Tetrahedron Letters 55 (2014) 6655–6657

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of (6*Z*,9*S*)-3,4-*trans*-9-hydroxy-3-methyldodec-*cis*-6-en-4-olide and (6*Z*)-3,4-*trans*-9-oxo-3-methyldodec-*cis*-6-en-4-olide γ-butyrolactones

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ARTICLE INFO

Article history:
Received 26 August 2014
Revised 11 October 2014
Accepted 11 October 2014
Available online 17 October 2014

Keywords:
γ-Butyrolactones
Ohira–Bestmann reagent
Regioselective epoxide ring-opening
Lindlar's catalyst
Total synthesis

ABSTRACT

The first total synthesis of (6*Z*,9*S*)-3,4-*trans*-9-hydroxy-3-methyldodec-*cis*-6-en-4-olide and (6*Z*)-3,4-*trans*-9-oxo-3-methyldodec-*cis*-6-en-4-olide was achieved in a convergent pathway. The salient features of our synthesis include Ohira–Bestmann reaction, regioselective alkyne addition to terminal epoxide, TEMPO/BAIB mediated oxidative lactonization, and partial hydrogenation.

Functionalized non-racemic γ-butyrolactones are not only useful starting materials for diverse natural products but also act as core structure of several potential bio-active compounds.[1]

Recently four new 13-carbon γ-butyrolactones (Fig. 1, **1**–**4**) were isolated from the cultures of the basidiomycetes family, *Trichaptum pargamenum* along with four new cadinane-type sesquiterpenes.[2] The mushroom *T. pargamenum* was used as a medicinal fungus for treating cancer, fungal, and bacterial diseases. The structural similarity of compounds **1**–**4** having the same (3*R*,4*S*) γ-lactone system connected by different *Z*-olefinic functionalities and its significant activity profile prompted us to embark on the first total synthesis of **1** and **2**.

Retrosynthetic analysis of compounds **1** and **2** is shown in Scheme 1. Accordingly, the target compounds could be obtained from **12** by partial hydrogenation,[3] deprotection of PMB-ether followed by oxidation. While the alkyne **12** in turn could be derived from deprotection of silyl ether followed by TEMPO/BAIB mediated intramolecular oxidative cyclization[4] of compound **10** that could be achieved by the coupling of two fragments **7** and **9**. Independently, the alkyne fragment **9** was synthesized from the commercially available *trans*-hex-2-en-1-ol, while the epoxy fragment **7** was synthesized from the known epoxy alcohol **5** by employing a few chemical manipulations.

Scheme 2 depicts the synthesis of epoxide fragment **7** and it was accessed from the known epoxy alcohol **5**.[5] Accordingly, epoxy alcohol **5** on treatment with Me_3Al[6] resulted in the corresponding 1,2-diol **6**[6b] as an exclusive isomer in 85% yield. Next, the diol **6** was subjected to mono tosylation ($TsCl/^nBu_2SnO/Et_3N/CH_2Cl_2$) followed by methanolysis (K_2CO_3/MeOH) to afford the desired chiral epoxide **7** (78% over two steps).

At the same time, synthesis of alkyne fragment **9** was achieved from the known primary alcohol **8**[7] (Scheme 3). The alcohol **8** was oxidized under Swern conditions followed by one carbon homologation reaction using Ohira–Bestmann reagent **A**[8] to furnish the required alkyne fragment **9** (78% over two steps).

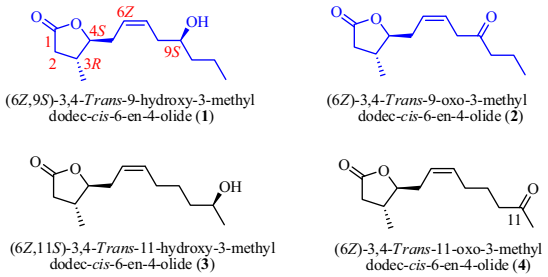

Figure 1. Structures of γ-butyrolactones (**1**–**4**).

