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A Baylis–Hillman approach to the synthesis of C_1–C_{11} fragment of caribenolide I

Matar Seck, Xavier Franck,*,† Blandine Seon-Meniel, Reynald Hocquemiller and Bruno Figadère*

Laboratoire de Pharmacognosie associé au CNRS (BioCIS), Faculté de Pharmacie, Université Paris-Sud, rue Jean-Baptiste, Clément 92296 Châtenay Malabry, France

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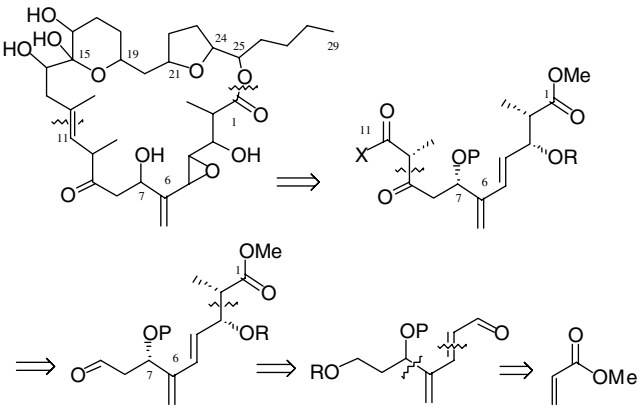
Abstract—Stereoselective synthesis of C_1–C_{11} fragment of caribenolide I, a potent antitumour macrolide isolated from a marine dinoflagellate *Amphidinium* sp. is described. The key steps rely on asymmetric aldol reactions, to control the absolute configurations of C_2, C_3 and C_{10} stereogenic centres.

Amphidinolides are members of a family of marine natural products that possess potent cytotoxic property against a number of tumour cells (e.g., murine lymphoma L1210, human epidermoid carcinoma KB and human colon tumour cells HCT116). They are isolated from marine dinoflagellates, *Amphidinium* sp., that are symbiotic of Okinawan marine flatworm *Amphiscolops* sp. Since the first isolation of an amphidinolide,[1] today more than 35 amphidinolides have been isolated and characterized.[2] Caribenolide I is a 26-membered macrolactone of this family,[3] and possesses an important in vitro cytotoxicity against human colon tumour cells of wild type as well as against those that have shown a multi-drug resistance phenotype ($IC_{50} = 0.001$ μg/mL or 1.6 nM, against HCT116/WT or HCT 116/VM 46). It is worth noting that this cytotoxicity is 100 times higher than that observed for amphidinolide B (IC_{50}/HCT116/WT = 0.122 μM), which was then considered as the most active amphidinolide.[4–7] Most importantly, caribenolide I shows an important in vivo activity against P388 tumour grafted mice (T/C = 150% at a dose of 0.03 mg/kg). As most of the amphidinolides, caribenolide I was isolated in minute amounts from dried cells (0.026% yield). If a few total syntheses of amphidinolides have appeared in the literature,[4] to the best of our knowledge, nothing has been reported concerning total or partial synthesis of caribenolide I, except a brief report by us.[8]

In continuation of our efforts to contribute to the structural elucidation of absolute and/or relative configurations of caribenolide I, along with the desire to possess a large quantity of such an extremely cytotoxic natural product, we decided to study the total synthesis of caribenolide I. We wish to report herein our results concerning the synthesis of the C_1–C_{11} skeleton of caribenolide I.

Our retrosynthetic strategy is described in Scheme 1, and shows that caribenolide I could be obtained by a convergent approach from C_{12}–C_{29} and C_1–C_{11} fragments.



Scheme 1.

* Corresponding authors. E-mail: bruno.figadere@cep.u-psud.fr
† New Address: UMR-CNRS 6014, IRCOF/LHO, Rue Tesniere, 76131 Mont Saint Aignan Cedex, France.

