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Approaches towards the total synthesis of carolacton: synthesis of C1–C16 fragment

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ABSTRACT

A stereoselective synthesis of the C1–C16 segment of biofilm inhibitor carolacton has been achieved. The synthetic strategy involves Sharpless asymmetric epoxidation, Roush crotylation, Steglich esterification, RCM reaction and selective reduction of a disubstituted olefin in the presence of a trisubstituted olefin using in situ generated diimide.

Introduction

Kirschning and Müller discovered carolacton **1** from the extract of a *Sorangium cellulosum* strain So ce96[1] in 2010. Carolacton **1** has shown high antibacterial activity against biofilms of *Streptococcus mutans*. **1** also exhibited an activity against the antibiotic-sensitive *Escherichia coli* strain *tolC*, (MIC 0.06 μg/mL), besides minor antifungal activity[2] and other applications.[3] Since the antibiotic resistance of bacteria in biofilms is found to be approximately 1000-fold higher than in planktonic form, there is an urgent need to develop new methods or tools to selectively destroy clinically relevant biofilms.[4]

Carolacton **1** is a 12-membered macrolide containing 8-stereogenic centres in addition to *trans*-1,2-diol moiety at C17–C18 in an open-chain conformation. It has a *trans* double bond at C15–C16 and a trisubstituted olefin with *E*-configuration at C7–C8. Besides the 12-membered macrolactone ring, **1** has a side chain (C1–C8) containing three stereocentres at C3, C4 and C6, a keto carbonic acid. So far two groups have reported[5] the total synthesis of carolacton, while two other groups reported[6] the synthesis of fragments of carolacton. Recently our group reported[7] the syntheses of macrolactone moiety of **1**, constituting the C7–C19 core. In continuation with our efforts on the total synthesis of **1**, herein we present our studies on the synthesis of C1–C16 fragment of **1**.

Results and discussion

Retrosynthetically, carolacton would be obtained via the cross metathesis (CM) of known 1,1-disubstituted olefin **2** (C7–C19) and terminal olefin **3** (C1–C7). Fragment **3** was prepared from a sequence of oxidation/Roush crotylation of alcohol **4**. A series of hydroboration and protecting group manipulations would give alcohol **4** from olefin **5**, which in turn was obtained from the corresponding Roche ester **6** (Scheme 1).

The known alcohol **7**,[8] on oxidation under Swern reaction and the Wittig reaction in refluxing benzene for 30 min afforded ester **8** in 93% yield (Scheme 2).

DIBAL-H reduction of **8** in CH_2Cl_2 at 0 °C for 1 h furnished the alcohol **9** in 82% yield. Sharpless asymmetric epoxidation of allylic alcohol **9** with (+)-DIPT, $Ti(O^iPr)_4$ and cumene hydroperoxide at −20 °C for 12 h gave epoxide **10** in 81% yield. Alcohol **10** was converted to the corresponding iodide **10a** using imidazole, Ph_3P and I_2[9] in THF at 0 °C–rt for 15 min (94% yield), which on reaction with NaI and zinc dust[10] in MeOH at reflux for 2 h furnished allylic alcohol **11** in 79% yield. Treatment of **11** with MeI and NaH in THF at 0 °C to room temperature for 4 h gave methyl ether **5** in 91% yield.

Hydroboration of terminal olefin **5** with 9-BBN[11] in THF afforded the alcohol **12** (72%), which on treatment with PMB-Br and NaH in THF for 6 h afforded the ether **13** in 80% yield. Deprotection of silyl ether **13** using TBAF at 0 °C to room temperature for 3 h gave alcohol **4** in 78% yield, which on subjected to Swern reaction conditions gave aldehyde **4a**. Roush crotylation[12]

