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Stereocontrolled synthesis of (±)-methyl 3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate, a major metabolite of Caribbean sponge, *Plakortis halichondrioides*, using reactions of alkylidenecarbenes in one pot

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Abstract—(±)-Methyl (2*Z*,6*R**,8*R**,9*E*)-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate, a major metabolite of the Caribbean sponge, was synthesized in a stereocontrolled manner from γ-caprolactone. The key step was one-pot generation of alkylidenecarbenes at two sites followed by 1,2 hydride shift and intramolecular 1,5 C–H insertion.

(−)-Methyl (2*Z*,6*R*,8*R*,9*E*)-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate (**1**) was isolated as a major metabolite of *Plakortis halichondrioides* in 1980,[1] and the absolute structure was determined in 1996 by chemical degradation.[2] Although the biological activity of the ester **1** itself was not reported, plakortone E (**2**), characterized to have the same carbon framework as **1**,[3] was found to exhibit the cytotoxic activity against a murine fibrosarcoma cell line (Fig. 1).[4] The family of plakortones (A–G), isolated from the genus *Plakortis*,[4,5] shows interesting biological activities, however, the stereochemistries of most of them are unknown. Therefore, development of a general synthetic strategy for them is widely required.[3,6] With the requirement in background, we chose the ester (±)-**1** as a synthetic target, since our methodology for 5,5-disubstituted 2-furanone from a secondary alcohol[7] appeared to be applicable for the synthesis (Scheme 1).

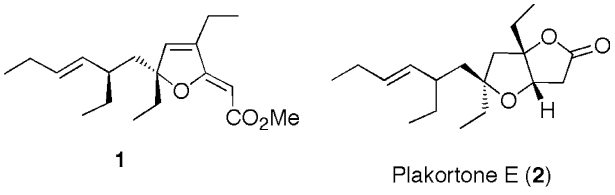
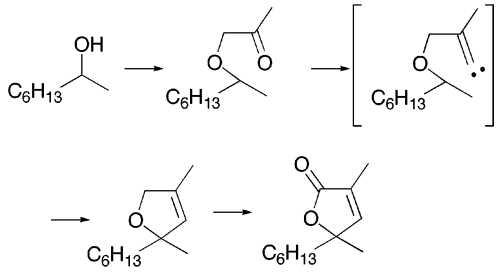


Figure 1.



Scheme 1.

Deprotonation of γ-caprolactone followed by alkylation with iodoethane in the presence of DMPU gave the substituted lactone as a 5:1 inseparable mixture of diastereomers (Scheme 2). The stereochemistry of the major product was anticipated as **3**[8] and confirmed by NMR experiments.[9] Lactone **3** was reduced with lithium aluminum hydride to diol **4**. After derivatization of **4** into bis-3,5-dinitrobenzoate **5**, the undesired diastereomer was removed by several recrystallization steps using

Keywords: (±)-Methyl (2*Z*,6*R**,8*R**,9*E*)-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate; Plakortone; Alkylidenecarbene; 1,2 Hydride shift; 1,5 C–H insertion.
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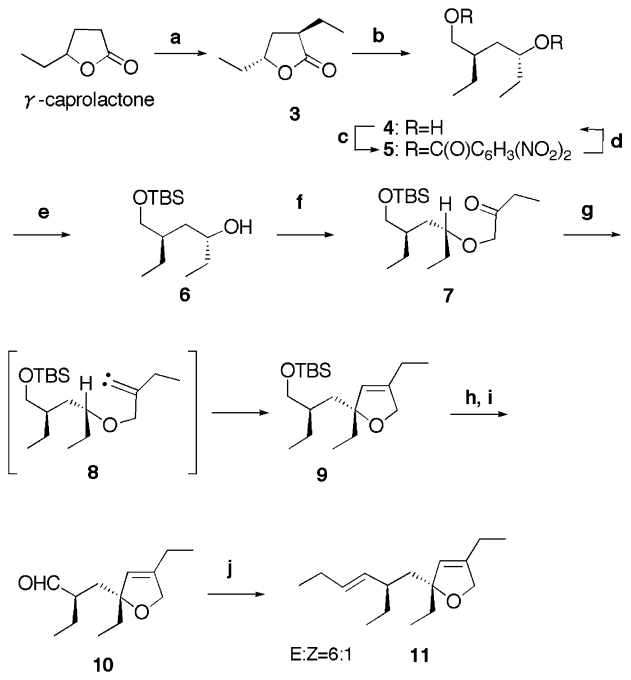
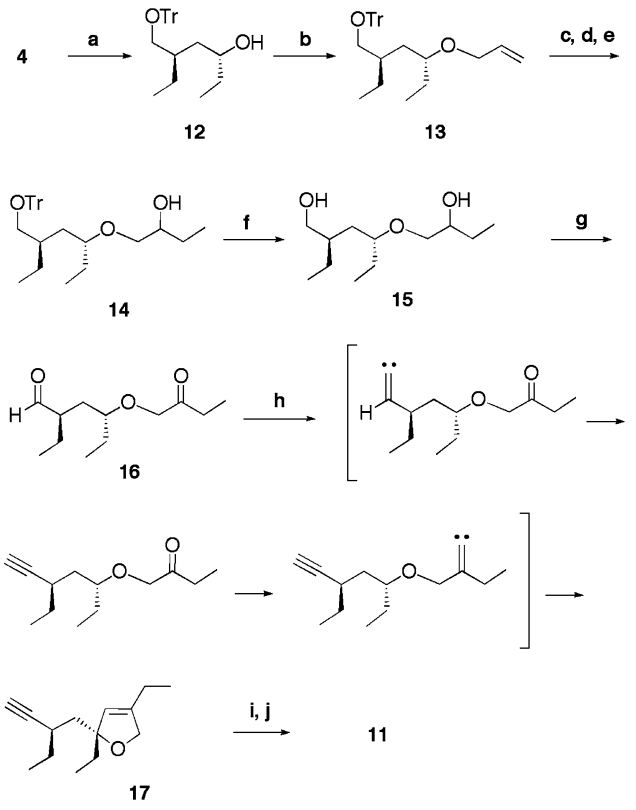


