Callipeltoside A: Assignment of Absolute and Relative Configuration by Total Synthesis**

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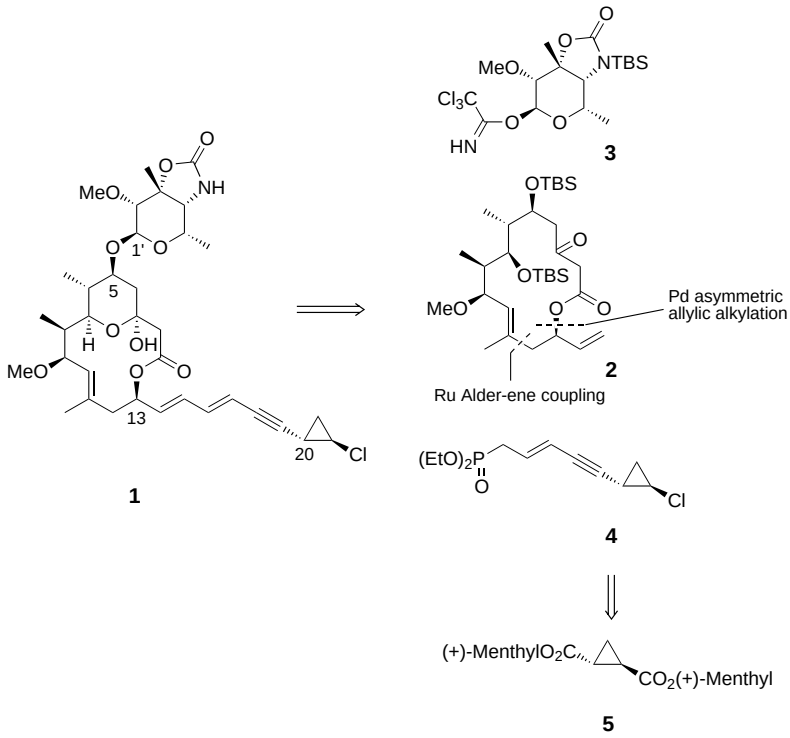
Callipeltoside A (**1**) was isolated by Minale and co-workers in 1996 from the shallow water sponge *callipelta sp.*, collected off the east coast of New Caledonia.[1] This new macrolide was found to inhibit the proliferation of NSCLC-L6 human bronchopulmonary nonsmall-cell-lung carcinoma (11.26 $\mu g\,mL^{-1}$) and P388 (15.26 $\mu g\,mL^{-1}$) cells in vitro.[1a] The small amount (3.5 mg) of **1** obtained led to the determination of its structure by extensive NMR spectroscopic studies. The relative stereochemical relationship of callipeltose to the macrolactone has been assigned based on two NOE interactions—an assignment supported by our recent total synthesis of deschlorocallipeltoside A.[1a, 2] Two main stereochemical issues remain unsolved: a) the absolute configuration, and b) the relative configuration of the *trans* chlorocyclopropane with regard to the macrolactone. Indeed, the isolation of the chlorocyclopropane from the rest of the molecule provides no detectable bias by NMR spectroscopy, as shown by the synthesis of two diastereoisomers of the aglycon of callipeltoside A by Paterson et al..[3] In spite of these structural ambiguities, many groups have embarked on the total synthesis of the compound, with different stereoisomers as targets.[4] We report the unambiguous assignment of the absolute and relative configuration of callipeltoside A by means of the total synthesis of several stereoisomers.

Our choice for the absolute configuration of the macrolactone that we synthesized has been dictated by analogy with a structurally similar molecule, auriside B. The absolute configuration of this marine macrolide has been determined by degradation studies, and its sugar moiety matches L-rhamnose.[5] Therefore, we chose L-rhamnose as starting material for the sugar synthesis. To the extent that the NOE correlation in the original structural determination is valid, the absolute configuration of the macrolactone then is also indicated. We based our strategy on our recent total synthesis of deschlorocallipeltoside A, in which the macrolactone **2** was obtained in 16 linear steps, highlighted by a ruthenium-catalyzed Alder-ene alkene–alkyne coupling, followed by a palladium-catalyzed asymmetric allylic alkylation to set the C13 stereocenter. The trichloroimidate **3** was obtained in 14 steps from L-rhamnose.[2]

