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Tetrahedron
Tetrahedron 63 (2007) 4887–4906

On the synthesis of cepacin A

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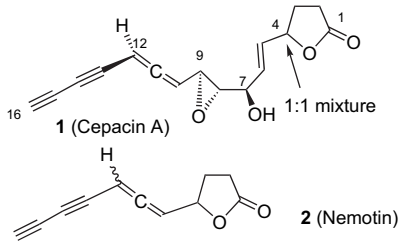
Received 29 January 2007; revised 12 March 2007; accepted 23 March 2007
Available online 25 March 2007

Abstract—Efforts directed toward a total synthesis of cepacin A is presented in full detail. The C-7, C-8, and C-9 stereogenic centers in the target molecule were derived from D-arabinose. The configuration of the allene axis was controlled at the bromoallenation step by the C-10 configuration of the precursor. An unexpected yet very interesting phenomenon was observed with the bromoallenation, where the α-isomer of the propargylic alcohol **31** was entirely resistant to the conditions that worked so well for its β-counterpart. The problem was eventually solved by careful tuning of the size of the neighboring groups based on the clue obtained from conformational analysis. The diyne moiety was incorporated into the molecular framework through a coupling of the TMS protected diyne with a proper bromoallene under the Sonogashira conditions with EtOAc as the solvent. Use of other solvents at this step led to complete failure.

1. Introduction

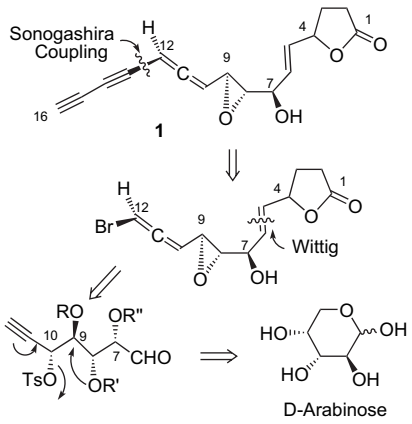
Cepacin A (**1**), a potent antibacterial substance produced by *Pseudomonas cepacia* SC 11,783, was isolated by Parker and co-workers in the 1980s.[1] By comparison of the UV and IR data with those of nemotin[2] (**2**) along with ^{1}H NMR analysis and chemical derivatization/degradation, the structure of cepacin A was proposed to be **1**. The absolute allene configuration was assigned on the basis of the optical rotation according to the rules of Lowe and Brewster.[3]



As cepacin A represents a novel type of antibacterials with an interesting structure containing a tightly packed challenging array of diyne–allene–epoxide–allylic alcohol–lactone functionalities, it makes a very attractive target for synthetic studies. Here in this article we wish to detail[4] our efforts toward synthesis of cepacin A in a hope to confirm the natural structure and find an entry to the chiral diyne–allene system.

2. Results and discussions

Our general strategy is shown in Scheme 1. Three of the four stereogenic centers (C-7, C-8, and C-9) were derived from D-arabinose, while the remainder (C-10) was intended to be created by a substrate-controlled asymmetric addition of acetylene to aldehyde. Installation of the diyne fragment was arranged at a late stage through a coupling reaction with a proper bromoallene. The stereochemistry of the allene axis was controlled by the configuration of the leaving group at the propargylic position (C-10). The lactone part was introduced through a Wittig reaction in connection with construction of the trans C=C double bond.



Scheme 1.

As in essentially all carbohydrate chiron-based syntheses, a major task in our endeavor is to differentiate the hydroxyl

Keywords: Antibiotics; Diynes; Allenes; Epoxides; Lactones.
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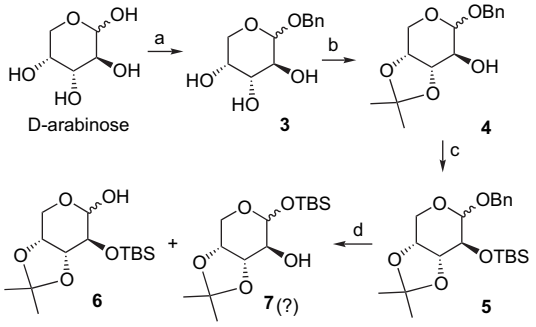
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.144

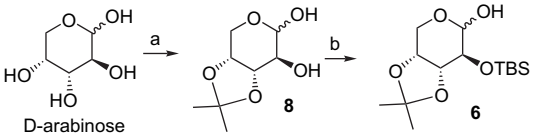
groups in the starting material. An approach (Scheme 2) in the literature[5] seemingly suitable for our purpose was then attempted.



Scheme 2. (a) $PhCH_2OH$/AcCl (cat), 84%; (b) $Me_2CO/CuSO_4$ (7.0 equiv)/concd H_2SO_4 (cat), 81%; (c) TBSCl (2.0 equiv)/imidazole/DMF/rt, 91%; (d) see the text.

Following a more recent literature procedure,[6] the hemiacetal OH in D-arabinose was replaced with a benzyl group. The resultant **3** was treated with acetone in the presence of $CuSO_4/H_2SO_4$ to yield the corresponding acetonide **4**. Protection of the hydroxyl group with TBSCl afforded **5**[5] smoothly. The final cleavage of the benzyl mixed acetal, however, did not proceed so well as expected. Catalytic hydrogenolysis over 10% Pd/C completely failed despite repeated tries. Li/naphthalene[7] system gave only a low yield (25%) of the desired **6** along with some unexpected products (seemed to be an α/β mixture of the TBS migrated product **7**).