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http://dx.doi.org/10.1016/j.tetlet.2014.10.066
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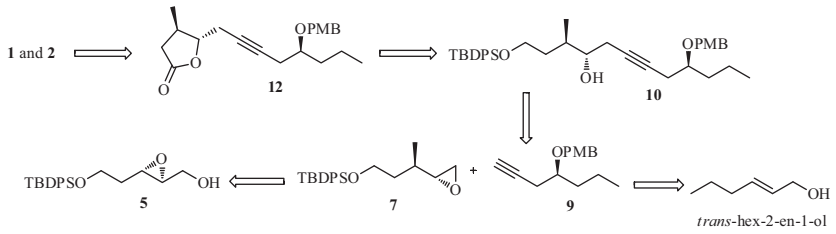
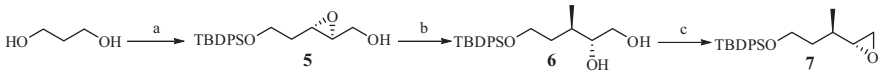
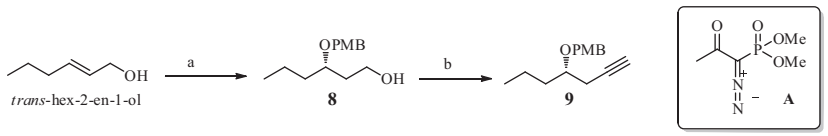


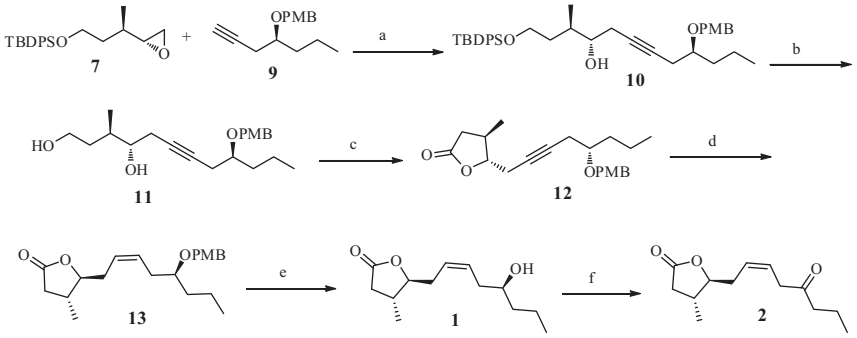
Scheme 1. Retrosynthesis of γ-butyrolactones **1** and **2**.



Scheme 2. Reagents and conditions: (a) Ref. 5; (b) Me_3Al, *n*-hexane, 0 °C, 3 h, 85%; (c) (i) TsCl, $^nBu_2SnO$, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, (ii) K_2CO_3, MeOH, 0 °C to rt, 3 h, 78% (over two steps).



Scheme 3. Reagents and conditions: (a) Ref. 7; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, (ii) **A**, K_2CO_3, MeOH, rt, 4 h, 78% (over two steps).



Scheme 4. Reagents and conditions: (a) *n*-BuLi, dry THF, −78 °C, 3 h, 80%; (b) TBAF, THF, rt, 12 h, 85%; (c) TEMPO, BAIB, CH_2Cl_2/H_2O (1:1), 12 h, 83%; (d) H_2/Pd–$BaSO_4$, quinoline, EtOAc, 1 h, 90%; (e) DDQ, CH_2Cl_2/H_2O (19:1), rt, 2 h, 92%; (f) DMP, CH_2Cl_2, 0 °C, 3 h, 88%.

The final stage of synthesis is the coupling of two fragments **7** and **9** (Scheme 4) followed by ensuing transformation. Thus, the alkyne **9** (Scheme 4) on regioselective addition under Yamaguchi conditions[9] to epoxide **7** led to the crucial intermediate **10** (80%). Compound **10** on desilylation using TBAF afforded diol **11** which on subsequent TEMPO/BAIB mediated intramolecular oxidative cyclization[4] resulted in the γ-lactone **12** (83%).

