scheme 5). Due to instability of TBS esters **16** on silica gel, **16** was converted into the corresponding methyl ester by treatment of **16** with tetrabutylammonium fluoride and methyl iodide in THF at room temperature for two hours.[12]

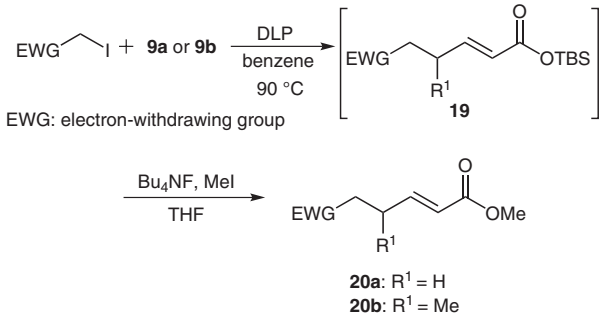
The silyl dienol ethers **9a** and **9b** were prepared by a two-step sequence. Treatment of *tert*-alcohol **18** with butyllithium followed by the addition of crotonyl chloride and 2-pentenoyl chloride afforded the corresponding esters **8a** and **8b** in 85% and 77% yield, respectively. When ester **8a** was treated with LDA in the presence of *tert*-butyldimethylsilyl chloride (TBSCl) in THF containing a small amount of HMPA, silyl dienol ether **9a** was prepared in 90% yield.

Compound **9a** was thermally stable but was decomposed to some extent during a column-chromatographic separation on silica gel. Thus, remaining reactions were carried out with the crude products without isolation of **9** (Scheme 6).

When a benzene solution of **9a** (1.5 equiv), iodomethyl phenyl sulfone (1.0 equiv), DLP initiator (0.1 equiv) was refluxed at 90 °C for five hours, **20a** was isolated in 89% yield via **19** (Scheme 7).[13] To determine the efficiency and scope of the present method, we performed additional experiments with several different alkyl iodides and bro-



Scheme 6 Preparation of silyl dienol ethers



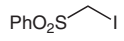
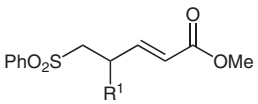
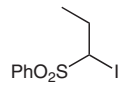
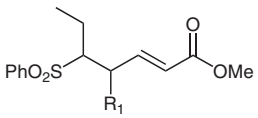
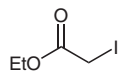
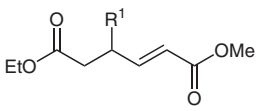
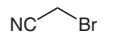
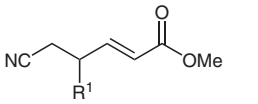
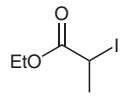
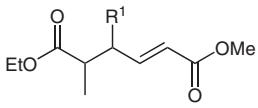
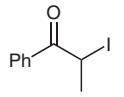
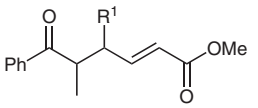
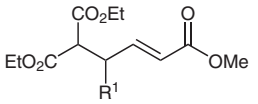
Scheme 7 Tin-free radical γ-alkylations

mides using **9a** and **9b**. As shown in Table 1, several activated alkyl iodides and bromides bearing α-electron-withdrawing substituents worked well, yielding the γ-alkylation products exclusively. It is also noteworthy that methyl-substituted dienol ether **9b** worked well without affecting the chemical yields significantly. Of synthetic importance is the exclusive formation of γ-alkylation products under tin-free radical conditions and there was no indication of the formation of α-alkylation products.

