Studies Directed to the Total Synthesis of Cepacin A

Preliminary Communication

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The synthesis of the bromoallenyl-substituted epoxide derivative **34** related to cepacin A (**1**) starting from D-arabinose as a chiral pool is reported.

Cepacin A [1] (**1**; see the *Figure*) is a potent antibacterial substance produced by *Pseudomonas cepacia*, SC 11,783 (a *Gram*-negative rod, motile by means of multitrious glagella) isolated from a soil sample of West Windsor, New Jersey, USA. The structure of cepacin A was established by spectroscopic means and chemical degradations, with the allene configuration assigned on the basis of the optical rotation according to the rules of *Lowe* and *Brewster* [2].

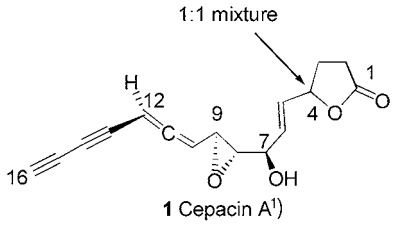


Figure. *The structure of natural cepacin A* (**1**)

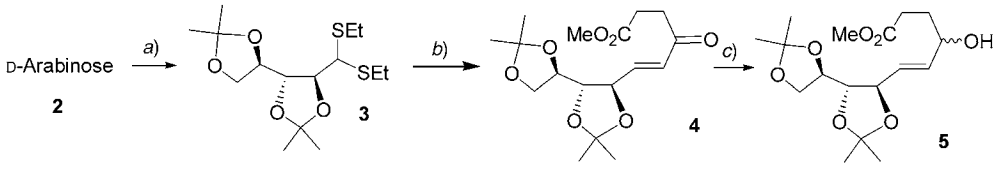
The structure of cepacin A (**1**) is completely different from those of the existing antibacterial drugs. Therefore, the investigation on this type of compounds might eventually lead to effective agents against the bacteria resistant to the existing drugs. The combination of the architectural complexity and the potential prospect as a new antibacterial agent make cepacin A (**1**) an attractive target for synthetic endeavors. Disclosed below are some of our efforts directed towards the total synthesis of **1**. Our synthesis tries to make full use of all chiral C-atoms of D-arabinose to construct the C(6)–C(10) moiety of cepacin A (**1**)[1]). The lactone part C(1)–C(5) was planned to be derived from levulinic acid (=4-oxopentanoic acid), while the dialkynyl group

[1]) Arbitrary numbering; the systematic name of cepacin A (**1**) is 5-{3-[3-(hepta-1,2-diene-4,6-diynyl)oxiranyl]-3-hydroxyprop-1-enyl}-4,5-dihydrofuran-2(3*H*)-one.

(C(13)–C(16)) should be introduced at a later stage *via* a coupling reaction with a bromoallene.

As shown in *Scheme 1*, D-arabinose was converted to dithioacetal **3** in 72% overall yield by known transformations [3]. The dithioacetal protecting group was hydrolyzed with $HgCl_2$ and HgO [4] (80% yield). The intermediate aldehyde was directly treated with $Ph_3P{=}CHCO(CH_2)_2CO_2Me$ to give **4**, the reagent being prepared from levulinic acid *via* bromination with Br_2 in MeOH [5] and subsequent treatment of the resulting methyl 5-bromolevulinate with Ph_3P in refluxing benzene followed by deprotonation with aq. Na_2CO_3 solution [6]. Reduction of the ketone carbonyl group of **4** with $NaBH_4$ in MeOH at 0° afforded alcohol **5** (diastereoisomer mixture) in 80% yield.