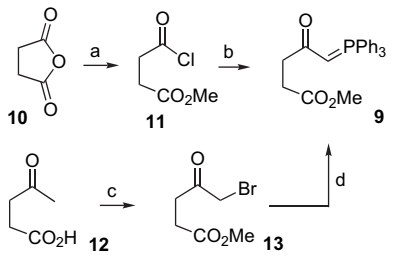
Through a more careful search of literature we then found that Kiso and Hasegawa[8] had developed a convenient procedure for making **8**. By using conventional silylation conditions we easily obtained the desired **6** (Scheme 3).



Scheme 3. (a) *p*-TsOH (cat)/$Me_2C(OMe)_2$/DMF/rt, 69%; (b) TBSCl/imidazole/DMF/rt, 60%.

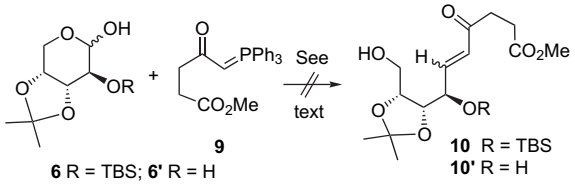
The Wittig reagent **9** needed for construction of the lactone moiety was then attempted using combinations of some known reactions (Scheme 4). We first tried to use the acid halide **11**[9] to react with $Ph_3P{=}CH_2$ as reported by Ronald and Wheeler[10] without success. Then we turned to the second route, making **9** through reaction of **13** with PPh_3.[11] Although preparation of **13** was somewhat tedious because of concurrent formation of over-brominated side products, enough amounts of **9** indeed could be obtained this way.

With both **6** and **9** in our hands, we proceeded to examine the Wittig reaction shown in Scheme 5. This was expected to be facile in the beginning as similar reactions[12] of **6** with $Ph_3P{=}CHCO_2Me$ were quite successful. However, to our surprise neither **6** nor its desilyl analogue **6′** led to the anticipated product(s). We tried many sets of reaction conditions (in CH_2Cl_2, DMF or toluene, at ambient or elevated temperatures, with or without added benzoic acid[12]) and always got



Scheme 4. (a) (i) MeOH/reflux; (ii) $SOCl_2$, 50% over two steps; (b) $Ph_3P{=}CH_2$/−78 °C to rt; (c) Br_2/MeOH/rt to reflux, 34%; (d) (i) Ph_3P/PhH/reflux; (ii) Na_2CO_3/H_2O, 59% over two steps.

either only recovered starting materials or a complicated product mixture.

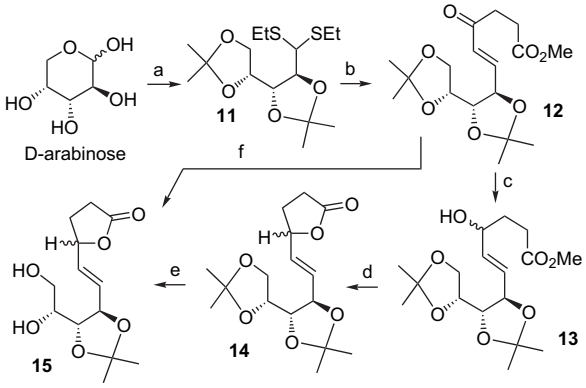


Scheme 5.

As the above failures were most likely caused by the great tendency of the aldehyde functionality to form a hemiacetal, we decided to modify our strategy of manipulating the carbohydrate chiron to avoid any possibility of cyclization to form a cyclic hemiacetal.

To this end, D-arabinose was treated sequentially with EtSH/6 N HCl and acetone/H_2SO_4 to yield **11** using a literature[13] procedure. The thioacetal protecting group was then removed with $HgCl_2/HgO$[14] (red) to free the aldehyde group. Further treatment with **9** afforded α,β-unsaturated ester **12** in 91% yield.

The ketone carbonyl group in **12** was reduced under the Luche[15] conditions ($CeCl_3/NaBH_4$), giving alcohol **13** as a mixture of the C-4 (cepacin numbering) epimers. As the epimers in this case were inseparable on silica gel, the mixture was used as such in the next step to give lactone **14**. The terminal acetonide was then selectively hydrolyzed with $CeCl_3\cdot 7H_2O/(CO_2H)_2/MeCN$[16] (Scheme 6) to yield diol **15**, paving the way for further elaborations.



Scheme 6. (a) (i) EtSH/6 N HCl, 78%; (ii) Me_2CO/concd H_2SO_4, 92%; (b) (i) $HgCl_2/HgO$ (red)/MeCN/H_2O, 80%; (ii) **9**/toluene/reflux, 91%; (c) $NaBH_4/CeCl_3\cdot 7H_2O$/MeOH, 80%; (d) *p*-TsOH/Me_2CO/reflux, 70%; (e) $CeCl_3\cdot 7H_2O/(CO_2H)_2$/MeCN, 40%; (f) *p*-TsOH/MeOH/reflux, 64%.