Synthesis of the C1–C13 Fragment of (+)-Callipeltoside A

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Received 5 March 2007

Abstract: The synthesis of the C1–C13 fragment of (+)-callipeltoside A has been achieved in 12 steps with an overall yield of 11%.

Key words: callipeltoside, crotyltitanation, vinyllithium

Callipeltoside A (Figure 1) is a polyketide isolated from the shallow water sponge *Callipelta sp.* collected off the east coast of New Caledonia.[2,3] This marine natural product was found to inhibit the proliferation of NSCLC-N6 (15.26 μg·mL^{-1}) and P388 (11.26 μg·mL^{-1}) cell lines in vitro. This compound consists of a 14-membered macrolide, containing a six-membered hemiacetal ring and a unique deoxyamino sugar, callipeltose, which is attached glycosidically at C5. Furthermore, a pendant dienyne side chain terminated by a *trans*-chlorocyclopropane ring is present at C13. The relative stereochemical relationship between the sugar moiety and the macrolactone has been proposed on the basis of 2D-NMR studies. However, due to the small amount of callipeltoside A, isolated from the natural source (3.5 mg from 2.5 kg of freeze-dried sponge, 1.4×10^{-4}% yield), its full structural determination and biological evaluation were limited. Thus, the synthesis of callipeltoside A was imperative to establish the absolute configuration of all the stereogenic centers and to further examine its anticancer properties.

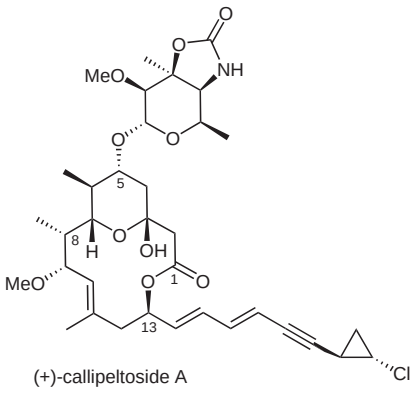
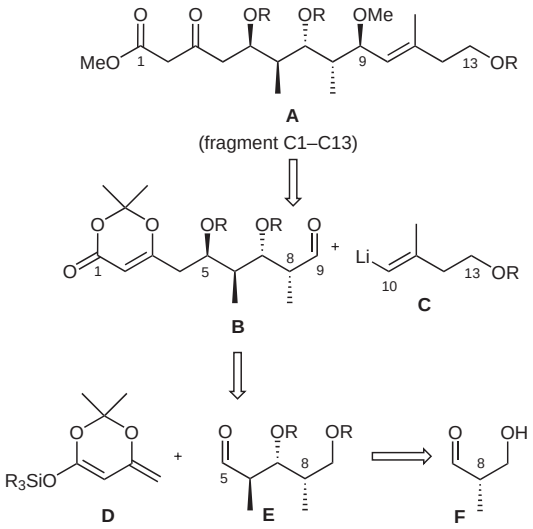


Figure 1 Structure of (+)-callipeltoside A

The relative stereochemistry of the chlorocyclopropyl side chain to the rest of the molecule and the absolute configurations of the stereogenic centers has been established by total synthesis. Up to now, four total syntheses[4] of the aglycon part of callipeltoside A have been published and synthetic efforts towards the aglycon part of callipeltoside A[5] have also been reported.

