Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 7401–7405
Tetrahedron Letters

Construction of the bicyclo[3.3.1]nonenone core by successive Michael reactions of 2-cyclohexenone derivatives

Ryukichi Takagi,* Takashi Nerio, Yukiko Miwa, Shuji Matsumura and Katsuo Ohkata*

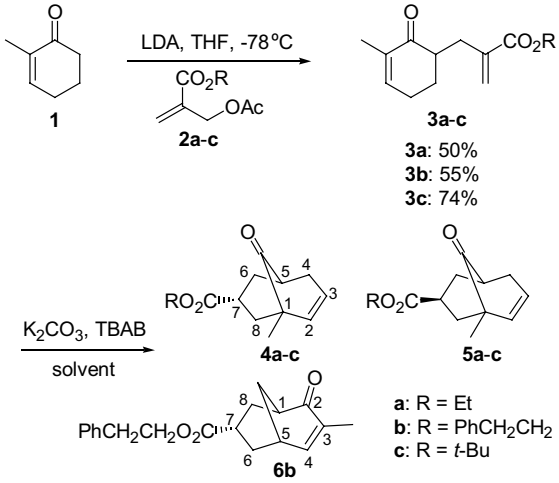
Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan

Received 28 July 2004; revised 6 August 2004; accepted 13 August 2004

Abstract—Construction of the bicyclo[3.3.1]nonenone core was achieved by stepwise annulation of 2-cyclohexenone derivatives and acrylates via successive Michael reactions. The process could also be effected by a one-pot procedure.

The bicyclo[3.3.1]nonane skeleton is often found in biologically active natural products such as Garsubellin A (Fig. 1).[1] Therefore, many types of synthetic methods for bicyclo[3.3.1]nonane derivatives have been reported.[2,3] They have also found use as synthetic intermediates for other ring systems.[4] Recently, polycyclic polyprenylated acylphloroglucinols featuring a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,9-trione core, have attracted attention as targets for organic synthesis.[5] Herein the construction of the bicyclo[3.3.1]nonenone core by stepwise and one-pot annulation of 2-cyclohexenone derivatives with acrylates via successive Michael reactions is described.

The stepwise annulation of 2-methyl-2-cyclohexenone **1** with acrylates **2a**–**c**[6] via successive Michael reactions was examined (Scheme 1). Annulation precursors **3a**–**c** were obtained by the intermolecular Michael reaction of **1** with acrylates **2a**–**c**, respectively (**3a**: 50%, **3b**: 55%, **3c**: 74%). The intramolecular Michael reaction of **3a**–**c** was performed under solid–liquid phase transfer conditions: a solution of the annulation precursors **3a**–**c** was stirred in the presence of K_2CO_3 as the base and tetrabutylammonium bromide (TBAB) as the phase transfer catalyst.[7] Upon treating annulation precursor **3a** with K_2CO_3 (3.0 equiv) and TBAB (1.0 equiv) (Table 1, entry 1), annulation proceeded at the α′-position of the carbonyl group with accompanied migration of the double bond to give α,α′-annulation products **4a** and **5a** (**4a**: 67%, **5a**: 4%). The relative stereochemistry of



Scheme 1.

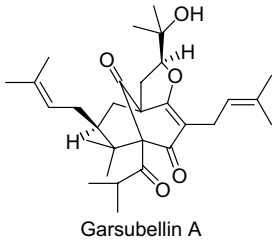


Figure 1.

Keywords: One-pot reaction; Bicyclo[3.3.1]nonenone; Successive Michael reaction.

* Corresponding authors. Tel.: +81 82 424 7432; fax: +81 82 424 0747; e-mail addresses: rtakagi@hiroshima-u.ac.jp; ohkata@sci.hiroshima-u.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.068

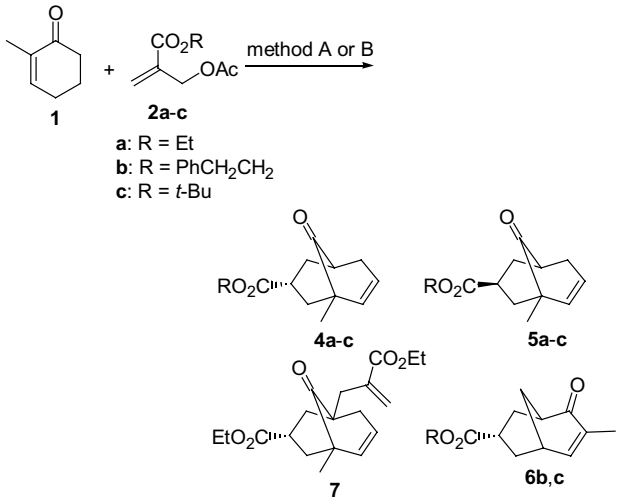
Table 1. Stepwise annulation between **1** and **2a–c**