Scheme 2. Reagents and conditions: (a) LDA, EtI, DMPU, THF, −78 °C (68%); (b) $LiAlH_4$, THF, 0 °C (98%); (c) 3,5-dinitrobenzoyl chloride, DMAP, Et_3N, CH_2Cl_2, rt (quant.); (d) NaOH, MeOH, rt (98%); (e)TBSCl, imidazole, rt (80%); (f) $N_2CHCOCH_2CH_3$, $Rh_2(oct)_4$, *i*-$PrEt_2N$, CH_2Cl_2, rt (66%); (g) $TMSC(Li)N_2$, THF, 0 °C (76%); (h) TBAF, THF, rt (63%); (i) IBX, DMSO, 50 °C; (j) $Ph_3PCHCH_2CH_3$, THF, −40 °C, *n*-BuLi, *t*-BuOH (19% in two steps).



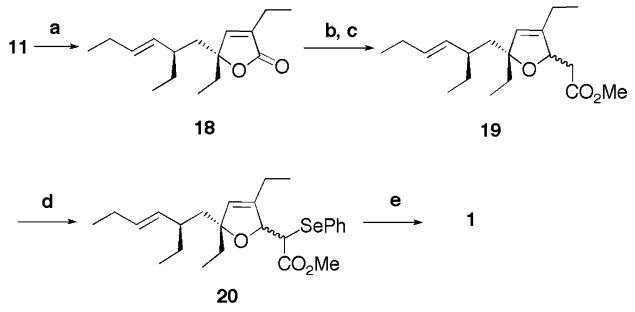
Scheme 3. Reagents and conditions: (a) TrCl, Et_3N, CH_2Cl_2, rt (92%); (b) allyl bromide, NaH, DMF, rt (91%); (c) OsO_4, NMO, THF–H_2O, rt (93%); (d) $NaIO_4$, THF–H_2O, rt; (e) EtMgBr, THF, rt (89% in two steps); (f) *p*-TsOH, MeOH, rt (83%); (g) Dess–Martin periodinane, CH_2Cl_2, rt (70%); (h) DAMP, *t*-BuOK, THF, −78 °C (69%); (i) *n*-BuLi, EtI, THF, rt (93%); (j) Na–NH_3, −30 °C (91%).

toluene–methanol (>99% de). Alkaline hydrolysis of **5** gave the pure diol **4**, whose primary hydroxyl group was protected as TBS ether. The secondary alcohol **6** was treated with 1-diazobutan-2-one in the presence of rhodium octanoate and diethylisopropylamine[10] to give keto ether **7**. Reaction of ketone **7** with lithiotrimethylsilyldiazomethane[11] in THF generated alkylidenecarbene **8** to produce dihydrofurane **9** in good yield. Removal of the silyl protecting group followed by IBX oxidation gave aldehyde **10**, which was subjected to *E* selective alkenation[12] to afford **11** as a major product.

While converting **4** to **11**, two problems were disclosed: (1) a large excess amount of explosive diazoketone and successive addition of expensive rhodium catalyst were necessary to complete the reaction from **6** to **7**, so the reaction was inappropriate for a large-scale experiment; (2) the *E* selectivity of the Wittig reaction with **10** was not high (6:1), and separation of the isomers was difficult.[13] We resolved the former problem by stepwise use of conventional good-yield reactions, and the latter by *E* selective reduction of the alkyne. Steps from **4** to **11** became longer as a result, however, the overall efficiency turned higher by using the one pot procedure to generate alkylidenecarbenes at two sites.