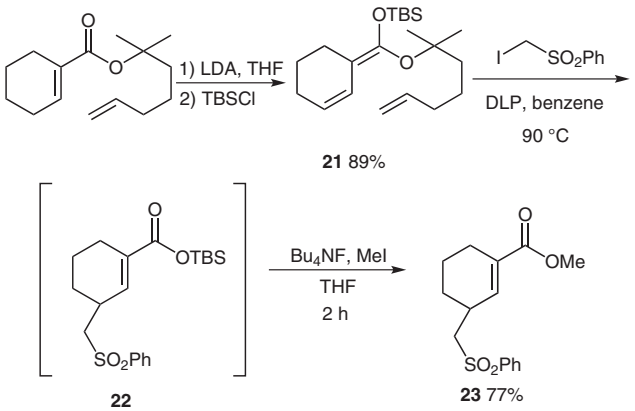
However, this method proved to be limited with respect to nucleophilic alkyl radicals. Irradiation (300 nm) of a benzene solution of **9a** with an equimolar amount of 1-iodoadamantane and DLP gave the starting iodide (95%). To further study the γ-radical alkylation, we prepared a cyclic silyl dienol ether **21**. When the ester was treated with LDA in the presence of TBSCl in THF containing a small amount of HMPA, **21** was obtained in 89% yield. When the radical reaction was carried out with **21** and iodomethyl phenyl sulfone in the presence of DLP initiator in benzene at 90 °C for five hours, the desired γ-alkylated product **23** was isolated in 77% yield (Scheme 8).

A sequential radical reaction involving the radical γ-alkylation and cyclization sequence was examined (Scheme 9). Treatment of **24** with **21** (1.5 equiv), DLP (0.1 equiv) in benzene at 90 °C for five hours afforded **25**. Treatment of **25** with benzenethiol and V-40 [1,1′-azobis(cyclohexanecarbonitrile)] initiator followed by addition of tetrabutylammonium fluoride and methyl iodide afforded **26** in 66% yield along with **27** (12%). Further treatment of **26** with MCPBA and subsequent elimination

Table 1 Tin-Free Radical γ-Alkylation[a]

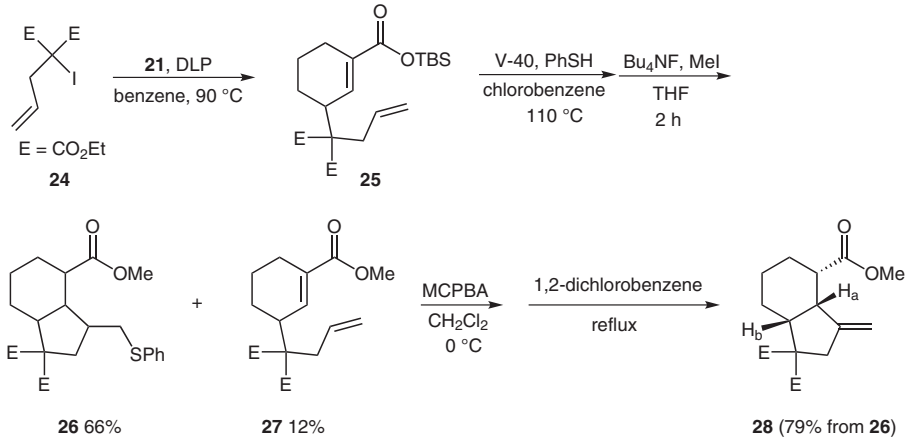
Entry	Substrate	Product	Yield (%)[b]	
			20a	**20b**
1			89	75
2			88	76[c]
3			84	82
4			89	77
5			82	73[d]
6			74	75[e]
7			73	71

[a] The reaction was carried out with lauroyl peroxide initiator in benzene at 90 °C for 5 h.
[b] Yield of isolated products.
[c] Ratio *syn*/*anti* = 1:1.7.
[d] Ratio *syn*/*anti* = 1:1.
[e] Ratio *syn*/*anti* = 1:1.7.



Scheme 8 Radical γ-alkylation of cyclic diene enol ether **21**

provided **28** in 79% yield (Scheme 9). From the ^1H–^1H COSY NMR spectrum and the decoupling technique, an NOE experiment of **28** showed 6.56% NOE between H_a (δ = 3.36 ppm) and H_b (δ = 2.65–2.73 ppm), indicative of a *cis*-fused bicyclic product.



Scheme 9 Radical cyclization via γ-alkylation

In conclusion, we have developed the radical-mediated γ-alkylation of α,β-unsaturated carboxylic esters via O-*tert*-alkyl dienol ethers under tin-free conditions, which appears to be a synthetically useful process.