Scheme 1

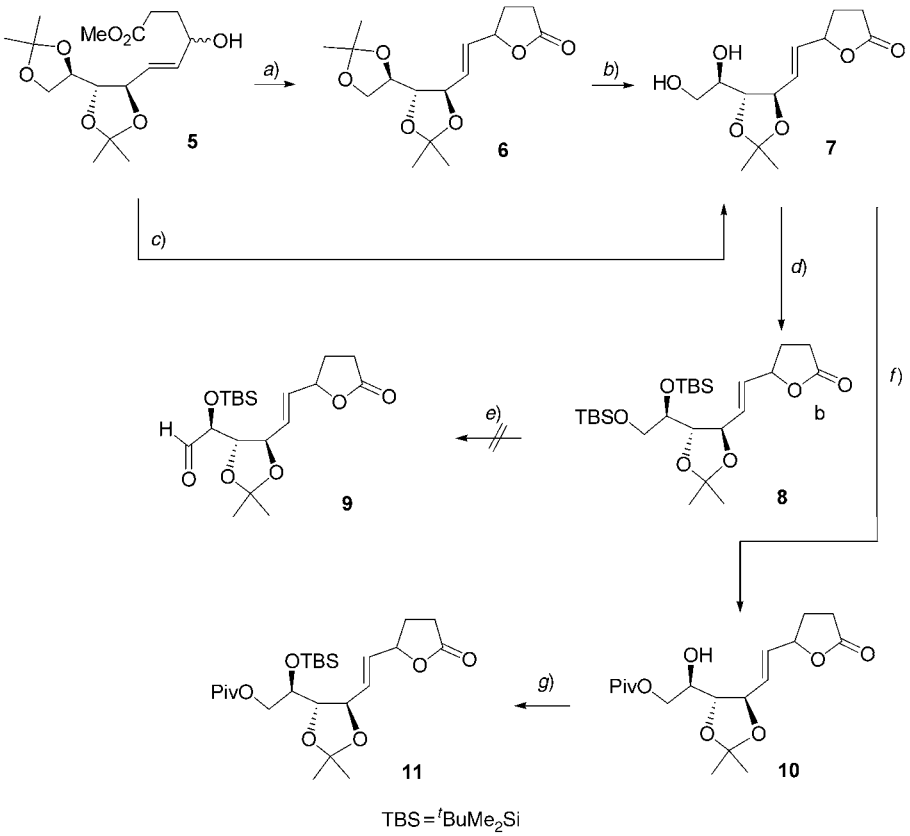


a) 1. EtSH, 6N HCl; 78%; 2. Me_2CO, conc. H_2SO_4; 92%. *b*) 1. $HgCl_2$, HgO (red), $MeCN/H_2O$; 80%; 2. $Ph_3P{=}CHCO(CH_2)_2CO_2Me$, toluene, reflux; 91%. *c*) $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, MeOH; 80%.

Treatment of **5** with catalytic amounts of TsOH in anhydrous acetone under reflux led to the formation of the lactone ring (*Scheme 2*). Partial hydrolysis of **6** under the conditions of *Xiao* and *Bai* [7] gave the desired diol **7** (mixture of diatereoisomers with respect to C(4)) in 40% yield. Later, we found that if MeOH was used as solvent, the lactonization and selective hydrolysis of the terminal acetonide moiety could be realized in a one-pot manner in *ca*. 64% yield. The diol moiety of **7** was protected as (*tert*-butyl)dimethylsilyl (^{t}BuMe$_2$Si) ether with the hope that selective oxidation of the primary silyl ether group of **8** with quinolinium fluorochromate (QFC) as reported by *Murugensan* and *Pandurangan* [8] would afford the desired aldehyde **9**. Unfortunately, this reagent did not work in our case. A longer reaction sequence was then attempted. First, the primary OH group of **7** was masked as pivaloyl (Piv) ester ($\rightarrow$**10**). Subsequent protection of the secondary OH group as a silyl ether ($\rightarrow$**11**), however, suffered seriously from low yields. These results incited us to search for better alternatives.