With the γ-lactone **12** in hand, we planned to accomplish the synthesis of target compounds **1** and **2**. Thus, partial hydrogenation of alkyne functionality in compound **12** using Lindlar's catalyst[3] (Pd/$BaSO_4$-quinoline) resulted in the *Z*-alkenyl γ-lactone **13** (90%). Finally, deprotection of PMB ether under DDQ conditions led to the natural product **1** (92%) which on Dess–Martin periodinane oxidation afforded the natural product **2** (88%). Although the spectral data (^{1}H NMR and ^{13}C NMR) of the synthetic compounds[10] were in good agreement with the reported data,[2] there is an inconsistency in the optical rotation value of synthetic compound **1** with the natural compound {Synthetic **1**: $[\alpha]_D^{25}$ −29.4 (*c* 0.55, MeOH); Natural **1**:[2] $[\alpha]_D^{24}$ +18.2 (*c* 0.20, MeOH)}. However, the optical rotation value for the synthetic **2** {$[\alpha]_D^{25}$ +60.8 (*c* 0.2, MeOH); Natural **2**:[2] $[\alpha]_D^{25}$ +68.4 (*c* 0.07, MeOH)} nearly matched. Since, the requisite stereogenic centers garnered in both the required fragments **7** and **9** involved the well established chemistry and unambiguously characterized by their data reported, this difference could have stemmed erroneously while assigning the C9 stereogenic center. Based on the analysis of spectral data[10,11] a structural revision for isolated compound **1** was felt necessary. Additionally, a correction in structural names of compounds **1** and **2** is needed. Accordingly, instead of (6*Z*,11*S*)-3,4-*trans*-9-hydroxy-3-methyldodec-*cis*-6-en-4-olide it may correctly be named as (6*Z*,9*S*)-3,4-*trans*-9-hydroxy-3-methyldodec-*cis*-6-en-4-olide **1** and (6*Z*,11*S*)-3,4-*trans*-9-oxo-3-methyldodec-cis-6-en-4-olide as (6*Z*)-3,4-*trans*-9-oxo-3-methyldodec-*cis*-6-en-4-olide **2**.

The stereochemistry at C9-stereocenter in compound **1** was further confirmed by ^{1}H NMR (600 MHz, $CDCl_3$) data and assignments were made with the aid of NOESY experiment.[11] The presence of NOE between C7H and C9H (Fig. 2) suggested the absolute configuration at C9 as '*S*'. This was further supported by NOE correlation between C6H and C4H, confirming the structure of **1** (Fig. 2). Thus the absolute stereochemistry at C9 is unequivocally established as '*S*' {Energy minimized structure, Fig. 2b}. Additional spectral analysis from HMBC correlations (Fig. 3) also supported the assigned structures of synthetic **1** and **2**.[11]

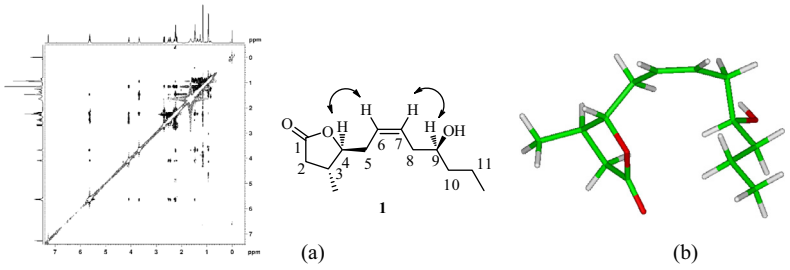


Figure 2. (a) NOESY spectrum (in $CDCl_3$) of **1** (b) energy minimized structure of **1**.

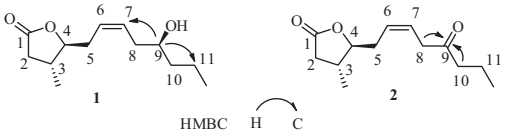


Figure 3. Key 2D NMR (HMBC) correlations of compounds **1** and **2**.

In summary, we have reported the first total synthesis of (6*Z*,9*S*)-3,4-*trans*-9-hydroxy-3-methyldodec-*cis*-6-en-4-olide **1** and (6*Z*)-3,4-*trans*-9-oxo-3-methyldodec-*cis*-6-en-4-olide **2** using Ohira–Bestmann reaction, regioselective alkyne addition to terminal carbon atom of epoxide, intramolecular TEMPO/BAIB mediated oxidative lactonization, and Lindlar's hydrogenation as the key steps.

Acknowledgements

The authors (G.R. and N.R.) thank CSIR, New Delhi, India for the financial support in the form of fellowships. All the authors thank CSIR, New Delhi for financial support as part of XII Five Year plan program under title TREAT (BSC-0116).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.066.

