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Total synthesis of two γ-butyrolactone containing compounds (*Z*,11*S*)-3,4-*trans*-11-hydroxy-3-methyldodec-*cis*-6-en-4-olide and (*Z*)-3,4-*trans*-11-oxo-3-methyldodec-*cis*-6-en-4-olide

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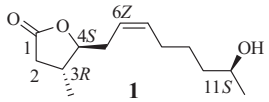
ABSTRACT

The first total synthesis of (*Z*,11*S*)-3,4-*trans*-11-hydroxy-3-methyldodec-*cis*-6-en-4-olide and (*Z*)-3,4-*trans*-11-oxo-3-methyldodec-*cis*-6-en-4-olide was accomplished using Jacobsen hydrolytic kinetic resolution, Ohira–Bestmann reaction, regioselective alkyne addition to terminal carbon atom of epoxide, intramolecular TEMPO/BAIB mediated oxidative lactonization and partial hydrogenation as the key steps.

The synthesis of substituted γ-butyrolactones generated considerable interest in the past few decades since γ-butyrolactones constitute an important structural motif in a number of bio-active natural products.[1] Very recently, Liu and co-workers isolated four new 13-carbon γ-lactone containing natural products from the cultures of the basidiomycetes family, *Trichaptum pargamenum*.[2] The mushroom *T. pargamenum* fungus is active against fungal, bacterial and cancer diseases. The chemical structures of the four new butyrolactone target molecules (Fig. 1) are endowed with the same 3-methyl γ-lactone moiety albeit connected by different *Z*-alkenyl substituents at C4 of the ring. Inspired by these interesting structural features and attractive bio-activity profile herein we describe the first total synthesis of γ-lactones **1** and **2**.

Retrosynthetic analysis (Scheme 1) suggests that compounds **1** and **2** could be obtained from the coupling of two fragments **10** and **13** to furnish the advanced intermediate **14** which on deprotection followed by intramolecular oxidation/cyclization leads to the lactone intermediate **16**. Conventional transformations of **16** would result in the target molecules, first to compound **1** and then to compound **2**. In turn, the acetylenic fragment **10** was synthesized from commercially available hex-5-en-1-ol, while the epoxy fragment **13** was synthesized from the known epoxy alcohol **11**[3] by employing a few chemical transformations.

Scheme 2 depicts the synthesis of acetylenic fragment **10** and it was accessed from the commercially available hex-5-en-1-ol. Accordingly, when hex-5-en-1-ol was treated with *p*-anisyl alcohol and Amberlyst-15 using reported procedure[4] it gave the PMB-ether **5** (85%). Subsequently, *m*-CPBA epoxidation of compound **5** followed by Jacobsen's hydrolytic kinetic resolution[5] using (*R*,*R*)-(salen)Co^{III}-OAc catalyst **A** afforded chiral epoxide **6**[6] (38% over two steps). The spectral data and optical rotation of compound **6**

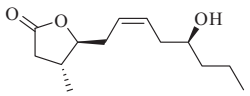


(6*Z*,11*S*)-3,4-*trans*-11-hydroxy-3-methyl dodec-*cis*-6-en-4-olide (lit.)[2]

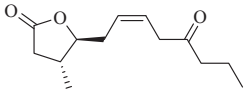
(6*Z*,11*S*)-3,4-*trans*-11-oxo-3-methyl dodec-*cis*-6-en-4-olide (lit.)[2]

(*Z*,11*S*)-3,4-*trans*-11-hydroxy-3-methyl dodec-*cis*-6-en-4-olide (revised)[14]

(*Z*)-3,4-*trans*-11-oxo-3-methyl dodec-*cis*-6-en-4-olide (revised)[14]



(*Z*,11*S*)-3,4-*Trans*-9-hydroxy-3-methyl dodec-*cis*-6-en-4-olide (**3**)



(*Z*)-3,4-*Trans*-9-oxo-3-methyl dodec-*cis*-6-en-4-olide (**4**)

Figure 1. Structures of γ-butyrolactones.