The route shown in *Scheme 3* appeared to work nicely all the way to aldehyde **9**. The treatment with $CeCl_3 \cdot 7\,H_2O$ and $(CO_2H)_2$ in MeCN [7] was much more effective on **3** than on **6**, giving the corresponding diol in 92% yield. The primary and secondary OH groups were readily protected as Piv ester ($\rightarrow$**12**) and silyl ether, respectively, yielding the fully protected intermediate **13**. The subsequent $HgCl_2$/HgO-mediated hydrolysis smoothly cleaved the dithioacetal to give the corresponding aldehyde. Further treatment with the *Wittig* reagent used before afforded ketone **14** in 94% yield. Reduction of **14** with $NaBH_4$ in MeOH at 0° yielded alcohol **15** as a mixture of two epimers, which (unlike **5**) could be separated from each other after repeated chromatography (SiO_2, CH_2Cl_2/AcOEt). One of the epimers of **15** (of unknown configuration at C(4)[1])) was stirred in refluxing benzene in the presence of traces of

Scheme 2

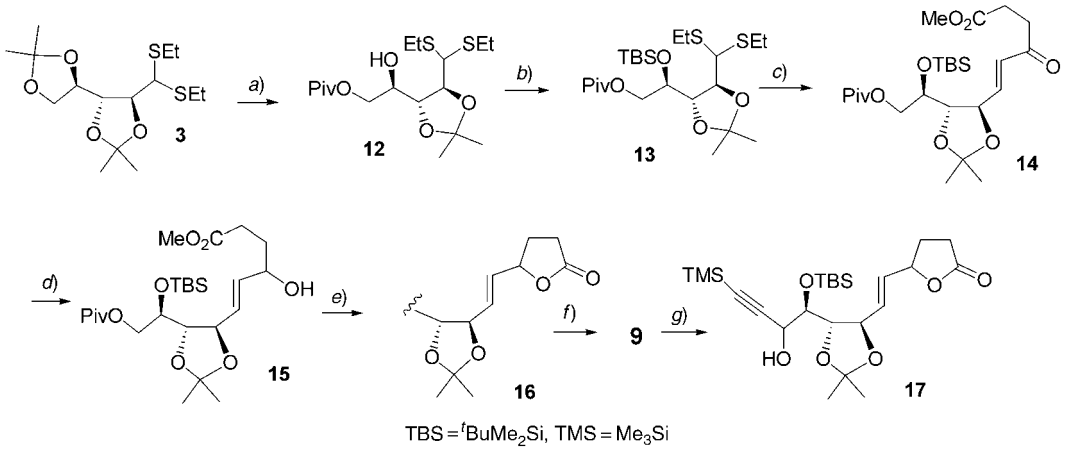


a) TsOH, Me_2CO, reflux; 70%. *b*) $CeCl_3 \cdot 7\,H_2O$, $(CO_2H)_2$, MeCN; 40%. *c*) TsOH, MeOH, reflux; 64%. *d*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, *N*,*N*-dimethylpyridin-4-amine (DMAP), DMF; 54%. *e*) Quinolinium fluorochromate (QFC). *f*) PivCl, Et_3N, CH_2Cl_2; 58%; *g*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, DMF; 52%.

pyridinum *p*-toluenesulfonate (PPTS) [9] leading to lactone **16** in quantitative yield. With the lactone moiety satisfactorily established, we directed our attention again to the other terminus of the C-chain. Cleavage of the Piv ester was rather difficult. Base-catalyzed hydrolysis (NaOMe or ^{t}BuOK in the corresponding alcohol) failed to result in a clean reaction. Finally, the Piv protecting group was removed by a diisobutylaluminium hydride (DIBAL-H) reduction, with concurrent partial reduction of the lactone to a hemiacetal. Oxidation of the hemiacetal back to the lactone and of the primary OH group into an aldehyde was realized by pyridinium chlorochromate (PCC) oxidation ($\rightarrow$ **9**). The yield of this step was, however, only 50%. Subsequent addition of the acetylide to aldehyde **9** to give **17** did not proceed as well either. It appeared to us that the sluggish reaction was caused by the serious steric crowding associated with the ^{t}BuMe$_2$Si group.