References and notes

1. (a) Ziegler, F. E.; Cain, W. T. *J. Org. Chem.* **1989**, *54*, 3347; (b) Braun, M.; Opdenbusch, K.; Unger, C. *Synlett* **1995**, 1174; (c) Ohba, M.; Izuta, R.; Shimizu, E. *Tetrahedron Lett.* **2000**, *41*, 10251; (d) Ghosh, A. K.; Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823; (e) Gudipati, V.; Curran, D. P.; Wilcox, C. S. *J. Org. Chem.* **2006**, *71*, 3599; (f) Yang, H.; Qiao, X.; Li, F.; Ma, H.; Xie, L.; Xu, X. *Tetrahedron Lett.* **2009**, *50*, 1110; (g) Ghosh, A. K.; Shurrush, K.; Kulkarni, S. *J. Org. Chem.* **2009**, *74*, 4508; (h) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; ; Pergamon: Oxford, 1991; Vol. 6, p 350.
2. Yang, X.-Y.; Feng, T.; Wang, G.-Q.; Ding, J.-H.; Li, Z.-H.; Li, Y.; He, S.-H.; Liu, J.-K. *Phytochemistry* **2014**, *104*, 89.
3. Lindlar, H.; Dubuis, R. *Organic Syntheses* In ; Wiley: New York, 1973; Collect. Vol. V, p 880.
4. Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.
5. Radha Krishna, P.; Jagannnadha Rao, T. *Tetrahedron Lett.* **2010**, *51*, 4017.
6. (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597; (b) Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1937**, *1992*, 33.
7. Radha Krishna, P.; Prabhakar, S. *Tetrahedron Lett.* **2007**, *54*, 3788.
8. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561; (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.
9. (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391; (b) Kishi, Y.; Seike, H.; Ghosh, I. *Org. Lett.* **2006**, *8*, 3865; (c) Radha Krishna, P.; Srinivas, R. *Tetrahedron Lett.* **2013**, *2007*, 48.
10. Spectral data of some selected compounds. *tert-Butyl((R)-3-((R)-oxiran-2-yl)butoxy)diphenylsilane* (**7**): $[\alpha]_D^{25}$ +15.2 (*c* 0.55, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71–7.64 (m, 4H), 7.46–7.34 (m, 6H), 3.77 (t, *J* = 6.0 Hz, 2H), 2.77–2.64 (m, 2H), 2.47 (m, 1H), 1.85 (m, 1H), 1.66–1.43(m, 2H), 1.05 (s, 9H), 0.90 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.9, 129.5, 127.5, 61.7, 56.7, 45.5, 36.9, 32.6, 26.8, 19.1, 15.4. HRMS calcd for $C_{22}H_{30}O_2Na$ $(M+Na)^+$ 377.1907, found 377.1906. *(S)-1-((Hept-1-yn-4-yloxy)methyl)-4-methoxybenzene* (**9**): $[\alpha]_D^{25}$ −12.4 (*c* 0.50, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.52 (m, 1H), 2.48–2.35 (m, 2H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.64–1.57 (m, 2H), 1.51–1.29 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 130.5, 129.2, 113.6, 81.3, 76.4, 70.9, 69.7, 55.1, 36.1, 23.7, 18.5, 13.9. HRMS calcd for $C_{15}H_{20}O_2Na$ $(M+Na)^+$ 255.1355, found 255.1356. *(3R,4S,9S)-1-(tert-Butyldiphenylsilyloxy)-9-(4-methoxybenzyloxy)-3-methyldodec-6-yn-4-ol* (**10**): $[\alpha]_D^{25}$ +21.0 (*c* 0.20, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72–7.63(m, 4H), 7.45–7.34 (m, 6H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.67 (m, 1H), 3.56–3.45 (m, 2H), 2.67 (br. S, 1H), 2.47–2.30 (m, 4H), 1.88 (m, 1H), 1.78 (m, 1H), 1.58 (m, 2H), 1.51–1.41 (m, 2H), 1.34 (m, 1H), 1.04 (s, 9H), 0.90–0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 135.5, 133.5, 130.6, 129.6, 129.2, 127.6, 113.7, 79.4, 78.2, 74.0, 70.8, 62.0, 55.2, 36.2, 34.9, 34.7. 