Primary alcohol of **4** was protected as triphenylmethyl ether (Scheme 3). Allylation of the secondary alcohol with allyl bromide in the presence of sodium hydride gave allyl ether **13** in good yield.[14] After cleavage of the double bond in **13** via dihydroxylation and glycol fission, Grignard reaction with ethylmagnesium bromide provided alcohol **14**. The triphenylmethyl group was removed under acidic conditions, and the primary and secondary alcohols in **15** were oxidized simultaneously with Dess–Martin periodinane to keto aldehyde **16**. The reaction of **16** and dimethyl diazomethylphosphonate (DAMP)[15] with *t*-BuOK proceeded cleanly in THF at −78 °C. The intermediate alkylidenecarbenes, generated from aldehyde and ketone in **16**, underwent 1,2 hydride shift and 1,5 C–H insertion, respectively, to give dihydrofurane **17**[16] in 69% yield. Only small amounts of unknown side products were observed by TLC analysis. When lithiotrimethylsilyldiazomethane was used in this conversion, the reaction was not as clean and the yield decreased to 43%. It is noteworthy that single, double and triple bonds (three σ bonds and three π bonds) were produced in this one-pot procedure. Alkylation of terminal alkyne in **17** with *n*-BuLi and iodoethane followed by reduction of the triple bond with Na–NH_3 afforded *E* alkene **11** as a sole product.

Allylic oxidation of **11** with PCC in 1,2-dichloroethane produced lactone **18** (Scheme 4). Now, the final task was to introduce a two-carbon chain into the furanone moiety. Direct conversion of **18** to **1**, using enolate anions prepared from methyl, ethyl or *t*-butyl acetates, was unsuccessful, probably due to the retro-aldol type reaction. Reduction of **18** with DIBAL followed by



Scheme 4. Reagents and conditions: (a) PCC, NaOAc, $ClCH_2CH_2Cl$, reflux (92%); (b) DIBAL, CH_2Cl_2, −78 °C; (c) $Ph_3PCHCO_2CH_3$, PhMe, reflux (79% in two steps); (d) LDA, PhSeCl, THF, −78 °C (66%); (e) 30%H_2O_2, $NaHCO_3$, THF, rt (56%).

treatment of the resultant hemiacetal with methyl (triphenylphosphoranylidene) acetate provided methyl ester **19**. Phenylselenenylation of **19** and the subsequent oxidation gave the target compound **1** as a single diastereomer. The ^1H and ^{13}C NMR spectra of the synthetic sample of **1** were identical with those of the authentic sample.[17]

In summary, we achieved an efficient and stereoselective synthesis of (±)-methyl (2*Z*,6*R**,8*R**,9*E*)-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate (**1**) in 19 steps, featuring the reactions of alkylidenecarbenes. This is the first total synthesis of **1**. Application of this study to the enantioselective total synthesis of **1** and plakortone E (**2**) is now in progress and the results will be reported in due course.

Acknowledgements

We thank Professor Abimael D. Rodríguez, University of Puerto Rico, for kindly providing us with the authentic sample of ester **1**.[1b]

References and notes

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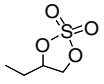
13. Yield of the Wittig reaction was also unsatisfactory, owing to unknown side reactions. Improvement of the yield and/or the stereoselectivity seemed to be not so easy, since many operations are in the procedure. We did not attempt optimization of conditions.
14. For shorter-step preparation of alcohol **14** or ketone **16**, alkylation of **12** was attempted with cyclic sulfate **21**, iodide **22**, and bromide **23**; however, sufficient yield or good reproducibility was not obtained.



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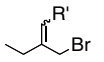

23 R' = Ph, heptyl

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16. ^1H NMR (400 MHz, $CDCl_3$): δ 5.33 (t, 1H, $J = 1.8$ Hz), 4.52 (s, 2H), 2.28–2.35 (m, 1H), 2.09 (q, 2H, $J = 7.4$ Hz), 2.01 (d, 1H, $J = 2.3$ Hz), 1.84 (dd, 1H, $J = 9.0$, 14.1 Hz), 1.67 (dd, 1H, $J = 3.4$, 14.1 Hz), 1.40–1.61 (complex m, 4H), 1.11 (t, 3H, $J = 7.6$ Hz), 1.00 (t, 3H, $J = 7.6$ Hz), 0.83 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.2, 11.5, 12.1, 20.2, 28.6, 29.4, 33.9, 45.2, 68.9, 77.5, 89.5, 93.5, 123.7, 142.0.
17. ^1H NMR (400 MHz, $CDCl_3$): δ 6.18 (br s, 1H), 5.23 (dt, 1H, $J = 6.3$, 15.0 Hz), 5.03 (dd, 1H, $J = 8.0$, 15.0 Hz), 4.80 (s, 1H), 3.69 (s, 3H), 2.13 (m, 2H), 1.94 (complex m, 3H), 1.88 (q, 1H, $J = 7.4$ Hz), 1.73 (complex m, 4H), 1.36 (m, 1H), 1.15 (t, 3H, $J = 7.4$ Hz), 0.95 (t, 3H, $J = 7.4$ Hz), 0.78 (t, 3H, $J = 7.4$ Hz), 0.77 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 7.9, 11.6, 11.8, 14.2, 18.6, 26.0, 29.7, 32.5, 39.9, 43.7, 50.3, 84.6, 97.2, 131.9, 134.5, 139.5, 139.7, 166.3, 171.6.