Entry	Subst.	K_2CO_3 (equiv)	TBAB (equiv)	Solvent	Conditions	Product[a]
1	**3a**	3.0	1.0	Toluene	80 °C, 30 h	**4a**: 67% **5a**: 4%
2	**3a**	1.2	0.2	Toluene	70 °C, 28 h	**4a**: 59% **5a**: 13%
3	**3b**	2.0	0.1	Toluene	80 °C, 91 h	**4b**: 36% **5b**: 29%
4	**3b**	2.0	1.0	THF	90 °C, 115 h	**4b**: 35% **5b**: 23% **6b**: 3%
5	**3b**	3.0	1.0	EtOH	90 °C, 3 h	**4a**: 10%
6	**3c**	2.0	1.0	THF	90 °C, 31 h	**4c**: 71% **5c**: 8%

[a] Isolated yield.

4a and **5a** was assigned by the coupling constant $^3J_{H7,H8exo}$ in ^1H NMR: **4a**: $^3J_{H7,H8exo}$ = 6.1 Hz; **5a**: $^3J_{H7,H8exo}$ = 12.8 Hz.[8] The amount of base did not affect the ratio of **4a** and **5a** to a large extent (K_2CO_3: 1.2 equiv, TBAB: 0.2 equiv, **4a**: 59%, **5a**: 13%, Table 1, entry 2). The annulation of phenylethyl ester **3b** in some solvents was next examined (Table 1, entries 3–5). The annulation of **3b** in both toluene and THF gave bicyclic compounds **4b** and **5b** with the same tendency (Table 1, entries 3 and 4, **4b**:**5b** = ca. 3:2). In the annulation of **3b**, a small amount of $PhCH_2CH_2OH$ was obtained as a consequence of slight decomposition. Isomerization studies between **4b** and **5b** indicated that **5b** was the thermodynamically favored product: the bicyclic compounds **4b** and **5b** were heated separately under the stepwise annulation conditions for 9 days. Although **5b** did not isomerize to **4b** at all (**4b**:**5b** = 0:100), **4b** isomerized somewhat to **5b** (**4b**:**5b** = 85:15). When THF was used as the solvent, bicyclic compound **6b**, an α,γ-annulation product, was also obtained (3%). The annulation of **3b** in EtOH gave bicyclic compound **4a**, generated by ester exchange, in low yield (10%, Table 1, entry 5). It is considered that the moderate yields (61–72%, Table 1, entries 1–4) arise from decomposition of the ester group. Treatment of **3c** with K_2CO_3 (2.0 equiv) and TBAB (1.0 equiv) gave the best results (**4c**: 71%, **5c**: 8%, Table 1, entry 6).[9]

Since the stepwise annulation of 2-methyl-2-cyclohexenone **1** with acrylates **2a–c** proceeded sufficiently, one-pot annulation via successive Michael reactions between 2-methyl-2-cyclohexenone **1** and acrylates **2a–c** (Scheme 2) was subsequently investigated. First, the one-pot annulation of **1** with **2a** by a one operation process was examined (method A): a mixture of **1**, **2a**, K_2CO_3 and TBAB was heated at 80 °C for 42 h in toluene. As a result, three bicyclic compounds **4a**, **5a**, and **7** were obtained (**4a**: 2%, **5a**: 2%, **7**: 15%, Table 2, entry 1). The bicyclic compound **7** most likely formed by Michael reaction of the annulation precursor **3a** with another molecule of acrylate **2a** at the α-position, prior to the intramolecular ring-closing Michael reaction. To avoid the generation of annulation products such as **7**, a one-pot annulation by two operations was examined: the annulation precursors **3b** and **3c** were generated in



Scheme 2.