Acknowledgment

We are grateful to the Center for Molecular Design & Synthesis, KEPCO, and BK21 for financial support.

References and Notes

(1) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, **1996**. (b) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *26*, 2433.

(2) (a) Lansbury, P. T.; Erwin, R. W. *Tetrahedron Lett.* **1978**, *19*, 2675. (b) Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602. (c) Lansbury, P. T.; Bebernitz, G. E.; Maynard, S. C.; Spagnuolo, C. J. *Tetrahedron Lett.* **1985**, *26*, 169. (d) Lansbury, P. T.; Spagnuolo, C. J.; Grimm, E. L. *Tetrahedron Lett.* **1986**, *27*, 2725.

(3) (a) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1974**, *96*, 5662. (b) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925. (c) Pitzele, B. S.; Baran, J. S.; Steinman, D. H. *Tetrahedron* **1976**, *32*, 1347. (d) Savu, P. M.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239.

(4) (a) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *20*, 3209. (b) Fleming, I.; Lee, T. V. *Tetrahedron Lett.* **1981**, *22*, 705.

(5) For other approaches, see: (a) Bryson, T. A.; Gammill, R. B. *Tetrahedron Lett.* **1974**, *15*, 3963. (b) Pitzele, B. S.; Baran, J. S. D.; Steinman, H. *Tetrahedron* **1976**, *32*, 1347. (c) Wenkert, E.; Goodwin, T. E.; Ranu, B. C. *J. Org. Chem.* **1977**, *42*, 2137. (d) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029. (e) Paquette, L. A.; Kinney, W. A. *Tetrahedron Lett.* **1982**, *23*, 131.

(6) (a) Kim, S.; Lim, C. J.; Song, C.; Chung, W.-j. *J. Am. Chem. Soc.* **2002**, *124*, 14306. (b) Kim, S.; Lim, C. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 5378.

(7) For other radical-mediated alkylations, see: (a) Watanabe, Y.; Yoneda, T.; Ueno, Y.; Toru, T. *Tetrahedron Lett.* **1990**, *31*, 6669. (b) Renaud, P.; Vionnet, J.-P.; Vogel, P. *Tetrahedron Lett.* **1991**, *32*, 3491. (c) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591. (d) Roepel, M. G. *Tetrahedron Lett.* **2002**, *43*, 1973. (e) Cai, Y.; Roberts, B. P. *Tetrahedron Lett.* **2003**, *44*, 4645.

(8) (a) Dannley, R. L.; Jalics, G. *J. Org. Chem.* **1965**, *30*, 3848. (b) Shubber, A. K.; Dannley, R. L. *J. Org. Chem.* **1971**, *36*, 3784.

(9) For tin-free radical reactions, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072; and references therein. (b) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 2524. (c) Kim, S.; Lim, C. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3265. (d) Kim, S.; Lim, C. J. *Bull. Korean Chem. Soc.* **2003**, *20*, 1219.

(10) Cai, Y.; Roberts, B. P.; Tocher, D. A.; Barnett, S. A. *Org. Biomol. Chem.* **2004**, *2*, 2517.

(11) (a) Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *47*, 6171. (b) Curran, D. P.; Kim, D.; Ziegler, C. *Tetrahedron* **1991**, *47*, 6189. (c) Curran, D. P.; Thoma, G. *J. Am. Chem. Soc.* **1992**, *114*, 4436. (d) Curran, D. P.; Thoma, G. *Tetrahedron Lett.* **1991**, *32*, 6307.