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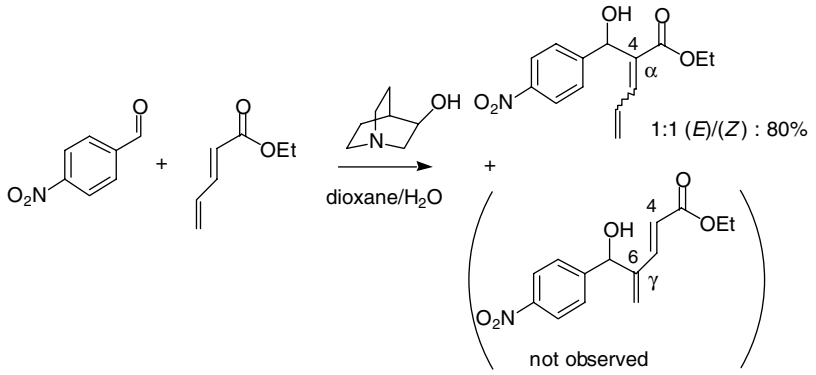
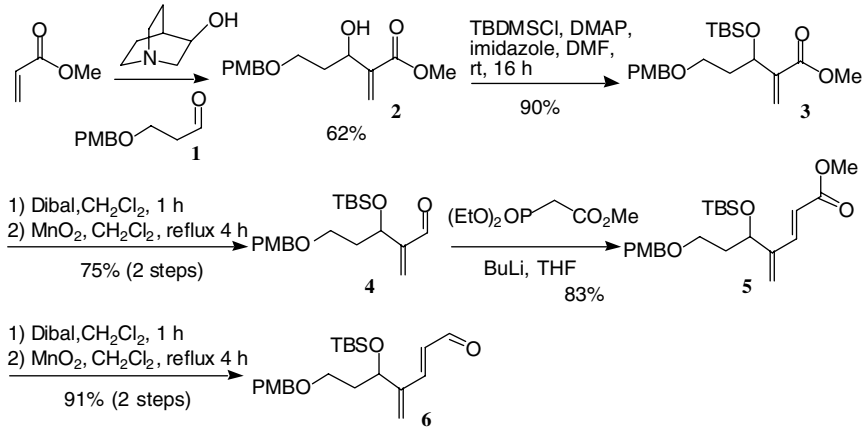
In this letter, we describe our efforts toward the preparation of the C_1–C_{11} fragment of caribenolide I, with a good control of the absolute configurations of four stereogenic centres (C_2, C_3, C_7 and C_{10}), among the 13 ones of caribenolide I, as shown in Scheme 1, with methods that could provide either epimer, for later comparisons with the natural product. The key reactions of this strategy rely on the use of asymmetric aldolisations to control the relative and absolute configurations of C_2 and C_3. Then, on a later stage of the synthesis the Sharpless asymmetric epoxidation of the so formed allylic alcohol will allow us to control the configurations of C_4 and C_5. The *exo* double bond is generated by a Baylis–Hillman reaction.

In a first attempt, we tried to introduce the diene moiety of our fragment possessing an allylic hydroxyl by a Baylis–Hillman reaction. This required to study the coupling reaction of an aldehyde with ethyl penta-2,4-dienoate (Scheme 2). To our knowledge, there are no reports in the literature on the Baylis–Hillman reaction with ethyl penta-2,4-dienoate as substrate.[9] Thus we decided to study a model reaction with 3-hydroxyquinuclidine (20% equiv) and 4-nitrobenzaldehyde (1 equiv) in a 1:1 dioxane and water mixture with ethyl penta-2,4-dienoate (2 equiv).[10] Under these reaction conditions, we were delighted to observe that a coupling product was obtained in 80% isolated yield as a 1:1 (*E*) and (*Z*) mixture,[11] after 5 h of reaction at room temperature. However, the compound so obtained is the un-wanted α-branched derivative (branching at C_4, caribenolide numbering), and none of the γ-alkylated products (branching at C_6, caribenolide numbering) was formed. By changing the amount of base, time of the reaction, solvent, no improvements in yield and/or regioselectivity were observed. Since the desired γ-regioisomer was not obtained, whatever the reaction conditions were, we did not apply this transformation to our synthon, and decided to build up step by step the required diene fragment, as shown in Scheme 3. However, the scope and limitations of this interesting reaction are now under studies in our laboratories.