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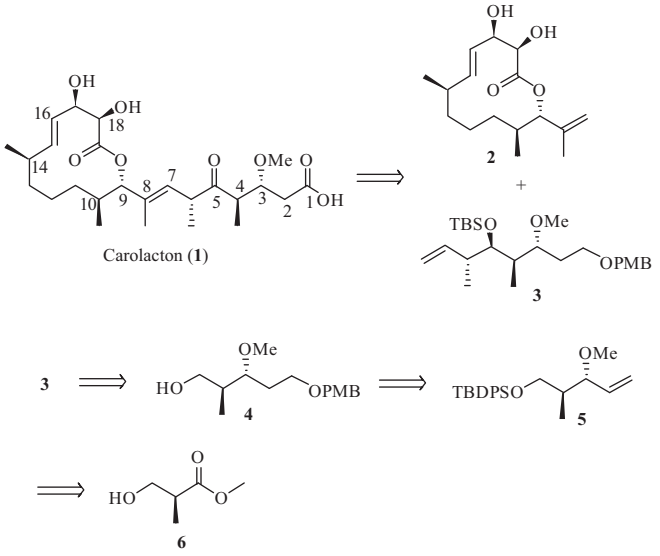
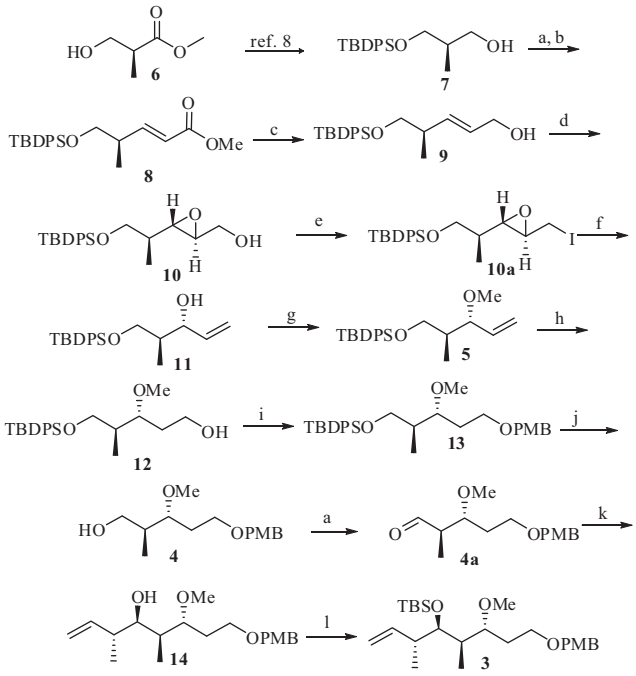


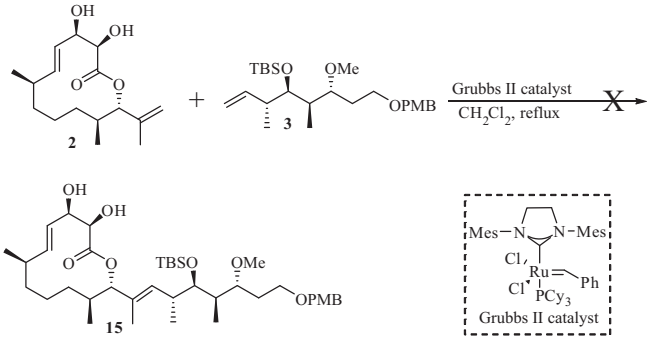
Scheme 1. Retrosynthetic analysis of carolacton **1**.