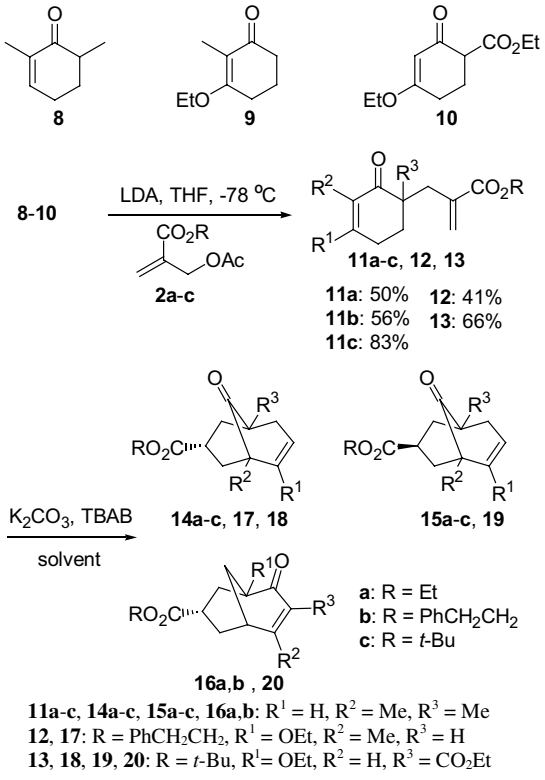
situ by treatment of **1** with LDA, followed by acrylates **2b** and **2c**, respectively. To the reaction mixture were added K_2CO_3 and TBAB, and the mixture was heated (method B, Table 2, entries 2–4).[10] With method B, the α,α′-annulation products **4b**,**c** and **5b**,**c** were obtained in moderate yields along with a small amount of α,γ-annulation products **6b**,**c**. In contrast with the stepwise annulation, the thermodynamically favored α,α′-annulation products **5b**,**c** were obtained as the major isomer in the one-pot annulation. The basic species (diisopropylamine, AcOLi) generated in situ in the one-pot reaction may effect to isomerization between **4b**,**c** and **5b**,**c**.

Next, the stepwise annulation of some di-substituted 2-cyclohexenones **8–10** with acrylates **2a–c** was examined (Scheme 3)[7] and the results are summarized in Table 3. The annulation precursors **11a–c**, **12**, and **13** were obtained by the Michael reaction of **8–10** with acrylates **2a–c**. Treatment of **11a–c** and **12** with K_2CO_3 and TBAB gave α,α′-annulation products **14a–c** and **17** as the major isomer, respectively (Table 3, entries 1–4). Annulation of **11c** and **12** gave rise to single products. When 3-ethoxy-6-ethoxycarbonyl derivative **13** was used

Table 2. One-pot annulation between **1** and **2a–c**

Entry	Acrylate	Method[a]	K_2CO_3 (equiv)	TBAB (equiv)	Conditions	Product[b]
1	**2a**	A	3.0	1.0	80 °C, 42 h	**4a**: 2% **5a**: 2% **7**: 15%
2	**2b**	B	1.6	0.02	80 °C, 24 h	**4b**: 6% **5b**: 12%
3	**2b**	B	2.0	1.0	80 °C, 40 h	**4b**: 9% **5b**: 20% **6b**: 2%
4	**2c**	B	3.0	1.0	90 °C, 18 h	**4c**: 16% **5c**: 28% **6c**: 7%

[a] Method A: **1**, **2a**, K_2CO_3, TBAB, toluene. Method B: (1) **1**, LDA, THF, −78 °C then **2**, −78 °C to rt. (2) K_2CO_3, TBAB.
[b] Isolated yield.



Scheme 3.

as the substrate, α,γ-annulation product **20** was obtained as the major product (Table 3, entry 5).

Table 4 summarizes the one-pot annulation between the cyclohexenone derivatives **8–10** and acrylates **2a–c** (Scheme 4). One-pot annulation of **8** in a one operation process (method A) proceeded in low yield to give annulation products **14a** and **21**, via successive Michael reactions (Table 4, entry 1). The one-pot annulation of **8** in two operations (method B)[10] gave annulation products with a higher ratio of the thermodynamically more stable **15b** and **15c** compared with the stepwise protocol (Table 4, entries 2 and 3). In the case of the reaction of **10** with **2c**, the ratios were similar with those of stepwise reactions (Table 4, entry 5).