To reduce the steric hindrance near the aldehyde group, we next chose to mask the secondary OH group of **12** as a triethylsilyl (Et_3Si) ether ($\rightarrow$ **18**; *Scheme 4*). With the

Scheme 3



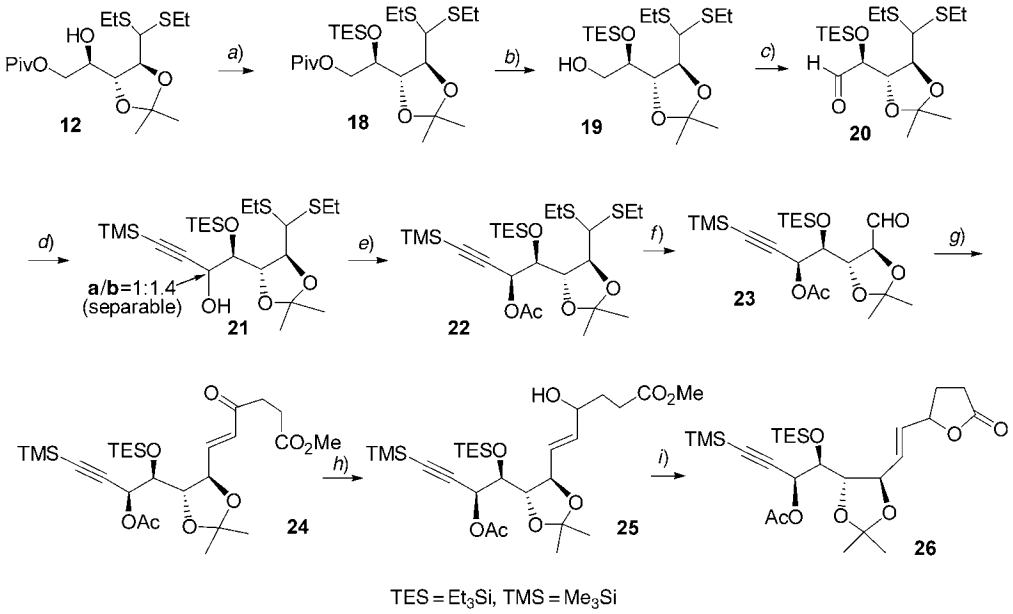
a) 1. $CeCl_3 \cdot 7\ H_2O$, $(CO_2H)_2$, MeCN; 92%; 2. PivCl, Et_3N, CH_2Cl_2; 77%. *b*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, DMF; 95%. *c*) 1. $HgCl_2$, HgO (yellow), MeCN/H_2O; 2. $Ph_3P{=}CHCO(CH_2)_2CO_2Me$, toluene, reflux; 94% from **13**. *d*) $NaBH_4$, MeOH; 71%. *e*) PPTS, PhH, reflux; 100%. *f*) 1. DIBAL-H, CH_2Cl_2, $-78°$; 95%; 2. PCC, NaOAc, CH_2Cl_2; 50%. *g*) $Me_3SiC{\equiv}CLi$, THF, $-78°$; 40%.

hope to avoid the undesired lactone reduction encountered with **16** during the Piv removal, we decided to cleave the Piv protection group at an earlier stage. Thus, reaction of **18** with DIBAL-H at $-78°$ led to **19** in 91% yield. By using $SO_3 \cdot Py$ [10] (which was much superior to other oxidants when substrates contained low-valent S-atoms), the primary alcohol **19** was readily oxidized to give aldehyde **20**. With the ^{t}BuMe$_2$Si group replaced by the smaller Et_3Si group, the addition of the acetylide now indeed proceeded smoothly, giving **21** in *ca.* 81% yield as a mixture of two epimers (**21a**/**21b** 1.4 : 1, separable by chromatography (SiO_2)). One of the isomers (later shown to be **21b** with (*S*)-configuration[2]) at the new stereogenic center) was converted into **22** with the intention to test later whether acetate could also serve as a leaving group in the bromoallene-formation step. The allene configuration was controlled by the propargylic OH group. Because much work had been done by the time when the configuration of the isomer that we picked at random was established to be 'wrong', and the allene isomer of cepacin was also one of the desired analogues for biological testing, we went on with **21b**.