(12) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

(13) **Typical Experimental Procedure**
A benzene solution (1 mL, 0.2 M in iodide) of iodomethyl phenyl sulfone (56 mg, 0.2 mmol), O-*tert*-alkyl dienol ether (**9a**, 93 mg, 0.3 mmol), and DLP (8 mg, 0.02 mmol) was degassed with nitrogen for 10 min and then the solution was stirred at 90 °C under nitrogen for 5 h. The solvent was evaporated under reduced pressure and the residue was diluted with THF (1 mL). Then, TBAF (240 μL, 0.24 mmol) and MeI (50 μL, 0.8 mmol) were added successively. The reaction mixture was allowed to stir at r.t. for 2 h. The reaction mixture was diluted with Et_2O, quenched with aq NH_4Cl and washed with H_2O and brine. The organic layer was dried over anhyd $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc–*n*-hexane (1:10) as eluant to give 5-benzenesulfonylpent-2-enoic acid methyl ester (**20a**, 45 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57–2.63 (m, 2 H), 3.16–3.20 (m, 2 H), 3.67 (s, 3 H), 5.79 (dt, *J* = 15.6, 1.3 Hz, 1 H), 6.78 (dt, *J* = 15.6, 6.8 Hz, 1 H), 7.53–7.57 (m, 2 H), 7.62–7.66 (m, 1 H), 7.86–7.89 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 51.5, 54.2, 123.1, 128.0 (C2), 129.4 (C2), 133.9, 138.6, 143.3, 166.0. IR (KBr): 1728, 1659, 1447, 1323, 1204, 766, 748 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{14}O_4S$ [M$^+$]: 254.0613; found: 254.0613.
Compound **20a** (entry 2): MW ($C_{14}H_{18}O_4S$): 282.35. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.5 Hz, 3 H), 1.60–

1.66 (m, 1 H), 1.84–1.87 (m, 1 H), 2.48–2.52 (m, 1 H), 2.68–2.72 (m, 1 H), 2.97–3.00 (m, 1 H), 3.67 (s, 3 H), 5.80 (dt, *J* = 15.6, 1.3 Hz, 1 H), 6.78 (dt, *J* = 15.6, 7.37 Hz, 1 H), 7.51–7.55 (m, 2 H), 7.60–7.64 (m, 1 H), 7.83–7.85 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 20.7, 30.0, 51.5, 64.6, 123.8, 128.7 (C2), 129.2 (C2), 133.8, 137.6, 143.4, 166.0. IR (KBr): 1729, 1658, 1447, 1320, 1214, 731, 691 cm^{-1}. HRMS: *m/z* calcd for $C_{14}H_{18}O_4S$ [M$^+$]: 282.0926; found: 282.0929.

Compound **20a** (entry 3): MW ($C_{10}H_{16}O_4$): 186.21. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3 H), 2.39–2.43 (m, 2 H), 2.46–2.51 (m, 2 H), 3.67 (s, 3 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 5.82 (dt, *J* = 15.7, 1.5 Hz, 1 H), 6.91 (dt, *J* = 15.7, 6.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 27.2, 32.4, 51.4, 60.5, 121.7, 146.9, 166.7, 172.1. IR (KBr): 1742, 1720, 1659, 1436, 1179, 1039, 859 cm^{-1}. HRMS: *m/z* calcd for $C_9H_{14}O_4$ [M$^+$]: 186.0892; found: 186.0893.

Compound **20a** (entry 4): MW ($C_7H_9NO_2$): 139.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47–2.55 (m, 4 H), 3.72 (s, 3 H), 5.93 (dt, *J* = 15.7, 1.54 Hz, 1 H), 6.89 (dt, *J* = 15.7, 6.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 27.7, 51.6, 118.2, 123.6, 143.3, 166.1. IR (KBr): 1730, 1663, 1437, 1275, 1213, 1162, 766, 748 cm^{-1}. HRMS: *m/z* calcd for $C_7H_9NO_2$ [M$^+$]: 139.0633; found: 139.0642.

Compound **20a** (entry 5): MW ($C_{10}H_{16}O_4$: 200.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 14.3 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 2.25–2.30 (m, 1 H), 2.50–2.57 (m, 2 H), 3.68 (s, 3 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 5.82 (dt, *J* = 15.6, 1.1 Hz, 1 H), 6.84 (dt, *J* = 15.6, 6.9 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 25.5, 35.8, 38.4, 51.4, 60.4, 122.8, 145.8, 166.6, 175.2. IR (KBr): 1740, 1720, 1659, 1436, 1275, 1196, 1180 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_{16}O_4$ [M$^+$]: 200.1049; found: 200.1041.