In summary, the construction of the bicyclo[3.3.1]nonenone core was achieved by the stepwise annulation of 2-cyclohexenones **1**, **8**, **9** and **10** with acrylates **2a–c** via successive Michael reactions. The annulation precursors **3a–c**, **11a–c**, **12**, and **13** reacted via the thermodynamically more stable enolate to furnish the bicyclo[3.3.1]-nonenone core by α′-annulation of the enolate. The annulation could also be carried out in a one-pot reaction to give the bicyclo[3.3.1]nonenone derivatives with the same tendency. Although bicyclic compounds are usually constructed via enamine derivatives of cyclic ketone, this reported procedure affords the bicyclo[3.3.1]nonenone derivatives directly from the cyclohexenone derivatives.

Table 3. Stepwise annulation between **8–10** and **2a–c**

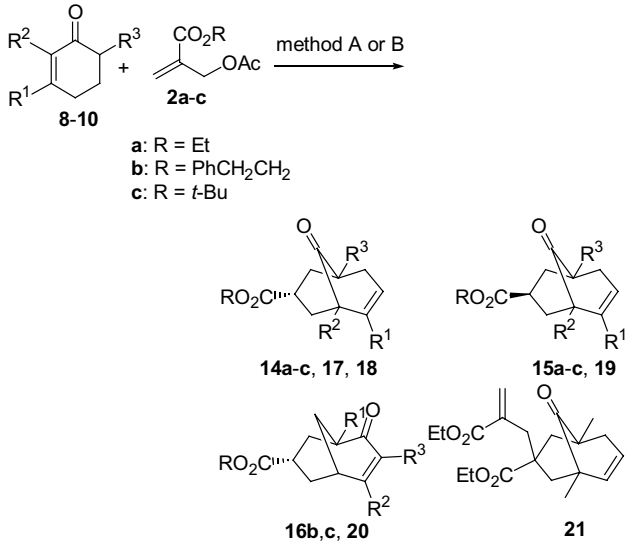
Entry	Subst.	K_2CO_3 (equiv)	TBAB (equiv)	Solvent	Conditions	Product[a]
1	**11a**	3.0	1.0	Toluene	80 °C, 6 h	**14a**: 65% **15a**: 13% **16a**: 4%
2	**11b**	2.0	1.0	Toluene	90 °C, 9 h	**14b**: 49% **15b**: 13% **16b**: 6%
3	**11c**	3.0	1.0	THF	90 °C, 23 h	**14c**: 91%
4	**12**	2.0	1.0	Toluene	80 °C, 54 h	**17**: 41%
5	**13**	3.0	1.0	THF	80 °C, 24 h	**18**, **19**: 17%[b,c] **20**: 48%

[a] Isolated yield.
[b] Purification by preparative TLC gave a mixture of diastereomers.
[c] The ratio of **18** and **19** was 10:7 according to the ^{1}H NMR.

Table 4. One-pot annulation between **8**–**10** and **2a**–**c**

Entry	Subst.	Acrylate	Method[a]	K_2CO_3 (equiv)	TBAB (equiv)	Conditions	Product[b]
1	**8**	**2a**	A	3.0	1.0	80 °C, 42 h	**14a**: 5% **21**: 12%
2	**8**	**2b**	B	3.0	1.0	80 °C, 47 h	**14b**: 29% **15b**: 16% **16b**: 15%
3	**8**	**2c**	B	3.0	1.0	90 °C, 18 h	**14c**: 34% **15c**: 32% **16c**: 4%
4	**9**	**2b**	B	3.0	1.0	80 °C, 13 h	**17**: 17%
5	**10**	**2c**	B	3.0	1.0	80 °C, 25 h	**18**, **19**: 31%[c,d] **20**: 35%

[a] Method A: **8**, **2a**, K_2CO_3, TBAB, toluene. Method B: (1) substrate (**8**, **9**, or **10**), LDA, THF, −78 °C then **2**, −78 °C to rt. (2) K_2CO_3, TBAB.
[b] Isolated yield.
[c] Purification by preparative TLC gave a mixture of diastereomers.
[d] The ratio of **18** and **19** was 25:6 according to the ^{1}H NMR.



Scheme 4.

Acknowledgements

NMR and MS measurements were made using JEOL JMN-LA500 and JEOL SX-102A, respectively, at the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University. We thank Dr. Yoshikazu Hiraga for NMR measurements (JEOL JMN-LA500) at the Hiroshima Prefectural Institute of Science and Technology. We thank Dr. Satoshi Kojima for prereading the manuscript.