Hydrolysis of the dithioacetal moiety of **22** was achieved most satisfactorily with I_2 and $NaHCO_3$ in acetone/H_2O at 0° [11] ($\rightarrow$**23**). The lactone moiety was then introduced *via* **24** and **25** by the same methodology as employed before. To simplify the spectra of the intermediates, we tried to use the *CBS* reagent (=(*S*)-*B*-methyloxazaborolidine/borane = (3a*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-[1,3,2]oxazaborole/borane; *CBS* = *Corey–Bakshi–Shibata*) [12] instead of $NaBH_4$ to stereoselectively reduce the ketone carbonyl group of **24**, although this was not

[2]) The configuration was established by a NOESY experiment with a sample prepared from **21** by removal of the Et_3Si group and protecting the two OH groups as an acetonide.

Scheme 4



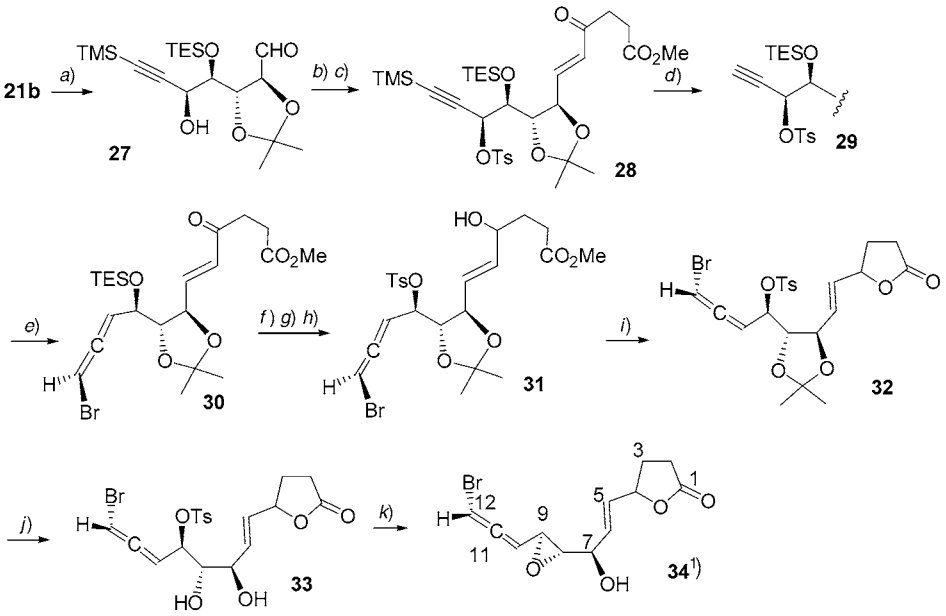
a) Et_3SiCl, 1*H*-imidazole, DMF, r.t.; 90%. *b*) DIBAL-H, CH_2Cl_2, −78°; 91%. *c*) $SO_3 \cdot Py$, $^iPr_2NEt$, DMSO/CH_2Cl_2 1:1, 0° to r.t.; 82%. *d*) $Me_3SiC{\equiv}CLi$, THF, −78°; 81%. *e*) Ac_2O, Et_3N, CH_2Cl_2, r.t.; 82%. *f*) I_2, $NaHCO_3$, Me_2CO/H_2O 5:1, 0°; 79%. *g*) $Ph_3P{=}CHCO(CH_2)_2CO_2Me$, toluene, reflux; 83%. *h*) BH_3/(*S*)-*B*-methyloxazaborolidine [12], 0°; 61%. *i*) PPTS, PhH, 40°; 59%.

necessary, the natural cepacin A (**1**) being a 1:1 epimer mixture with respect to this new stereogenic center. A single isomer **25** of undetermined configuration was obtained in 61% yield (along with some unreduced **24**). Unfortunately, the PPTS-catalyzed lactonization of **25** to **26** occurred in only moderate yield (59%) (*cf.* **5** → **6** and **15** → **16**). But by that time, our synthesis along another route (*Scheme 5*) carried out in parallel to that shown in *Scheme 4* proceeded very well and, therefore, no further attempts were made to carry on with acetate **26**.