Compound **20a** (entry 6): MW ($C_{14}H_{16}O_3$): 232.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 7.0 Hz, 3 H), 2.30–2.36 (m, 1 H), 2.66–2.72 (m, 1 H), 3.54–3.59 (m, 1 H), 3.67 (s, 3 H), 5.84 (dt, *J* = 15.6, 1.5 Hz, 1 H), 6.91 (dt, *J* = 15.6, 6.9 Hz, 1 H), 7.43–7.46 (m, 2 H), 7.52–7.54 (m, 1 H), 7.90–7.92 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 35.4, 39.8, 51.4, 122.8 (C2), 128.7 (C2), 133.1, 135.8, 146.3, 166.6, 202.4. IR (KBr): 1733, 1712, 1688, 1449, 1434, 971, 705 cm^{-1}. HRMS: *m/z* calcd for $C_{14}H_{16}O_3$ [M$^+$]: 232.1099; found: 232.1086.

Compound **20a** (entry 7): MW ($C_{12}H_{18}O_6$): 258.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 6 H), 2.73–2.77 (m, 2 H), 3.44 (t, *J* = 7.44 Hz, 1 H), 3.68 (s, 3 H), 4.18 (q, *J* = 7.1 Hz, 4 H), 5.87 (dt, *J* = 15.6, 1.5 Hz, 1 H), 6.86 (dt, *J* = 15.6, 7.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (C2), 31.0, 50.6, 51.5, 61.7 (C2), 123.8, 144.0, 166.3, 168.2 (C2). IR (KBr): 1755, 1720, 1661, 1436, 1151, 1036, 774 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{18}O_6$ [M$^+$]: 258.1103; found: 258.1128.

Compound **20b** (entry 1): MW ($C_{13}H_{16}O_4S$): 268.32. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 8.9 Hz, 3 H), 2.90–2.96 (m, 1 H), 3.06 (dd, *J* = 14.1, 6.3 Hz, 1 H), 3.17 (dd, *J* = 14.1, 6.6 Hz, 1 H), 3.65 (s, 3 H), 5.72 (dd, *J* = 15.6, 1.0 Hz, 1 H), 6.71 (dd, *J* = 15.6, 7.6 Hz, 1 H), 7.50–7.55 (m, 2 H), 7.59–7.63 (m, 1 H), 7.84–7.90 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 31.6, 51.5, 60.9, 120.9, 127.8 (C2), 129.2 (C2), 133.7, 139.4, 149.5, 166.3. IR (KBr): 1721, 1659, 1447, 1305, 1209, 766, 747 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{16}O_4S$ [M$^+$]: 268.0769; found: 2268.0751.

Compound **20b** (entry 2): MW ($C_{15}H_{20}O_4S$): 296.38. Ratio *syn*/*anti* = 1.67:1 (from ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ(*anti*) = 0.90 (t, *J* = 7.5 Hz, 3 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.67–1.70 (m, 1 H), 1.84–1.88 (m, 1 H), 2.88–2.91 (m, 1 H), 3.05–3.12 (m, 1 H), 3.69 (s, 3 H), 5.77 (dd, *J* = 15.7, 1.4 Hz, 1 H), 6.99 (dd, *J* = 15.7, 7.0 Hz, 1 H), 7.51–7.55 (m, 2 H), 7.60–7.63 (m, 1 H), 7.84–7.87 (m, 2 H); δ(*syn*) = 0.85 (t, *J* = 7.5 Hz, 3 H), 1.21 (d, *J* = 7.0 Hz, 3 H), 1.67–1.70 (m, 1 H), 1.84–1.88 (m, 1 H), 2.95–2.99 (m, 1 H), 3.05–3.12 (m, 1 H), 3.68 (s, 3 H), 5.76 (dd, *J* = 15.7, 1.7 Hz, 1 H), 6.83 (dd, *J* = 15.7, 6.3 Hz, 1 H), 7.51–7.55 (m, 2 H), 7.60–7.63 (m, 1 H), 7.84–7.87 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 13.0, 13.1, 13.4, 17.8, 18.9, 34.5, 34.8, 51.5, 51.6, 69.1, 70.5, 121.1, 121.9, 128.4 (C2), 128.6 (C2), 129.2 (C2), 129.3 (C2), 133.6, 133.7, 138.7, 138.9, 148.3, 150.5, 166.4, 166.5. IR (KBr): 1727, 1656, 1447, 1303, 1197, 765, 728 cm^{-1}. HRMS: *m/z* calcd for $C_{15}H_{20}O_4S$ [M$^+$]: 296.1082; found: 296.1089.