References and notes

1. For some recent reports on natural products bearing a bicyclo[3.3.1]nonanone core: (a) Cuesta-Rubio, O.; Padron, A.; Castro, H. V.; Pizza, C.; Rastrelli, L. *J. Nat. Prod.* **2001**, *64*, 973; (b) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701; (c) Nakatani, M.; Abdelgaleil, S. A. M.; Kurawaki, J.; Okamura, M.; Iwagawa, T.; Doe, M. *J. Nat. Prod.* **2001**, *64*, 1261; (d) Weng, J.-R.; Lin, C.-N.; Ţsao, L.-T.; Wang, J.-P. *Chem. Eur. J.* **2003**, *9*, 1958; (e) Šavikin-Fodulović, K.; Aljančić, I.; Vajs, V.; Menković, N.; Macura, S.; Gojgić, G.; Milosavljević, S. *J. Nat. Prod.* **2003**, *66*, 1236; (f) Hua, Y.; Liu, H.-Y.; Ni, W.; Chen, C.-X.; Lu, Y.; Wang, C.; Zheng, Q.-T. *J. Nat. Prod.* **2003**, *66*, 898; (g) Lin, Y.-L.; Wu, Y.-S. *Helv. Chim. Acta* **2003**, *86*, 2156; (h) Wu, J.; Zhang, S.; Xiao, Q.; Li, Q.; Huang, J.; Long, L.; Huang, L. *Tetrahedron Lett.* **2004**, *45*, 591; (i) Stierle, D. B.; Stierle, A. A.; Hobbs, J. D.; Stokken, J.; Clardy J. *Org. Lett.* **2004**, *6*, 1049.
2. For reviews: (a) Peters, J. A. *Synthesis* **1979**, 321; (b) Butkus, E. *Synlett* **2001**, 1827.
3. (a) Barluenga, J.; Ballesteros, A.; Santamaría, J.; de la Rúa, R. B.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc.* **2000**, *122*, 12874; (b) Byeon, C.-H.; Hart, D. J.; Lai, C.-S.; Unch, J. *Synlett* **2000**, 119; (c) Camps, P.; González, A.; Muñoz-Torrero, D.; Simon, M.; Zúñiga, A.; Martins, M. A.; Font-Bardia, M.; Solans, X. *Tetrahedron* **2000**, *56*, 8141; (d) Yang, J.-D.; Kim, M.-S.; Lee, M.; Baik, W.; Koo, S. *Synthesis* **2000**, 801; (e) Klaic, L.; Velkovic, J.; Mlinaric-Majerski, K. *Synth. Commun.* **2002**, *32*, 89; (f) Simon, C.; Peyronel, J.-F.; Clerc, F.; Rodriguez. J. *Eur. J. Org. Chem.* **2002**, 3359; (g) Barluenga, J.; Ballesteros, A.; de la Rúa, R. B.; Santamaría, J.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc.* **2003**, *125*, 1869.
4. (a) Miesch, M.; Mislin, G.; Franck-Neumann, M. *Synlett* **1996**, 385; (b) Momose, T.; Toshima, M.; Seki, S.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1315; (c) Geirsson, J. K. F.; Eiriksdottir, E. G. *Synlett* **2001**, 664; (d) Gambacorta, A.; Tofani, D.; Lupattelli, P.; Tafi, A. *Tetrahedron Lett.* **2002**, *43*, 2195.
5. (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724; (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807; (c) Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134; (d) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943; (e) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859; (f) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621; (g) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619; (h) Kras, G. A.; Nguyen, T.; Jeon, I. *Tetrahederon Lett.* **2003**, *44*, 659; (i) Klein, A.; Miesch, M. *Tetrahederon Lett.* **2003**, *44*, 4483; (j) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113.
6. Villiéras, J.; Rambaud, M. *Synthesis* **1982**, *9*, 924.
7. Typical procedure for the stepwise annulation: To a solution of **3c** (93.6 mg, 0.37 mmol) in THF (2.0 mL) were

added K_2CO_3 (103.5 mg, 0.75 mmol) and TBAB (120.9 mg, 0.38 mmol). The mixture was stirred at 90 °C for 31 h. After complete consumption of **3c** by GC monitoring, the mixture was cooled to rt and quenched with 1 N HCl. The resulting mixture was extracted with ether. The combined organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, and evaporated. The resulting residue was purified by preparative TLC (silica gel, hexane/EtOAc = 10/1) to give annulation products **4c** and **5c** (**4c**: 71%, **5c**: 8%, Table 1, entry 6).

