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Contribution to the total synthesis of caribenolide I

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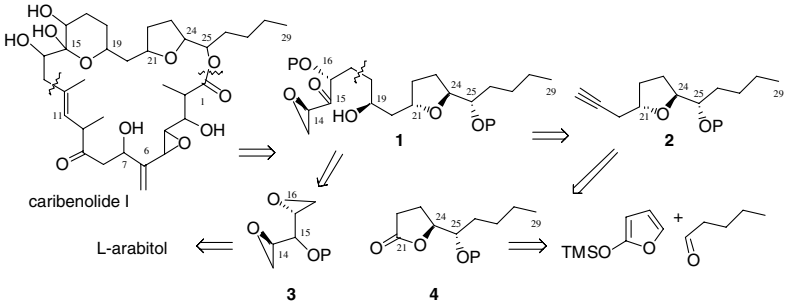
Abstract—Stereoselective synthesis of C_{13}–C_{29} fragment of caribenolide I, a potent antitumour macrolide isolated from a marine dinoflagellate *Amphidinium* sp. is described. The key step relies on a highly diastereoselective C-glycosylation, using a bulky chiral oxazolidin-2-thione, to control the absolute configuration of C_{21}. The C_{24} and C_{25} stereogenic centres were controlled by the enantioselective vinylogous Mukayiama aldol reaction, whereas C_{14} and C_{16} stereogenic centres were built from a chiral bis-epoxide.

Caribenolide I[1] is a 26-membered macrolactone belonging to the Amphidinolides family,[2] a new class of marine natural products isolated from marine dinoflagellates, *Amphidinium* sp., that are symbiotic of Okinawan marine flatworm *Amphiscolops* sp. and possessing potent cytotoxic property against a number of tumour cells. Caribenolide I exhibits an impressive in vitro cytotoxicity against human colon tumour cells of wild type as well as against those that have acquired a multi-drug resistance phenotype ($IC_{50} = 1.6$ nM, against HCT116/WT or HCT116/VM46). In addition, caribenolide I displays an important in vivo activity against P388 tumour grafted mice ($T/C = 150\%$ at a dose of 0.03 mg/kg). In continuation of our efforts to contribute to the structural elucidation of caribenolide I, along with the desire to possess a large quantity of this extremely cytotoxic marine natural product, we embarked on the total synthesis of caribenolide I.[3,4] Thus we report therein our results concerning the synthesis of the enantio-pure C_{13}–C_{29} skeleton of caribenolide I.

Our retrosynthetic strategy, described in Scheme 1, shows that caribenolide I could be obtained by a convergent approach and by a coupling reaction of C_{13}–C_{29} and C_1–C_{12} fragments. In this work we describe our efforts towards the enantioselective preparation of one diastereomer of the C_{13}–C_{29} fragment of caribenolide I, with a good control of the absolute configurations



Scheme 1.

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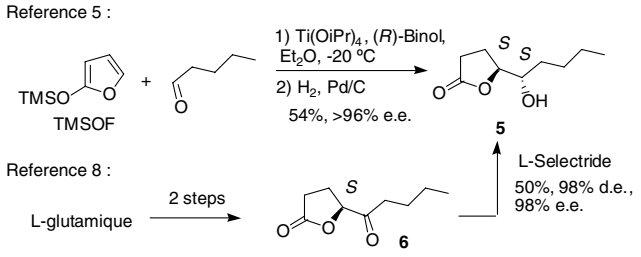
of six stereogenic centres (C_{14}, C_{16}, C_{19}, C_{21}, C_{24} and C_{25}), among the 13 ones of caribenolide I, as shown in Scheme 1, with methods that could provide either enantiomer, for later comparisons with the natural product.

The key reactions of this strategy rely on the use of a vinylogous Mukayiama aldol reaction[5] to control the relative and absolute configurations of C_{24} and C_{25}. Then, the highly diastereoselective C-glycosylation with a chiral oxazolidin-2-thione[6] allows the control of the configuration of C_{21}. The two C_{14} and C_{16} stereogenic centres are brought by the chiral and known bis-epoxide,[7] while C_{19} is introduced by reduction of the corresponding carbonyl derivative.