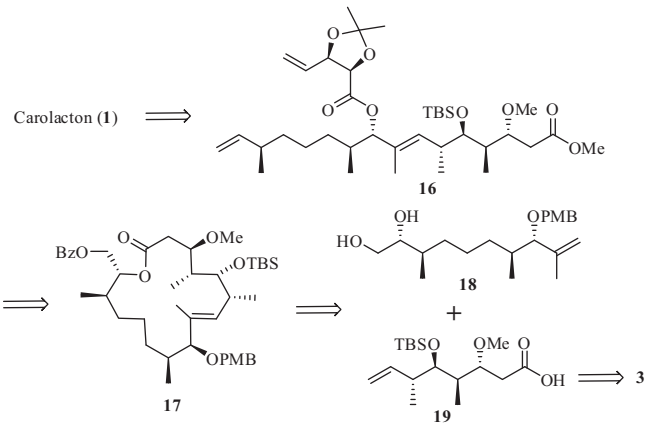
Scheme 2. Synthesis of segment **3**. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h and then Et_3N; (b) $Ph_3P{=}CHCOOMe$, benzene, reflux, 30 min, 93%; (c) DIBAL-H, CH_2Cl_2, 0 °C–rt, 1 h, 82%; (d) (+)-DIPT, $Ti(O^iPr)_4$, cumenehydroperoxide, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 12 h, 81%; (e) imidazole, Ph_3P, I_2, 0 °C–rt, THF, 15 min, 94%; (f) NaI, Zinc dust, MeOH, reflux, 2 h, 79%; (g) MeI, NaH, THF, 0 °C–rt, 4 h, 91%; (h) (i) 9-BBN, THF; (ii) 4 N NaOH, 30% H_2O_2, THF, 0 °C–rt, 7 h, 72%; (i) NaH, PMBBr, THF, 0 °C–rt, 6 h, 80%; (j) TBAF, THF, 0 °C–rt, 3 h, 78%; (k) (i) *trans*-2-butene, KO^{t}Bu, *n*-BuLi, $B(O^iPr)_3$, THF then 1 N HCl, (−)-DIPT; (ii) 4 Åmolecular sieves, toluene, −78 °C, 8 h, 84%; (l) TBSOTf, 2,6-lutidine, 0 °C–rt, 2 h, 91%.

of aldehyde **4a** using in situ generated (*E*)-crotyl boronate, generated from *trans*-2-butene, KO*t*-Bu, *n*-BuLi, $B(O^iPr)_3$ and (−)-DIPT, afforded the alcohol **14** exclusively in 84% yield. Silylation of **14** with TBSOTf and 2,6-lutidine in CH_2Cl_2 for 2 h furnished ether **3** in 91% yield.

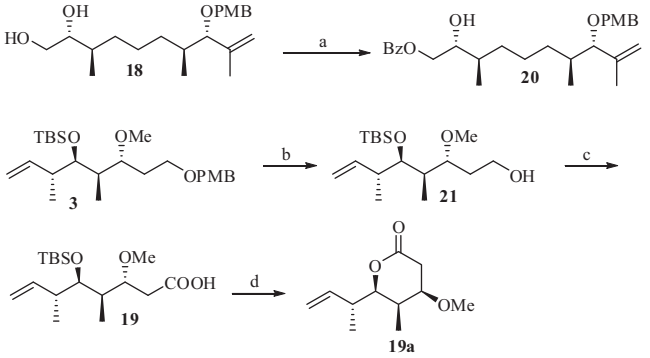
According to the retrosynthetic strategy, introduction of the trisubstituted olefin (C7–C8) accomplished by subjecting **2** and **3** to cross metathesis[13] (Scheme 3) by using Grubbs II catalyst in



Scheme 3. Synthesis of segment **15**.



Scheme 4. Retrosynthetic analysis of carolacton **1**.



Scheme 5. Synthesis of **19a**. Reagents and conditions: (a) BzCl, Bu_2SnO, Et_3N, CH_2Cl_2, rt, 30 min, 81%; (b) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C–rt, 1 h, 97%; (c) TEMPO, BAIB, CH_2Cl_2/H_2O (1:1), 0 °C–rt, 1.5 h, 74%; (d) 1 N HCl, MeOH, rt, 1.5 h, 85%.

CH_2Cl_2 was unsuccessful to provide **15** at room temperature as well as at reflux temperature.

After failing to obtain tri-substituted olefin **15** via Grubbs cross metathesis reaction, a new route was envisioned. It was proposed to create a segment with trisubstituted double bond (C7–C8) by RCM reaction.[14] Thus, in a new retroanalysis, by two iterative esterifications and RCM reactions, **1** was envisaged from **16** by RCM reaction, while **16** in turn would be synthesized from the lactone **17**, which in turn could be realized from known diol **18**[7] and acid **19** by esterification and RCM. **19** in turn was planned from **3** (Scheme 4).