This other route started from **21b** (*Scheme 5*). The dithioacetal moiety of **21b** was hydrolyzed with I_2 and $NaHCO_3$ as in the previous route, the formed aldehyde **27** immediately treated with $Ph_3P{=}CHCO(CH_2)_2CO_2Me$, and the propargylic OH group converted to the corresponding tosylate (→ **28**) to ensure higher reactivity in the subsequent bromoallene-formation step. The Me_3Si group at the acetylene terminus of **28** was removed with K_2CO_3 in MeOH/THF 2:1 at 0° (92%). Further treatment of propargyl tosylate **29** with anhydrous LiBr in the presence of CuBr in refluxing THF under N_2 according to the procedure reported by *Mann et al.* [13] afforded bromoallene derivative **30** in 61% yield, along with 27% of unreacted **29**. The TES protecting group was then cleaved (97%) yield, the resulting OH group was transformed into the tosylate (72%), and the ketone carbonyl group was reduced with borane/(*S*)-*B*-methyloxazaborolidine [12] to afford the hydroxy derivative **31** (of undetermined configuration; 77%). On treatment with PPTS, **31** was readily converted into lactone **32** (85%), whose

acetonide moiety was then removed by the reaction with propane-1,3-dithiol in CH_2Cl_2 with $BF_3 \cdot OEt_2$ as catalyst (69%). Finally, diol **33** was treated with K_2CO_3 in Et_2O/MeOH 50:1 to generate the bromoallenyl-substituted epoxide derivative **34**[3]) in 77% yield.

Scheme 5



a) I_2, $NaHCO_3$, Me_2CO/H_2O 5:1, 0°. *b*) $Ph_3P{=}CHCO(CH_2)_2CO_2Me$, toluene, 70–80°; 73% from **21b**. *c*) TsCl, Et_3N, DMAP, CH_2Cl_2, 0° to r.t.; 74%. *d*) K_2CO_3, MeOH/THF 2:1, 0°; 92%. *e*) LiBr, $CuBr \cdot Me_2S$, THF, reflux; 61% (84% based on consumed **29**). *f*) Bu_4NF, THF; 97%. *g*) TsCl, Et_3N, DMAP, CH_2Cl_2, 0° to r.t.; 72%. *h*) $BH_3 \cdot SMe_2$/(*S*)-*B*-methyloxazaborolidine [12] 0°; 77%. *i*) PPTS, PhH, 40–50°; 85%. *j*) $HS(CH_2)_3SH$, $BF_3 \cdot OEt_2$, CH_2Cl_2; 69%. *k*) K_2CO_3, Et_2O/H_2O 50:1; 77%.

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[3]) Data of **34**: $[\alpha]_D^{20} = -123.5$ ($c = 0.6$, $CHCl_3$). FT-IR (film): 3438, 1957, 1770, 1183 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$; δ in ppm, J in Hz[1]): 6.25 (*d*, $J = 5.7$, H–C(12)); 6.00–5.89 (*m*, H–C(5), H–C(6)); 5.16 (*dd*, $J =$ 7.9, 5.6, H–C(10)); 5.03 (*m*, H–C(4)); 4.26 (*m*, H–C(7)); 3.55 (*dd*, $J = 8.1$, 2.0, H–C(9)); 3.07 (*m*, H–C(8)); 2.62–2.54 (*m*, CH_2(2)); 2.48 (*m*, 1 H–C(3)); 2.10 (*d*, $J = 6.9$, OH); 2.05 (*m*, 1 H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$; δ in ppm[1]): 204.65 (C(11)); 176.80 (C(1)); 130.97 (C(5) or C(6)); 129.95 (C(6) or C(5)); 98.11 (C(10)); 79.49 (C(4)); 74.86 (C(12)); 69.73 (C(7)); 61.58 (C(8)); 52.00 (C(9)); 28.40 (C(2)); 28.24 (C(3)); assignments by COSY and HMQC experiments. EI-MS (*m*/*z* (%)): 161 (5.1, C(12) to C(8) fragment), 159 (5, C(12) to C(8) fragment), 142 (6), 141 (7, C(7) to C(1) fragment), 123 (10), 113 (9), 95 (30), 81 (100). HR-ESI-MS: 322.9879 ($[M + Na]^+$, $C_{12}H_{13}O_4BrNa^+$; calc. 322.9889).

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