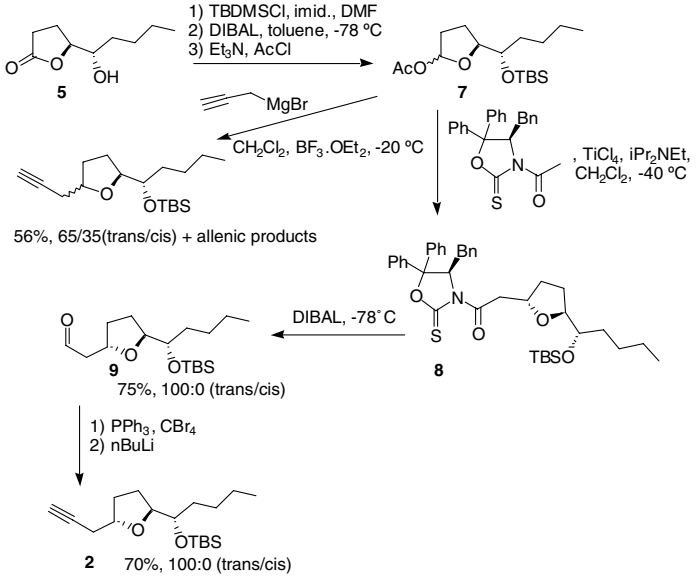
The key lactone fragment **5** could be prepared through two different approaches: (i) vinylogous Mukayiama aldol reaction of trimethylsilyloxyfuran (TMSOF)[5] with pentanal affords the desired *threo*-butenolide in 54% and 96% ee, followed by quantitative hydrogenation; (ii) L-glutamic acid route through the 3 steps—nitrous deamination–acylation–diastereoselective reduction (Scheme 2).[8] Then the free hydroxyl of the lactone **5** was protected as a *tert*-butyldimethylsilyl ether under usual reaction conditions (TBDMSCl, DMAP, imidazole, DMF).[9] The next step required to introduce a propargyl chain and this was tentatively performed by addition at −20 °C in CH_2Cl_2 of propargyl Grignard reagent (prepared in diethyl ether) to acetate **7** derived from lactone **5**. Unfortunately, the desired product was obtained in the presence of the allenic derivatives and as cis/trans mixtures.[10]

We thus decided to use the chiral titanium enolate of the *N*-acetyl(*R*)-5,5-diphenyl-4-benzyloxazolidin-2-thione (prepared from 1 equiv of *i*Pr_2NEt and 1 equiv of $TiCl_4$ at −40 °C in CH_2Cl_2) which reacted with acetate **7** to afford the coupled product **8** as a single trans isomer (as shown by NOE NMR studies).[6] DIBAL treatment of the crude adduct, followed by purification by flash chromatography led to the pure *trans* aldehyde **9** in 75% yield and to the chiral (*R*)-oxazolidin-2-thione in 92% isolated yield. The Corey–Fuchs–MacKelvie reaction[11] gave, from **9**, the expected alkyne **2** in two steps and in 70% overall yield (Scheme 3), through the 1,1-dibromovinyl derivative intermediate.