In the absence of solvent, 3-paramethoxylbenzyloxypropanal **1** with methyl acrylate and racemic 3-hydroxyquinuclidine led to the desired racemic allylic alcohol **2** in 62% isolated yield.[10] Then, protection of the latter as a *tert*-butyldimethylsilyl ether was performed under usual conditions (TBDMSCl, DMAP, imidazole, DMF),[12] and afforded the expected silyl ether **3** in 90% yield. Then for introduction of a two carbon unit through a Wittig–Horner reaction, methyl ester **3** was converted into its corresponding aldehyde in two steps; first DIBAL reduction in dichloromethane[13] afforded



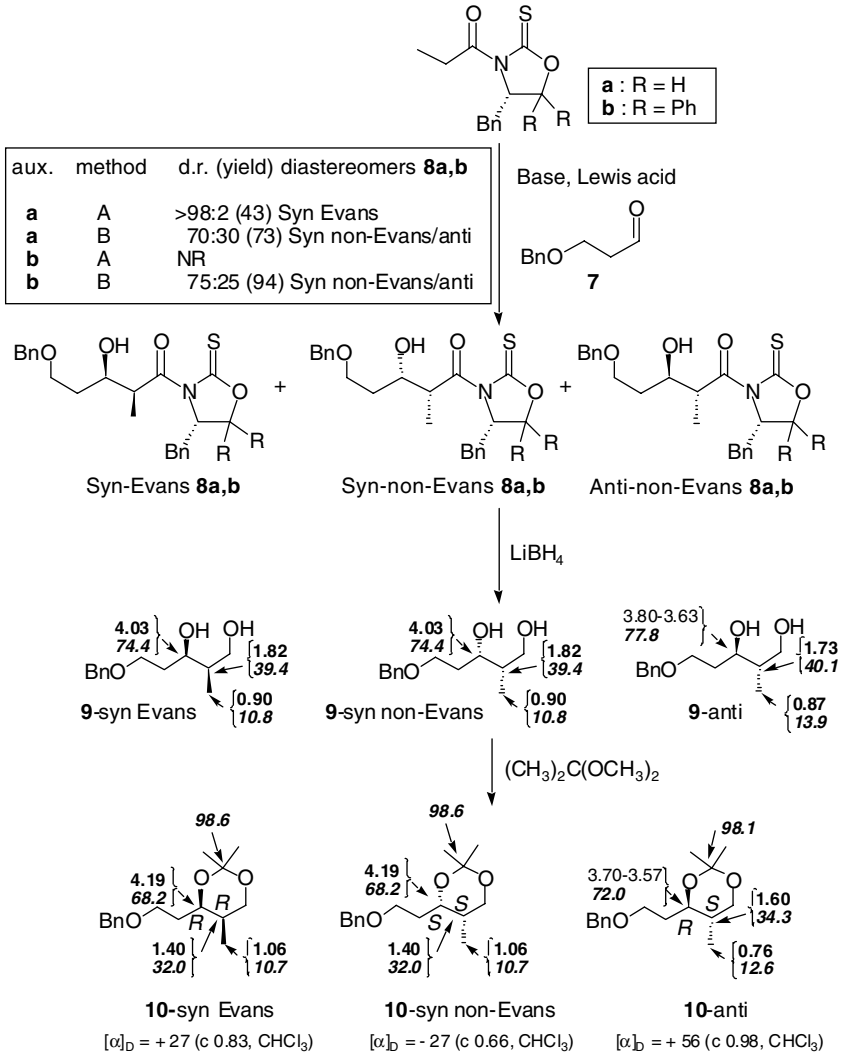
Scheme 2.