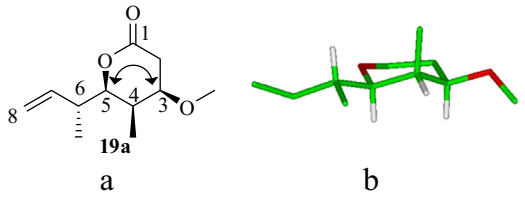
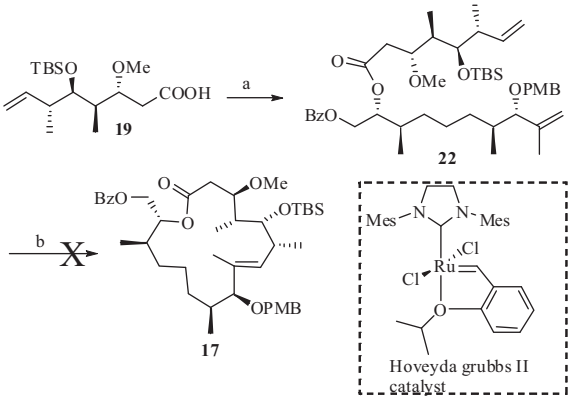


Figure 1. (a) The NOE correlation between C3-H/C5-H of **19a**, (b) energy minimized structure of **19a**.



Scheme 6. Synthesis of segment **17**. Reagents and conditions: (a) **23**, DCC, DMAP, CH_2Cl_2, 0 °C–rt, 12 h, 69%; (b) Grubbs II generation catalyst, CH_2Cl_2/toluene, reflux or Hoveyda Grubbs II generation catalyst, CH_2Cl_2/toluene, reflux.

Accordingly, known diol **18** on mono benzoylation with benzoyl chloride, Bu_2SnO and Et_3N in CH_2Cl_2 at room temperature for 30 min furnished benzoate **20** in 81% yield (Scheme 5). For the synthesis of acid **19**, compound **3** was treated with DDQ in CH_2Cl_2/H_2O (19:1) at room temperature for 1 h to afford alcohol **21** (97%), which upon oxidation using TEMPO and iodobenzene diacetate[15] in CH_2Cl_2/H_2O (1:1) at room temperature for 1.5 h furnished acid **19** in 74% yield.

To establish the configuration in **19**, the acid treated with 1 N HCl in MeOH gave lactone **19a** (85%) by a concomitant desilylation and lactonization reaction. The structure of **19a** was established by ^1H NMR (500 MHz, $CDCl_3$) data and assignments were made using TOCSY and NOESY experimental data. The characteristic NOE correlation between C3-H/C5-H in **19a** [Fig. 1a] suggested that both protons are 1,3-diaxial. The energy minimized structure as shown in Figure 1b is also in agreement with the assigned structure from NMR data.