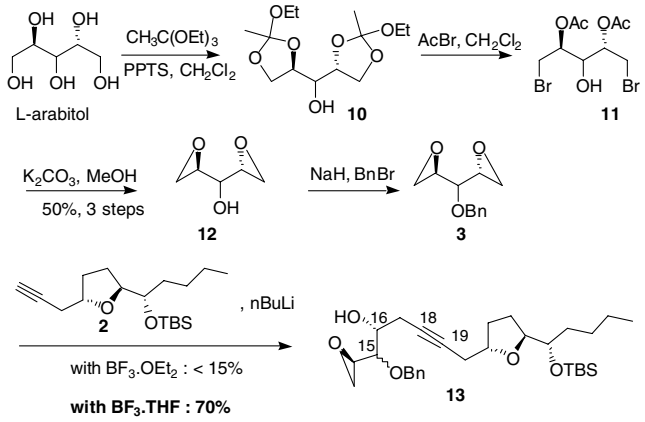
The required bis-epoxide was prepared from L-arabitol, as reported,[7] through slightly modified procedures (Scheme 4). Indeed, L-arabitol was treated with ethyl orthoacetate in dichloromethane in the presence of PPTS, to give bicyclic orthoester **10** that was directly treated with acetyl bromide in dichloromethane to afford dibromo-diacetate **11**. The latter, under potassium carbonate treatment in methanol, gave rise to the desired bis-epoxide **12** in 50% overall yield for the last 3 steps. Compound **12** was then protected as a benzyl ether (NaH, BnBr, DMF) in a moderate 50% yield. Recovery of the starting material and protection allow us to obtain the desired benzyl ether **3** in a final 75% yield. Then, the coupling reaction between alkyne **2** and protected bis-epoxide **3** was performed by *n*BuLi metallation, followed by $BF_3{\cdot}OEt_2$ catalyzed opening of the epoxide.[12] Under these reaction conditions, the expected mono-coupled product **13** was obtained in



Scheme 2.



Scheme 3.

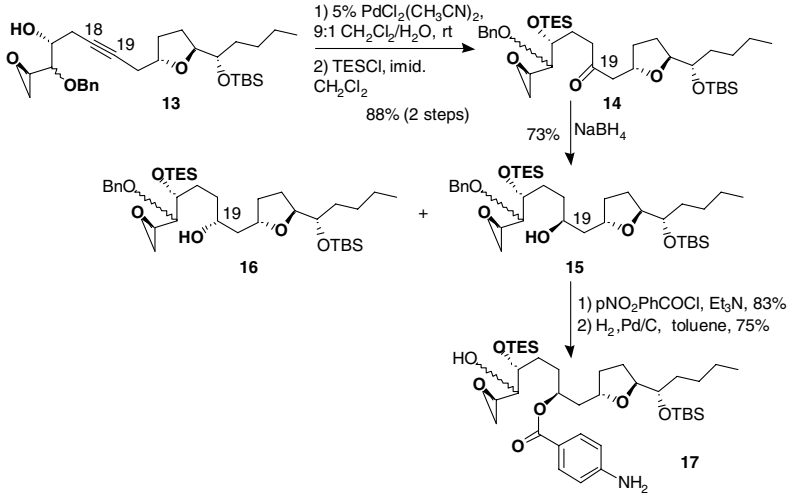


Scheme 4.

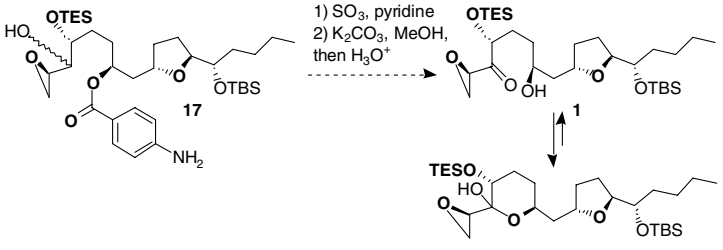
trace amount. Several small-scale trials were performed without much improvement for the chemical yield. We thus decided to work on a larger scale and to use BF_3·THF as Lewis acid, which has been reported for improving the yield of such a reaction.[13] Indeed, under these reaction conditions the expected coupled product **13** was now obtained in a satisfying 70% yield. It is worth noting that the mono-coupled product is obtained as a 60:40 diastereomeric mixture due to the new stereogenic centre bearing the OBn group (C_{15}, caribenolide numbering), that will be oxidized to the carbonyl derivative later on.