Scheme 3.

the desired primary alcohol which was oxidized by manganese oxide (MnO_2) treatment,[14] affording the required aldehyde **4** in 75% yield for the two steps. The latter was then treated by methyl diethylphosphonoacetate, to give the (*E*) unsaturated ester **5** in 83% yield.[15] Then, reduction of the latter (DIBAL in dichloromethane) and manganese oxide oxidation of the so-obtained allylic alcohol afforded the desired aldehyde **6** in 91% overall yield (Scheme 3).

Then, the two stereogenic centres at C_2 and C_3 (caribenolide numbering) could be introduced by an asymmetric aldol reaction. Indeed, the carbon–carbon bond formation mediated by an aldol reaction is one of the most powerful methods in organic synthesis for the control of the absolute configurations of the newly formed stereogenic centres. Dibutylboron triflate enolates of chiral *N*-acyl oxazolidinones and titanium enolates of chiral *N*-acyl oxazolidin-2-thiones have been shown to provide comparable levels of stereoselectivity.[16–19] If the Evans' boron-mediated oxazolidinones give only the 'syn-Evans' aldols, with Crimmins' titanium-mediated oxazolidin-2-thiones, it is possible to get separately either one of the two syn products: the 'syn-Evans' and 'syn-non-Evans' aldols, depending on the amount of titanium tetrachloride ($TiCl_4$) and amine used. To study the influence of a remote protected hydroxy such as OBn, a model reaction was first studied with two oxazolidin-2-thiones **a** and **b**[20] and aldehyde **7**, under the reaction conditions described by Crimmins et al. In order to attribute both the relative and absolute configurations of aldols **8a**,**b** after separation by flash chromatography on silica gel, they were reduced in high yields by $LiBH_4$ to afford the corresponding 1,3-diols **9**, which were then quantitatively protected as acetonides **10** (Scheme 4). Comparisons of the ^1H and ^{13}C NMR data of diols **9**, with the known syn diol,[21] and anti diol,[22] allowed us to determine the syn and anti relative configuration of aldols **8a**,**b**. Whereas comparisons of the specific rotations ($[\alpha]_D$) of acetonides **10** with the known **10**-*anti* acetonide[23] allowed us to unambiguously attribute the absolute configurations of the obtained acetonides (since the specific rotation of diols **9** is low, and thus subject to experimental errors). These measures, combined with the comparisons of the ^1H NMR of the acetonides, allowed us to unambiguously secure the attribution of the absolute configurations of the newly created stereogenic centres in **8a**,**b** (Scheme 4).