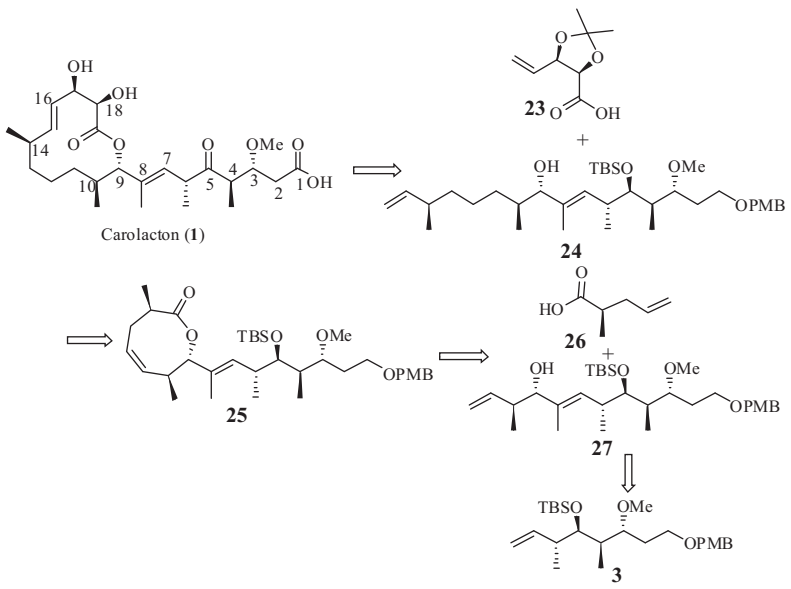
Further, Steglich esterification of acid **19** with alcohol **20** using DCC and DMAP in CH_2Cl_2 at room temperature for 12 h furnished bis-olefin **22** in 69% yield (Scheme 6). However, diene **22** on treatment either with Grubbs II generation catalyst or with Hoveyda–Grubbs II generation catalyst in CH_2Cl_2 as well as in toluene at reflux for 12 h failed to give the required lactone **20**. Having been unsuccessful in introducing the trisubstituted olefin at the C7–C8 position, we sought to perform a Wittig olefination to overcome the unreactivity.

According to the modified retroanalysis (Scheme 7), **1** could be obtained from acid **23**[7] and alcohol **24**, while **24** in turn could be synthesized from the eight membered lactone **25**. Esterification of acid **26** with alcohol **27** and followed by RCM of the resulting ester would give **25**, while **27** would be synthesized from **3**.

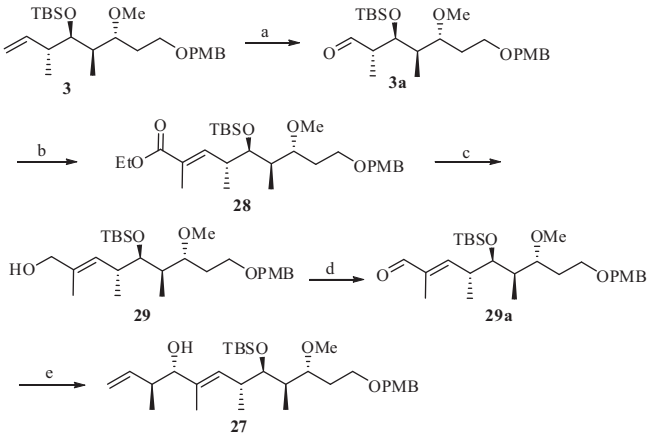
Accordingly, olefin **3** subjected to ozonolysis[16] in CH_2Cl_2 at −78 °C for 15 min gave aldehyde, which on treatment with $Ph_3P{=}C(Me)CO_2Et$[17] in refluxing benzene for 1 h afforded **28** in 90% yield (Scheme 8). Reduction of ester **28** using DIBAL-H in dry CH_2Cl_2 at 0 °C for 1 h furnished allylic alcohol **29** in 87% yield, which upon subjected to Swern oxidation gave aldehyde **29a**. Roush crotylation of **29a** using in situ generated (*E*)-crotyl boronate (generated from *trans*-2-butene, KO*t*-Bu, *n*-BuLi, $B(O^iPr)_3$ and (+)-DIPT) afforded alcohol **27** in 67% yield.

Steglich esterification of known chiral acid **26**[18] with alcohol **27** using DCC and DMAP in CH_2Cl_2 at room temperature for 12 h furnished the bis-olefin **30** in 91% yield (Scheme 9). RCM reaction of diene **30** with Hoveyda Grubbs II generation catalyst[19] in toluene at reflux for 18 h afforded eight membered lactone **25** in 35% yield. The addition of 10 equiv of 1,4-benzoquinone as additive accelerated the RCM reaction and the diene was completely consumed in 3 h to give lactone **25** in 66% yield (Scheme 9).