Compound **20b** (entry 3): MW ($C_{10}H_{16}O_4$): 200.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.7 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 2.27 (dd, *J* = 15.3 Hz, 7.2 Hz, 1 H), 2.36 (dd, *J* = 15.3, 7.1 Hz, 1 H), 2.77–2.84 (m, 1 H), 3.67 (s, 3 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 5.79 (dd, *J* = 15.7, 1.2 Hz, 1 H), 6.86 (dd, *J* = 15.7, 7.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 18.9, 32.9, 40.3, 51.4, 60.4, 119.8, 152.0, 166.9, 171.5. IR (KBr): 1738, 1722, 1658, 1276, 1177, 765, 748 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_{16}O_4$ [M$^+$]: 200.1049; found: 200.1048.

Compound **20b** (entry 4): MW ($C_8H_{11}NO_2$): 153.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.8 Hz, 3 H), 2.35–2.46 (m, 2 H), 2.68–2.75 (m, 1 H), 3.70 (s, 3 H), 5.87 (dd, *J* = 15.7, 1.2 Hz, 1 H), 6.82 (dd, *J* = 15.7, 7.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 23.6, 33.1, 51.6, 117.5, 121.6, 148.7, 166.3. IR (KBr): 1728, 1659, 1436, 1277, 1197, 765, 749 cm^{-1}. HRMS: *m/z* calcd for $C_8H_{11}NO_2$ [M$^+$]: 153.0790; found: 153.0781.

Compound **20b** (entry 5): MW ($C_{11}H_{18}O_4$): 214.25. Ratio *syn*/*anti* = 1:1 (from ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ(*syn*) = 1.02 (d, *J* = 3.4 Hz, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 2.31–2.38 (m, 1 H), 2.55–2.65 (m, 1 H), 3.68 (s, 3 H), 4.06–4.14 (m, 2 H), 5.78 (dd, *J* = 15.7, 11.7 Hz, 1 H), 6.87 (dd, *J* = 15.7, 7.7 Hz, 1 H); δ(*anti*) = 1.03 (d, *J* = 3.2 Hz, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 2.41–2.48 (m, 1 H), 2.55–2.65 (m, 1 H), 3.69 (s, 3 H), 4.06–4.14 (m, 2 H), 5.79 (dd, *J* = 15.6, 10.8 Hz, 1 H), 6.77 (dd, *J* = 15.6, 8.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 14.1, 14.2, 14.8, 15.5, 17.6, 38.9, 39.5, 43.9, 44.5, 51.4, 51.5, 60.3, 60.4, 120.6, 121.3, 150.9, 151.4, 166.8, 166.9, 174.8, 175.0. IR (KBr): 1735, 1723, 1658, 1435, 1277, 1243, 765, 748 cm^{-1}. HRMS: *m/z* calcd for $C_{11}H_{18}O_4$ [M$^+$]: 214.1205; found: 214.1203.