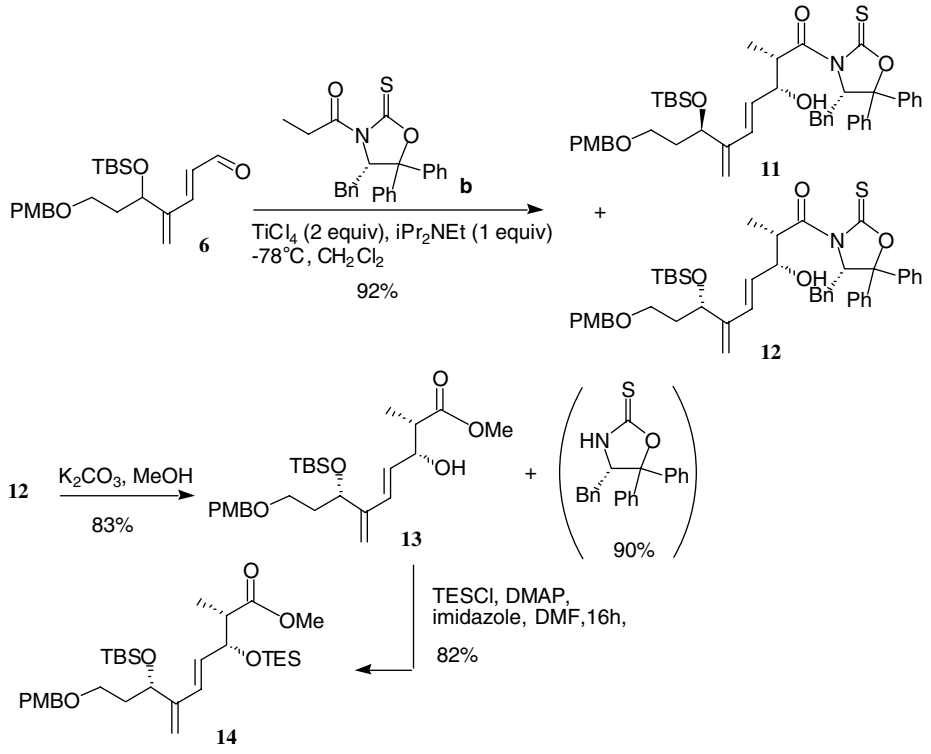


Scheme 4.

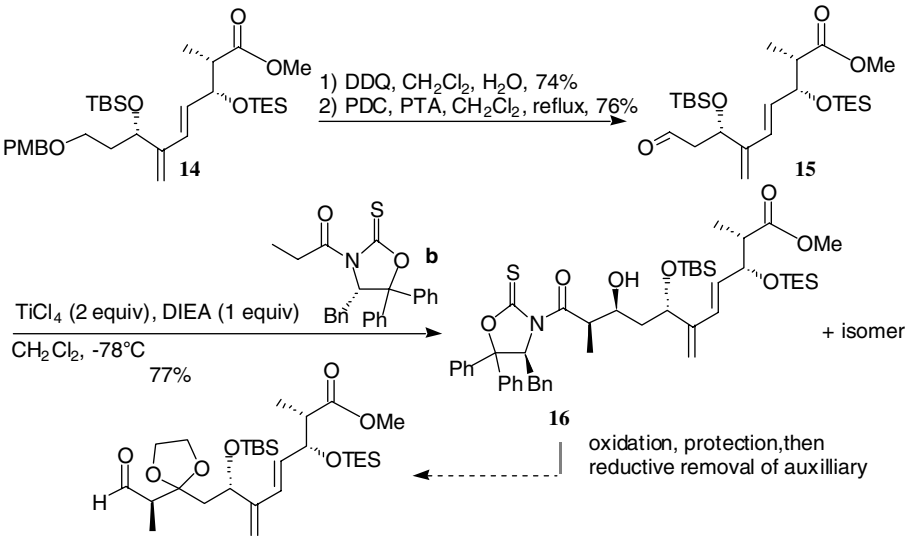
When the titanium enolate derived from oxazolidin-2-thione **a** (1 equiv $TiCl_4$, 2.5 equiv TMEDA, CH_2Cl_2, −78 °C, method A)[18] reacted with 1 equiv of aldehyde **7**, the syn Evans aldol adduct **8a** was obtained albeit in a moderate 43% yield but with an excellent diastereoselectivity (>98:2). Again, the stereochemistry of the compound was secured through the reduction forming the intermediate diol **9** and preparation of acetonide **10**. Surprisingly, adduct **8a** was obtained with a low diastereoselectivity (dr = 70:30), when the titanium enolate derived from oxazolidin-2-thione **a**, prepared from 2 equiv $TiCl_4$, and 1.1 equiv of DIEA in CH_2Cl_2, at −78 °C (method B),[18] reacted with 1 equiv of aldehyde **7**. The major diastereomer was determined as the syn non-Evans aldol **8a**, after reduction to diol **9** and formation of acetonide **10**. The minor diastereomer however was surprisingly identified as the anti adduct **8a** (and not the syn Evans product as expected). The partial formation of anti isomer **8a**, under these reaction conditions, is reported for the first time, as far as we are aware, but can be related to the observed reverse selectivity when other chiral enolates react with aldehydes bearing at the 3-position a chelating group such as a benzyloxy function.[24] However, when 3-tris-isopropylsilyloxy propanal was treated by the titanium enolate of **a**, prepared through method B, the syn non-Evans aldol was now obtained as the sole product in 60% yield (result not shown).