8. The coupling constants (2.1–2.5 Hz) between $H6_{exo}$ and $H4_{exo}$ were observed in the ^1H NMR of **14a–c** and **15a–c**. The long range couplings indicate the preferred conformer of six-membered ring in the bicyclo[3.3.1]nonenone core.
9. (a) Spectral data of **4c**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 3H, 1-CH_3), 1.47 (s, 9H, C(C**H**$_3$)$_3$), 1.81 (dd, J = 6.4, 14.0 Hz, 1H, $H8_{exo}$), 1.99–2.08 (m, 1H, $H6_{exo}$), 2.52 (tt, J = 1.7, 7.0 Hz, 1H, $H4_{exo}$), 2.59–2.65 (m, 3H, H5, H7, $H8_{endo}$), 2.74–2.81 (m, 2H, $H4_{endo}$, $H6_{endo}$), 5.30 (ddd, J = 1.1, 1.7, 9.4 Hz, 1H, H2), 5.59–5.64 (m, 1H, H3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3 (1-CH_3), 28.0 (×3, C(**C**H$_3$)$_3$), 34.8 (C6), 36.3 (C4), 37.7 (C7), 41.5 (C8), 44.9 (C5), 46.3 (C1), 80.7 (**C**(CH$_3$)$_3$), 128.6 (C3), 133.5 (C2), 173.0 (CO_2), 216.3 (CO); HRMS (EI) calcd for $C_{15}H_{22}O_3$ [M^+] 250.1569. Found 250.1577; Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.16; H, 8.65. (b) Spectral data of **5c**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H, 1-CH_3), 1.43 (s, 9H, C(C**H**$_3$)$_3$), 1.73 (t, J = 12.8 Hz, 1H, $H8_{exo}$), 1.96–2.04 (m, 2H, $H8_{endo}$, $H6_{exo}$), 2.09–2.15 (m, 1H, $H6_{endo}$), 2.47 (ddd, J = 1.4, 3.6, 18.6 Hz, 1H, $H4_{exo}$); 2.66–2.70 (m, 1H, H5), 2.72–2.80 (m, 1H, $H4_{endo}$), 3.02 (tt, J = 4.6, 12.8 Hz, 1H, H7), 5.35 (ddd, J = 1.4, 2.4, 9.4 Hz, 1H, H2), 5.90 (dt, J = 3.6, 9.4 Hz, 1H, H3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1 (1-CH_3), 28.0 (×3, C(**C**H$_3$)$_3$), 36.9 (C7), 37.7 (C4), 38.5 (C6), 43.1 (C8), 44.3 (C5), 46.0 (C1), 80.6 (**C**(CH$_3$)$_3$), 129.1 (C3), 133.3 (C2), 173.9 (CO_2), 215.4 (CO); HRMS (EI) Calcd for $C_{15}H_{22}O_3$ [M^+] 250.1569. Found 250.1570; Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.02; H, 8.88.
10. Typical procedure for one-pot annulation (method B): To a solution of LDA [diisopropylamine (0.08 mL, 0.58 mmol), *n*-BuLi (1.56 M in THF, 0.31 mL, 0.48 mmol), THF, 0 °C, 30 min] was added a solution of **8** (50.2 mg, 0.40 mmol) in THF (0.5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. Then, a solution of acrylate **2c** (81.2 mg, 0.48 mmol) in THF (0.5 mL) was added to the mixture at −78 °C. After the reaction mixture was allowed to warm to rt over 6 h, to the reaction mixture was added K_2CO_3 (167.7 mg, 1.21 mmol) and TBAB (130.9 mg, 0.41 mmol). The mixture was stirred at 90 °C for 18 h. After complete consumption of **3c** by GC monitoring, the mixture was cooled to rt and quenched with 1 N HCl. The resulting mixture was extracted with ether. The combined organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, and evaporated. The resulting residue was purified by preparative TLC (silica gel, hexane/EtOAc = 10/1) to give annulation products **14c**, **15c** and **16c** (**14c**: 34%, **15c**: 32%, **16c**: 4%, Table 4, entry 3).