Compound **20b** (entry 6): MW ($C_{15}H_{18}O_3$): 246.30. Ratio *syn*/*anti* = 1.67:1 (from ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ(*anti*) = 1.03 (d, *J* = 6.8 Hz, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 2.76–2.84 (m, 1 H), 3.47–3.54 (m, 1 H), 3.66 (s, 3 H), 5.77–5.85 (m, 1 H), 6.94 (dd, *J* = 15.7, 7.4 Hz, 1 H), 7.42–7.47 (m, 2 H), 7.51–7.55 (m, 1 H), 7.87–7.93 (m, 2 H); δ(*syn*) = 1.02 (d, *J* = 6.6 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 2.76–2.84 (m, 1 H), 3.38–3.41 (m, 1 H), 5.77–5.85 (m, 1 H), 6.87 (dd, *J* = 15.6, 8.9 Hz, 1 H), 7.42–7.47 (m, 2 H), 7.51–7.55 (m, 1 H), 7.87–7.93 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 14.9, 16.0, 18.4, 38.2, 39.4, 44.6, 45.2, 51.4, 51.5, 120.5 (C2), 121.3, 128.1 (C2), 128.7 (C2), 133.0, 133.1, 136.4, 136.8, 151.3, 151.9 (C2), 166.8, 166.9, 202.6, 203.2. IR (KBr): 1722, 1681, 1655, 1449, 1277, 765, 748 cm^{-1}. HRMS: *m/z* calcd for $C_{15}H_{18}O_3$ [M$^+$]: 246.1256; found: 246.1255.

Compound **20b** (entry 7): MW ($C_{13}H_{20}O_6$): 272.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 3.04–3.10 (m, 1 H), 3.30 (d, *J* = 8.5 Hz, 1 H), 3.68 (s, 3 H), 4.13 (t, *J* = 7.1 Hz, 2 H), 4.17 (t, *J* = 7.1 Hz, 2 H), 5.83 (dd, *J* = 15.6, 0.7 Hz,

1 H), 6.87 (dd, *J* = 15.6, 8.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0, 17.3, 36.2, 51.4, 56.7, 61.4, 61.5, 121.4, 149.3, 166.6, 167.6, 167.7. IR (KBr): 1756, 1722, 1658, 1436, 1300, 1278, 1234, 988 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{20}O_6$ [M$^+$]: 272.1260; found: 272.1271.

Compound **23**: MW ($C_{15}H_{18}O_4S$): 294.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.44 (m, 1 H), 1.50–1.56 (m, 1 H), 1.68–1.74 (m, 1 H), 1.87–1.93 (m, 1 H), 2.10–2.17 (m, 1 H), 2.21–2.27 (m, 1 H), 2.85–2.89 (m, 1 H), 3.04 (dd, *J* = 14.1, 6.9 Hz, 1 H), 3.13 (dd, *J* = 14.1, 6.1 Hz, 1 H), 3.66 (s, 3 H), 6.74–6.75 (m, 1 H), 7.52–7.56 (m, 2 H), 7.60–7.64 (m, 1 H), 7.88–7.90 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 23.8, 27.8, 31.1, 51.6, 60.4, 127.8, 129.3, 132.1, 133.7, 139.0, 139.7, 167.3. IR (KBr): 1715, 1447, 1276, 1255, 1151, 1086, 719 cm^{-1}. HRMS: *m/z* calcd for $C_{15}H_{18}O_4S$ [M$^+$]: 294.0926; found: 294.0936.

Compound **28**: MW ($C_{18}H_{26}O_6$): 338.39. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.95 (m, 1 H), 1.17–1.25 (m, 8 H), 1.49–1.59 (m, 1 H), 1.74–1.80 (m, 2 H), 2.62–2.73 (m, 2 H), 2.79–2.84 (m, 1 H), 3.28–3.36 (m, 2 H), 3.65 (s, 3 H), 4.07–4.22 (m, 4 H), 4.55–4.57 (m, 1 H), 4.90–4.91 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0, 21.5, 23.2, 24.6, 37.8, 41.9, 44.4, 45.4, 51.5, 60.9, 61.4, 61.5, 107.4, 145.4, 169.5, 171.7, 174.9. IR (KBr): 1731, 1446, 1268, 1254, 1224, 1058, 1038, 1015 cm^{-1}. HRMS: *m/z* calcd for $C_{18}H_{26}O_6$ [M$^+$]: 338.1729; found: 338.1750.