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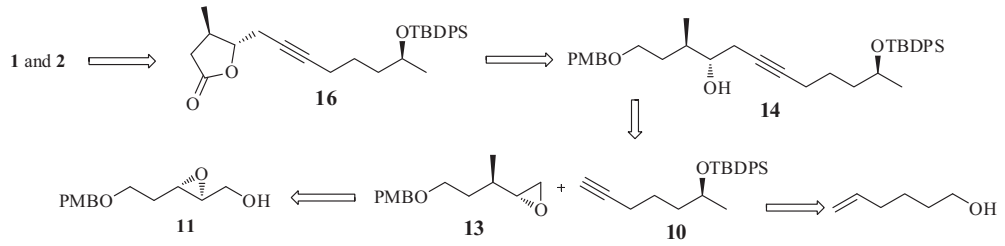
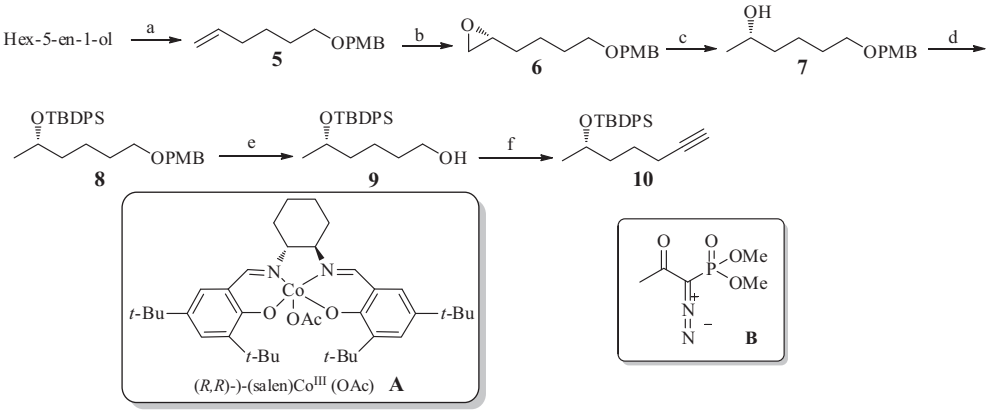


Scheme 1. Retrosynthesis of γ-lactones **1** and **2**.



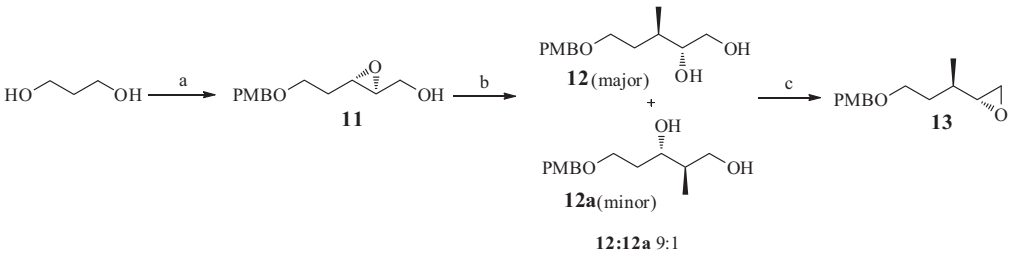
Scheme 2. Reagents and conditions: (a) *p*-anisyl alcohol, Amberlyst-15, CH_2Cl_2, reflux, 5 h, 85%; (b) (i) m-CPBA, $CHCl_3$, 0 °C, 3 h, (ii) (*R*,*R*)-salen-Co^{III}(OAc)-A (0.5 mol %), 0.55 equiv H_2O, 0 °C, 24 h, 38% (over two steps); (c) LAH, THF, 0 °C to rt, 3 h, 89%; (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 2 h, 94%; (e) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C to rt, 1 h, 90%; (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, (ii) **B**, K_2CO_3, MeOH, rt, 4 h, 80% (over two steps).

were in good agreement with reported values. (Optical rotation of synthetic **6** $[\alpha]_D^{25}$ +3.8 (*c* 1.0, $CHCl_3$) reported lit.[6] $[\alpha]_D^{25}$ +4.1 (*c* 1.0, $CHCl_3$).) Next, reductive epoxide ring-opening reaction with hydride ($LiAlH_4$/THF/0 °C to rt) furnished the secondary alcohol **7** (89%). Compound **7** on silylation (TBDPSCl/imidazole/CH_2Cl_2) gave fully protected compound **8** (94%). Oxidative deprotection of *p*-methoxybenzyl ether **8** with DDQ afforded primary alcohol **9** (90%). Finally oxidation of alcohol **9** under Swern conditions followed by one carbon homologation reaction using Ohira–Bestmann reagent **B**[7] furnished the required acetylenic fragment **10**[8] (80% over two steps).