26.7, 24.9, 24.0, 19.1, 18.5, 15.9, 14.1. HRMS calcd for $C_{37}H_{50}O_4NaSi$ $(M+Na)^+$ 609.3370, found 609.3366. *(3R,4S,9S)-9-(4-Methoxybenzyloxy)-3-methyldodec-6-yne-1,4-diol* (**11**): $[\alpha]_D^{25}$ +6.6 (*c* 0.30, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.43, (d, *J* = 11.3 Hz, 1H), 3.80 (s, 3H), 3.72 (m, 1H), 3.62 (m, 1H), 3.54–3.43 (m, 2H), 2.77 (br s, 1H), 2.51–2.28 (m, 4H),1.86–1.17 (m, 7H), 0.96–0.84 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 134.7, 130.4, 129.3, 127.6, 113.7, 79.6, 78.0, 74.0, 70.7, 60.5, 55.2, 36.1, 35.8, 35.7, 29.6, 26.5, 25.5, 23.8, 18.6, 16.7, 14.0. HRMS calcd for $C_{21}H_{32}O_4Na$ $(M+Na)^+$ 371.2192, found 371.2193. *(4R,5S)-5-((S)-5-(4-Methoxybenzyloxy)oct-2-ynyl)-4-methyldihydrofuran-2(3H)-one* (**12**): $[\alpha]_D^{25}$ +10.0 (*c* 0.30, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.13 (q, *J* = 5.6 Hz, 1H), 3.81(s, 3H), 3.48 (m, 1H), 2.76 (dd, *J* = 17.5, 8.6 Hz, 1H), 2.64–2.56 (m, 2H), 2.54–2.35 (m, 2H), 2.18 (dd, *J* = 17.3, 8.1 Hz, 1H), 1.72–1.23 (m, 4H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.0, 159.0, 130.6, 129.2, 113.6, 84.4, 80.1, 75.4, 70.7, 55.2, 36.7, 36.1, 34.6, 29.6, 24.1, 23.9, 14.0. HRMS calcd for $C_{21}H_{32}O_4Na$ $(M+Na)^+$ 362.2352, found 362.2332. *(4R,5S)-5-((S,Z)-5-(4-Methoxybenzyloxy)oct-2-enyl)-4-methyldihydrofuran-2(3H)-one* (**13**): $[\alpha]_D^{25}$ +150.0 (*c* 0.10, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.70–5.45 (m, 2H), 4.52–4.39 (m, 2H), 4.05 (q, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 3.43 (m, 1H), 2.65 (dd, *J* = 16.6,7.5 Hz, 1H), 2.55–2.15 (m, 5H), 1.57–1.20 (m, 5H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 159.0, 130.9, 129.5, 129.2, 124.6, 113.6, 86.5, 78.0, 70.7, 55.2, 36.9, 36.2, 35.1, 31.9, 31.4, 29.6, 18.6, 17.6, 14.1. HRMS calcd for $C_{21}H_{30}O_4Na$ $(M+Na)^+$ 369.2036, found 369.2034. *(6Z,9S)-3,4-trans-9-hydroxy-3-methyl dodec-cis-6-en-4-olide* (**1**): $[\alpha]_D^{25}$ −29.4 (*c* 0.55, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.70–5.55 (m, 2H), 4.08 (m, 1H), 3.67 (m, 1H), 2.69 (dd, *J* = 16.6,7.5 Hz, 1H), 2.58–2.42 (m, 2H), 2.33–2.14 (m, 4H), 1.53–1.39 (m, 3H), 1.38–1.23 (m, 1H),1.15 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 129.3, 126.1, 86.5, 71.0, 39.1, 37.0, 35.4, 35.3, 31.4, 18.8, 17.5, 14.0. HRMS calcd for $C_{13}H_{22}O_3Na$ $(M+Na)^+$ 249.1461, found 249.1458. *(6Z)-3,4-trans-9-oxo-3-methyl dodec-cis-6-en-4-olide* (**2**): $[\alpha]_D^{25}$ = +60.8 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77 (m, 1H), 5.65 (m, 1H), 4.08 (m, 1H), 3.19 (d, *J* = 7.1 Hz, 2H), 2.68 (dd, *J* = 16.9, 7.7 Hz, 1H), 2.50–2.37 (m, 4H), 2.26 (m, 1H), 2.18 (m, 1H), 1.70–1.52 (m, 2H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.2, 176.1, 126.6, 124.8, 86.1, 44.4, 41.5, 36.9, 35.2, 31.5, 17.4, 17.1, 13.6. HRMS calcd for $C_{13}H_{21}O_3$ $(M+H)^+$ 225.1485, found 225.1481.
11. As suggested by referee, HSQC, HMBC and NOESY experiments were conducted for the thorough analysis of the structures of synthetic compounds **1** and **2**. All the data is incorporated as Supporting information.