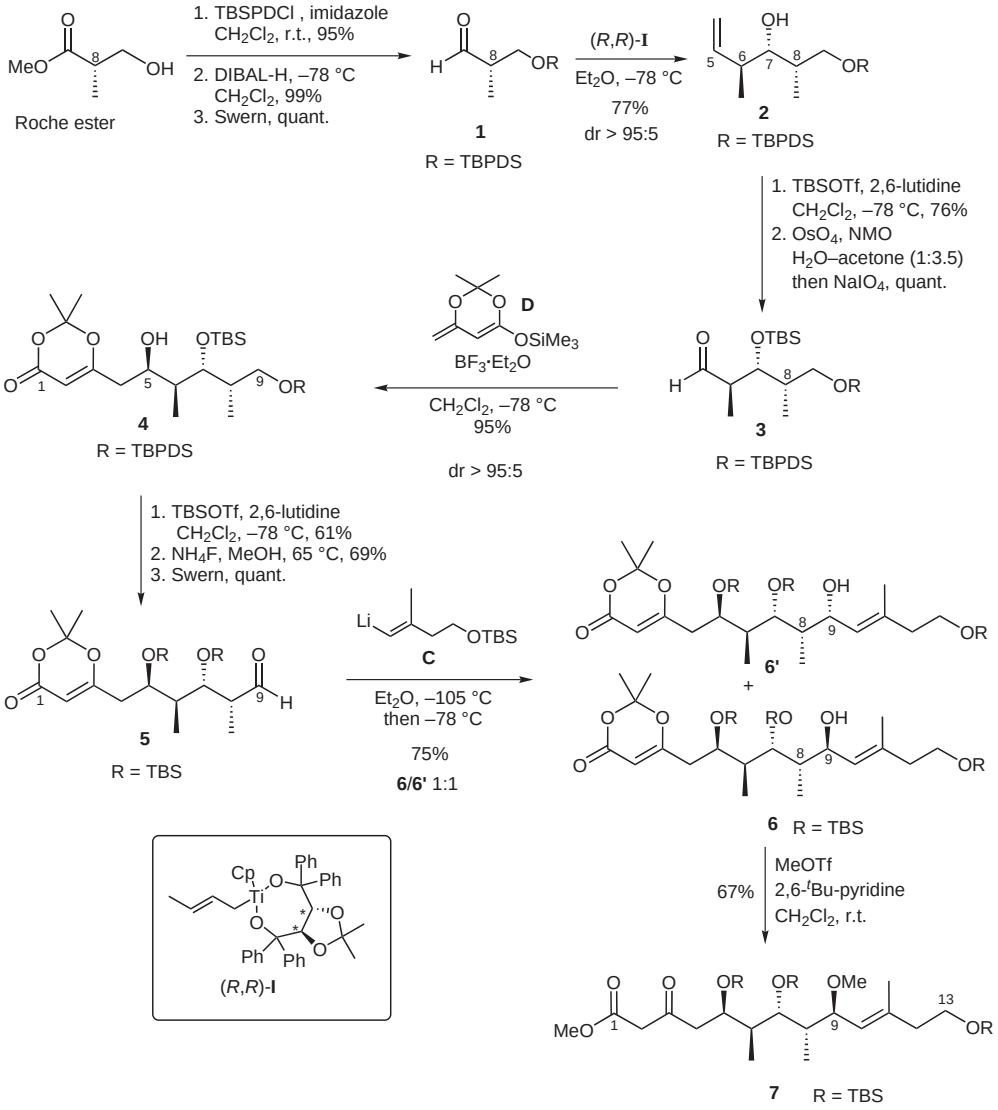
When this work was started, only the synthesis of the aglycone of callipeltoside A had been published and later on, it was revealed to be the aglycone of (+)-callipeltoside A.[4a] Here, we would like to report the synthesis of the C1–C13 fragment of (+)-callipeltoside A based on the addition of the vinyllithium reagent **C** to aldehyde **B**, which possesses 4 of the 9 stereogenic centers present in the macrolactone of (+)-callipeltoside A. The control of the stereogenic center at C5 was envisaged by addition of the vinyl silylenol ether **D** to an aldehyde of type **E** according to Felkin–Anh control. This latter aldehyde of type **E** would be issued from an enantioselective crotyltitanation[6] applied to an aldehyde of type **F**, which would in turn be synthesized from the Roche ester (Scheme 1).



Scheme 1 Retrosynthetic analysis of the C1–C13 fragment of (+)-callipeltoside A

The synthesis (Scheme 2) began with the preparation of aldehyde **1** from the Roche ester in three steps. After protection of the primary hydroxy group using chloro-*tert*-butyldiphenylsilane (TBDPSCl, imidazole, CH_2Cl_2, r.t., 95%), DIBAL-H reduction of the ester (DIBAL-H, CH_2Cl_2, –78 °C, 99%) and a Swern oxidation, aldehyde **1** was isolated in 94%, the stereogenic center of which corresponds to the C8 stereogenic center present in

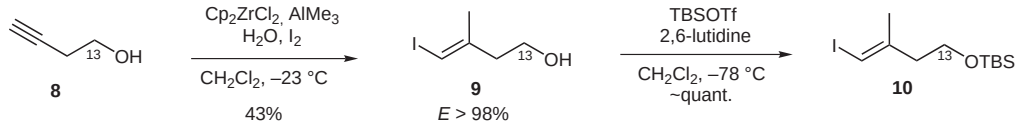
SYNLETT 2007, No. 9, pp 1461–1463
Advanced online publication: 23.05.2007
DOI: 10.1055/s-2007-980367; Art ID: G04907ST