Then, we were pleased to observe that the homo-propargylalkyne can be converted regioselectively into the corresponding γ-hydroxy ketone by palladium catalysis ($PdCl_2(CH_3CN)_2$, 5 mol %) in a 9/1 dichloromethane/water mixture at room temperature and in a high yield (Scheme 5).[14] Regioselective hydration of the triple bond at C_{19} may be rationalized by invoking a pallado-dihydrofuran intermediate. Protection of the free hydroxyl of the γ-hydroxy ketone as a tri-ethylsilyl ether was then performed under usual reaction conditions (TESCl, DMAP, imidazole),[15] to give ketone **14**[16] in 88% yield for the last two steps. Ketone **14** was then reduced into the corresponding alcohol; when L-Selectride was used as reducing reagent, a 60:40 mixture of **15** and **16** diastereomers was obtained in 57% overall yield, whereas with $NaBH_4$, a 1:1 mixture of **15** and **16** was obtained in 73% yield. Both C_{19} diastereomers (caribenolide numbering) were easily separated by flash chromatography, and absolute configurations at C_{19} are being determined through the NMR studies of the corresponding Mosher's esters.[17]

Both compounds **15** and **16** were then protected as *para*-nitrobenzoate (*para*-nitrobenzoyl chloride, Et_3N) in good yields, and then hydrogenation (H_2, Pd/C, toluene) removed the benzyl group and reduced the nitro



Scheme 5.



Scheme 6.

function into the amino group, affording the free alcohol **17** in 75% yield (only product obtained from **15** is shown in Scheme 5). Oxidation of the secondary alcohol of **17** to the carbonyl derivative and removal of the *para*-aminobenzoate group will give the δ-hydroxy ketone **1** which under acidic conditions should be in equilibrium with the thermodynamic tetrahydropyran cyclized product (Scheme 6). These transformations are now under study in our laboratories.

In conclusion, we have prepared enantioselectively the C_{13}–C_{29} skeleton of caribenolide I with an excellent control of the absolute configurations of the stereogenic centres in 15 steps. The strategy used therein will allow us to prepare several diastereomers of the target molecule by varying the reaction conditions, chiral catalysts and starting material, for further comparisons with the natural product. The connection with the C_1–C_{12} fragment[4] is now under study in our laboratories.

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16. Spectroscopic data of ketone **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.04 (s, 6H); 0.58 (m, 6H); 0.88 (br s, 12H); 0.93 (t, 9H, $J = 8.0$ Hz); 1.20–1.49 (m, 8H); 1.62–2.20 (m, 6H); 2.30–2.54 (m, 3H); 2.58 (dd, 0.4×1H, $J = 2.7$, 4.7 Hz); 2.64–2.73 (m, 1H); 2.76 (m, 1H); 2.82 (t, 0.4×1H, $J = 4.5$ Hz); 2.84 (dd, 0.6×1H, $J = 2.6$, 5.5 Hz); 2.91 (t, 0.4×1H, $J = 6.1$ Hz); 3.10 (m, 0.4×1H); 3.18 (q, 0.6×1H, $J = 3.1$ Hz); 3.42 (t, 0.6×1H, $J = 3.6$ Hz); 3.54 (m, 0.6×1H); 3.58 (m, 0.4×1H) 3.81 (m, 1H); 3.89 (m, 1H); 4.19 (m, 0.4×1H); 4.26 (m, 0.6×1H); 4.49 (dd, 0.6×1H, $J = 1.34$, 12.0 Hz); 4.59 (d, 0.4×1H, $J = 11.8$ Hz); 4.66 (d, 0.6×1H, $J = 12.0$ Hz); 4.83 (d, 0.4×1H, $J = 11.8$ Hz); 7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −4.7; −4.2; 4.9; 5.0; 6.9; 14.0; 18.2; 22.8; 26.0; 26.3; 27.3; 27.5; 27.8; 29.7; 32.4; 38.4; 39.7; 43.9; 44.7; 48.7; 48.8; 51.0; 53.1; 72.1; 73.1; 74.9; 75.1; 78.2; 81.5; 82.8; 127.5; 127.6; 127.8; 128.0; 128.2, 138.3; 138.4 ; 208.7; 208.8. ESI–MS *m*/*z*: 671 ($M+Na^+$, 100). IR ($CHCl_3$) cm^{-1}: 2955; 2925; 2875; 2855; 1715; 1460; 1415; 1360; 1250; 1090; 1005; 940; 835; 775; 735.
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