Then, we were pleased to observe that when the titanium enolate derived from oxazolidin-2-thione **b** (prepared from 2 equiv $TiCl_4$, 1.1 equiv of DIEA, in CH_2Cl_2, at −78 °C, method B) reacted with 1 equiv of aldehyde **7**, the syn non-Evans adduct **8b** was obtained with a slightly higher diastereoselectivity (75:25) and the minor diastereomer was again securely determined as the anti adduct **8b**. The combined yield was slightly better than with chiral auxiliary **a** (94% vs 73%). Unfortunately, the titanium enolate derived from oxazolidin-2-thione **b**, prepared from 1 equiv of $TiCl_4$, and 2.5 equiv of TMEDA in CH_2Cl_2 at −78 °C (method A), did not react with aldehyde **7** (despite several trials where the temperature varied from −78 °C to rt).

Then, aldehyde **6** is now engaged in an asymmetric aldol reaction using method B (2 equiv of $TiCl_4$ and 1.1 equiv of DIEA) to prepare the titanium enolate of the bulky chiral *N*-propionyl oxazolidin-2-thione **b**.[20] The reaction affords only the syn non-Evans aldols **11** and **12** in 92% chemical yield, and as a 1:1 mixture. The relative and absolute configurations are supposed to be as depicted in the scheme, based on the published data[18,25] and on the above observations (reduction of the amide function to the corresponding alcohol and formation of the 1,3-acetonides on related cases showed the syn non-Evans relationship, see Ref. 8). At this stage the mixture of the two diastereomers is due to the non-controlled stereogenic centre at C_7 (caribenolide numbering), but fortunately the two compounds could be separated by flash chromatography. Both aldols **11** and **12** were then converted into their corresponding methyl esters (by K_2CO_3 treatment in the presence of methanol) in high yield,[20] and the chiral auxiliary recovered in typical 90–92% yield, after purification by flash chromatography (only conversion of **12** to **13** is represented in Scheme 5). Then the free hydroxyl of **13** was protected as a triethyl silyl ether by usual treatment (TESCl, DMAP, imidazole),[26] to afford the expected silyl ether **14**. Oxidative removal



Scheme 5.



Scheme 6.

of the paramethoxybenzyl group (DDQ, CH_2Cl_2, H_2O)[27] of **14**, and PDC oxidation of the primary alcohol so obtained[28] gave the expected aldehyde **15** in 56% overall yield.

A second aldol reaction using method B conditions with the *N*-propionyl oxazolidin-2-thione **b** and aldehyde **15**, as described above, afforded unexpectedly a mixture of the major syn non-Evans aldol **16** with an isomer (dr = 70:30, supposed to be the anti isomer, as depicted in the model study in Scheme 4, may be due to the presence of a protected hydroxyl at β-position of carbonyl) in 77% combined yield (Scheme 6). However, oxidation of the carbinol of both isomers will give rise to the same oxo derivative. Indeed, oxidation of alcohol **16** followed by protection of the carbonyl and reductive removal of the chiral auxiliary (e.g., DIBAL reduction) will give rise to the expected aldehyde that is required for the coupling reaction with the C_{12}–C_{29} fragment of caribenolide I.

In conclusion, we have described herein a very efficient stereoselective synthesis of the enantiopure C_1–C_{11} skeleton of caribenolide I, in 13 steps with a good control of the configurations of the newly built stereogenic centres. In principle, all diastereomers are accessible, depending on the reaction conditions used for the aldol reactions, using our bulky oxazolidin-2-thione **b**.

Diastereoselective epoxidation of the so obtained allylic alcohol will be performed at a later stage, because of the high chemical reactivity of such an allylic epoxide, and the connection of this fragment with other parts of the molecule is now under study in our laboratories.

Acknowledgement

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