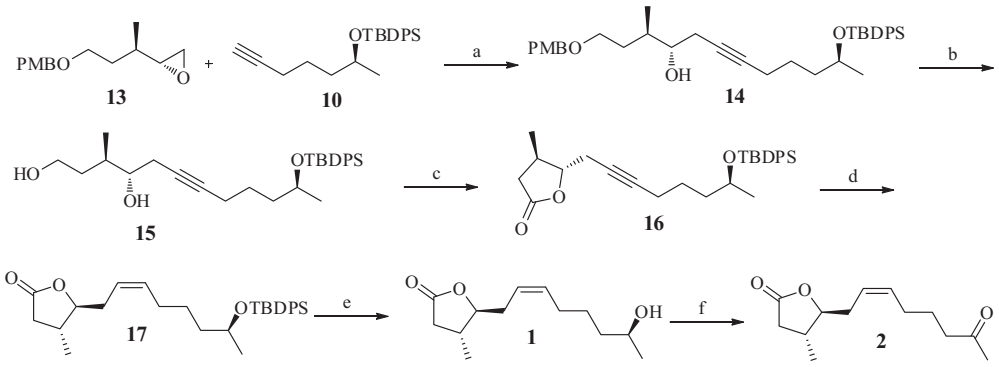
Synthesis of the other coupling partner **13** was commenced from known epoxy alcohol **11**[3] (Scheme 3). Accordingly, epoxide **11** on treatment with Me_3Al[9] resulted in the corresponding 1,2-diol (**12**) along with its regioisomer 1,3-diol (**12a**) in a 9:1 ratio as an inseparable mixture (90% combined yield). Hence, the mixture of isomeric diols 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 **13** (73% over two steps after purification by chromatography).

Next, regioselective addition of alkyne **10** (Scheme 4) to epoxide **13** under Yamaguchi conditions[10] led to the advanced intermediate **14** (74%). Oxidative deprotection of *p*-methoxybenzyl ether **14** with DDQ resulted in 1,4 diol **15** (86%). Subsequently, the diol **15** was subjected to oxidative lactonization in the presence of [bis(acetoxy)iodo]benzene/2,2,6,6-tetramethylpiperdin-1-oxyl[11] to obtain **16** (81%). Partial hydrogenation of the alkyne functionality in the γ-lactone **16** using Lindlar's catalyst[12] ($Pd/BaSO_4$-quinoline) resulted in γ-lactone **17** (88%). Finally, cleavage of the silyl ether under TBAF conditions led to the natural product **1** (90%) which was subjected to Dess–Martin periodinane oxidation to afford the natural product **2** (92%).

The structures of synthetic compounds **1** and **2** were confirmed by comparing their spectral data[2,13] (^1H and ^{13}C NMR) with the reported values and found in good agreement (see SI). However, the specific rotation of synthetic **1** observed as $[\alpha]_D^{25}$ −28.0 (*c* 0.5, MeOH) varied from the reported value of $[\alpha]_D^{25}$ +36.5 (*c* 2.08, MeOH).[2] On the other hand, when the optical rotation of synthetic **2** was checked it was found to be: $[\alpha]_D^{25}$ +16.2 (*c* 0.25, MeOH) against the reported value of $[\alpha]_D^{25}$ +19.9 (*c* 0.23, MeOH). The



Scheme 3. Reagents and conditions: (a) Ref. 3; (b) Me_3Al, CH_2Cl_2, 0 °C, 3 h, 90% (combined yield); (c) (i) TsCl, ${}^nBu_2SnO$, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, (ii) K_2CO_3, MeOH, 0 °C to rt, 5 h, 73% (over two steps).



Scheme 4. Reagents and conditions: (a) ^{n}BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 3 h, 74%; (b) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C to rt, 1 h, 86%; (c) TEMPO, BAIB, CH_2Cl_2/H_2O (1:1), 0 °C to rt, 5 h, 81%; (d) H_2/Pd-$BaSO_4$, quinoline, EtOAc, 8 h, 88%; (e) TBAF, THF, 0 °C to rt, 8 h, 90%; (f) DMP, CH_2Cl_2, 0 °C to rt, 1 h, 92%.

discrepancy in the sign of optical rotation for compound **1** may be due to an error while assigning the absolute stereochemistry at C11 of natural product, since all the asymmetric carbon atoms (C3, C4 and C11) in synthetic compounds **1** and **2** were derived from the known chiral precursors, whose chiral integrity and optical purity were unambiguously established in the literature earlier. Consequently, synthetic **1** cannot be the enantiomer of the natural product **1**. Moreover oxidation of synthetic compound **1** led to compound **2** whose spectral data (^{1}H, ^{13}C) and optical rotation were in good agreement with the reported data.

In summary, we have accomplished the first total synthesis of compounds **1** and **2** in 7.9% and 7.3% overall yields, respectively, starting from hex-5-en-1-ol using Jacobsen's kinetic resolution, regioselective alkyne addition to terminal carbon atom of epoxide, intramolecular TEMPO/BAIB mediated oxidative lactonization and Lindlar's hydrogenation as the key steps. Accordingly, compounds **1** and **2** are renamed as (*Z*,11*S*)-3,4-*trans*-11-hydroxy-3-methyldodec-*cis*-6-en-4-olide and (*Z*)-3,4-*trans*-11-oxo-3-methyldodec-*cis*-6-en-4-olide, respectively.[14]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.021.

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13. For spectral and experimental data of selected compounds see Supporting information.
14. The renaming of compounds **1** and **2** were made as suggested by reviewers.