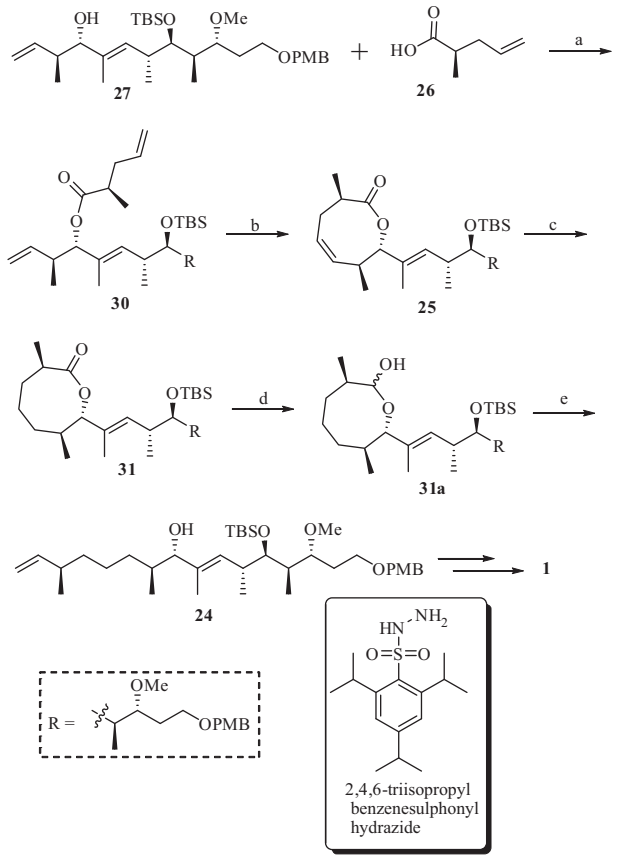
After having eight membered ring in the hand the next target was selective reduction of disubstituted olefin in the presence of a trisubstituted olefin in **25**, thermal decomposition of 2,4,6-



Scheme 7. Retrosynthetic analysis of carolacton **1**.



Scheme 8. Synthesis of segment **27**. Reagents and conditions: (a) O_3, CH_2Cl_2, Me_2S, −78 °C, 15 min; (b) $Ph_3P{=}C(Me)CO_2Et$, benzene, reflux, 1 h, 90%; (c) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 87%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (e) *trans*-2-butene, KO^{t}Bu, *n*-BuLi, B(O^{i}Pr)$_3$, 1 N HCl, (+)-DIPT, 4 Å molecular sieves, toluene,−78 °C, 7 h, 67%.



Scheme 9. Synthesis of **24**. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C–rt, 12 h, 91%; (b) Hoveyda Grubbs II Generation catalyst, 1,4-benzoquinone, toluene, reflux, 3 h, 66%; (c) 2,4,6-triisopropylbenzenesulphonyl hydrazide, Et_3N, 1,2-dichloro ethane, 60 °C, 65%; (d) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 90%; (e) PPh_3–CH_3Br, *n*-BuLi, THF, 0 °C–rt, 3 h, 55%.

triisopropylbenzenesulfonyl hydrazide[20] in the presence of Et_3N in 1,2-dichloroethane at 80 °C gave the expected product **31** in 65% yield. In order to introduce the terminal olefin, lactone **31** was subjected to reduction using 1 equiv of DIBAL-H[21] in dry CH_2Cl_2 at −78 °C for 30 min to afford the lactol **31a** (90%), which on one carbon homologation by the subsequent reaction with (methylene)triphenyl phosphorane in THF at −20 °C for 3 h gave **24** in 55% yield.

Thus, the synthesis of **24** constitutes the synthesis of the C1–C16 fragment of carolacton **1**. Esterification of **24** and macrocyclization of the resulting ester followed by deprotection would give the target molecule carolacton **1**.

Conclusions

In summary, our stereoselective synthesis of the C1–C16 segment began from (*S*)-Roche ester. The synthetic strategy involved Sharpless asymmetric epoxidation, Roush crotylation, RCM reaction, Steglich esterification and diimide reduction of a disubstituted olefin in the presence of a trisubstituted olefin as the key reactions.

Acknowledgements

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Supplementary data

Supplementary data (full experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.03.002.

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