Scheme 2 Synthesis of the C1–C13 fragment

callipeltoside A. In order to control the C6 and C7 stereogenic centers, aldehyde **1** was treated with the highly face-selective crotyltitanium complex (*R*,*R*)-**I**[6] (Et_2O, –78 °C) to produce the *anti*/*syn*-triad **2** in 77% yield and with a diastereomeric ratio superior to 95:5. The latter product was then protected with TBSOTf (2,6-lutidine, CH_2Cl_2, –78 °C, 76%) and an oxidative cleavage of the terminal double bond using OsO_4, NMO [H_2O–acetone (1:3.5)] followed by the addition of $NaIO_4$, led to aldehyde **3** in quantitative yield. The addition of the vinyl silylenol ether **D** on the previously prepared aldehyde **3**, in the presence of $BF_3{\cdot}OEt_2$ (3 equiv, CH_2Cl_2, –78 °C), resulted in the exclusive formation of the aldol condensation product **4** in 95% yield and with an excellent Felkin–Anh control (dr > 95:5). Protection of the hydroxy group of **4** (TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 61%) followed by the deprotection of the primary hydroxy group using NH_4F (MeOH, 65 °C, 69% yield) and a Swern oxidation (quantitative yield) afforded aldehyde **5**. In order to synthesize the C1–C13 fragment of callipeltoside A, the coupling reaction between aldehyde **5** with vinyllithium **C** was investigated. An ethereal solution of vinyllithium was added to a solution of aldehyde **5** (1 equiv) in Et_2O at –78 °C which provided the coupling products **6** and **6′** in an equimolar ratio with a global yield of 75%. These two compounds were separated by flash chromatography on silica gel and the *syn*,*anti*,*syn*,*anti*-stereopentad **6** was isolated. We have to point out that vinyllithium **C** was prepared from the corresponding vinyliodide **10** by an iodide–metal exchange (*n*-BuLi, Et_2O, –78 °C), and the vinyliodide was obtained in two steps from but-3-ynol **8** (Scheme 3). Compound **6** was then converted into **7**[7] in 67% yield in a one-pot protection–deprotection reaction using four equivalents of MeOTf [2,6-*tert*-butylpyridine (6 equiv), CH_2Cl_2, r.t.].

The C1–C13 fragment of (+)-callipeltoside A was synthesized in 12 steps with an overall yield of 11% (Scheme 2). Due to the versatility of the reactions used, the total synthesis of (+)- as well as (–)-callipeltoside A will be reported in due course.



Scheme 3 Synthesis of the C10–C13 fragment

Acknowledgment

One of us (L.B.) thanks Rhodia and the CNRS for a grant and we also thank Rhodia for financial support.

References and Notes

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(7) Compound **7**: R_f = 0.75 (eluent: hexane–EtOAc, 80:20); $[\alpha]_D^{20}$ –3.5 (*c* 1.0, $CHCl_3$). IR: 2940, 1750, 1720, 1630, 1470, 1460, 1250, 1090 cm^{-1}. ^1H NMR: δ = 4.82 (d, *J* = 9.9 Hz, 1 H), 4.21 (d, *J* = 5.5 Hz, 1 H), 3.99 (m, 1 H), 3.70–3.52 (m, 6 H), 3.50 (s, 2 H), 3.11 (s, 3 H), 2.80 (dd, *J* = 15.8, 5.1 Hz, 1 H), 2.72 (dd, *J* = 15.8, 4.8 Hz, 1 H), 2.22 (t, *J* = 7.0 Hz, 2 H), 1.69 (m, 1 H), 1.62 (s, 3 H), 1.42 (m, 1 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.86–0.79 (3 s, 27 H), 0.68 (d, *J* = 6.6 Hz, 3 H), 0.08–0.02 (6 s, 18 H) ppm. ^{13}C NMR: δ = 201.2 (s), 167.4 (s), 137.6 (s), 126.5 (d), 78.5 (d), 70.4 (d), 70.1 (d), 62.0 (t), 55.1 (q), 52.0 (q), 50.4 (t), 48.7 (t), 45.2 (d), 43.0 (t), 39.6 (d), 25.9 (3 q), 25.8 (3 q), 25.6 (3 q), 18.2 (s), 18.1 (s), 18.0 (s), 17.1 (q), 11.3 (q), 10.5 (q), –4.0 (q), –4.3 (q), –4.5 (q), –4.6 (q), –4.8 (q), –5.5 (q) ppm.