Our convergent approach is illustrated in Scheme 1.[6] Callipeltoside A comes from a late-stage coupling of the side chain by an Emmons–Wadsworth–Horner olefination, followed by a Schmidt glycosidation. The synthesis of the side chain **4** takes advantage of the modified Stille reaction described by Shen[8a] to form internal alkynes, and uses Yamamoto's method[8b, c] to access easily multigram quantities of both enantiomers of **5**. Scheme 2 illustrates the synthesis of the side chain **4**, performed for both enantiomers. The synthesis starts from the commercially available (for both enantiomers)[7] dimenthyl succinate (**6**) to form known cyclopropane **5** with almost perfect diastereoselectivity after one recrystallization in methanol.[8a, b] One of the menthyl esters was transformed into known acid chloride **7** in excellent yield by using a literature procedure.[9] Acid chloride **7** was transformed into chloride **8** by using the Barton–Crich–Motherwell decarboxylation in carbon tetrachloride.[10]



Scheme 1. Retrosynthesis of callipeltoside A (**1**). TBS = *tert*-butyldimethylsilyl.

A careful study of this reaction proved that, unlike most of the literature precedents, the low-yielding step of this two-step one-pot process is not the formation of the Barton ester, but the radical reaction.[11] Indeed, the direct radical reaction of the pure Barton ester (prepared from the corresponding carboxylic acid, tributylphosphane, and 2,2′-dithiobis(pyridine-*N*-oxide)[11a]) in the same conditions, gave similar yields to the two-step process (ca. 60%). Our optimized conditions

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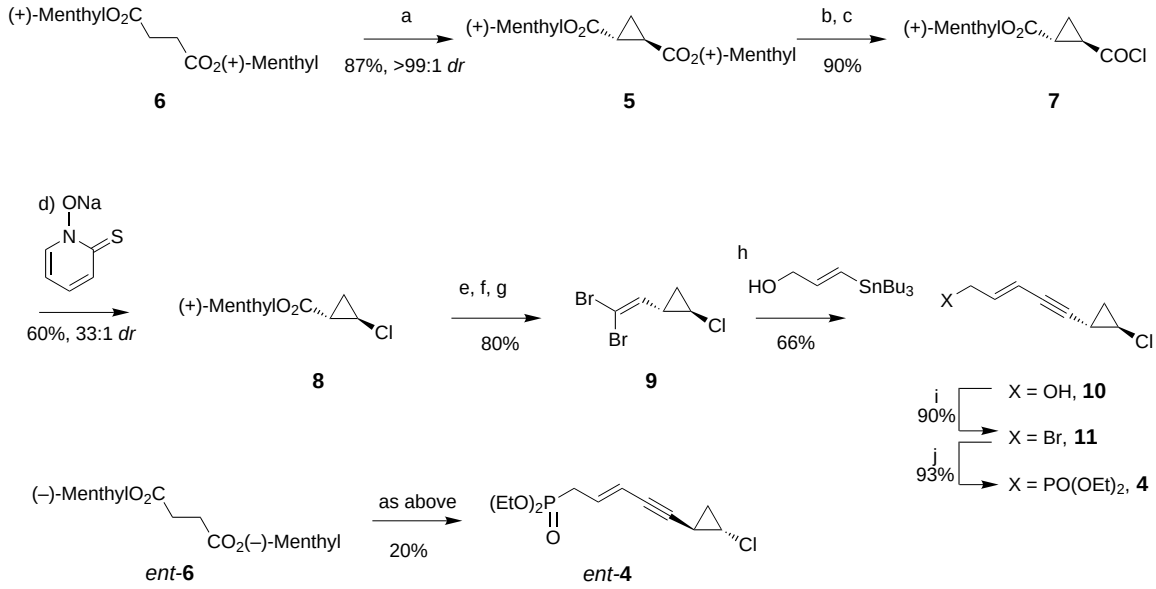
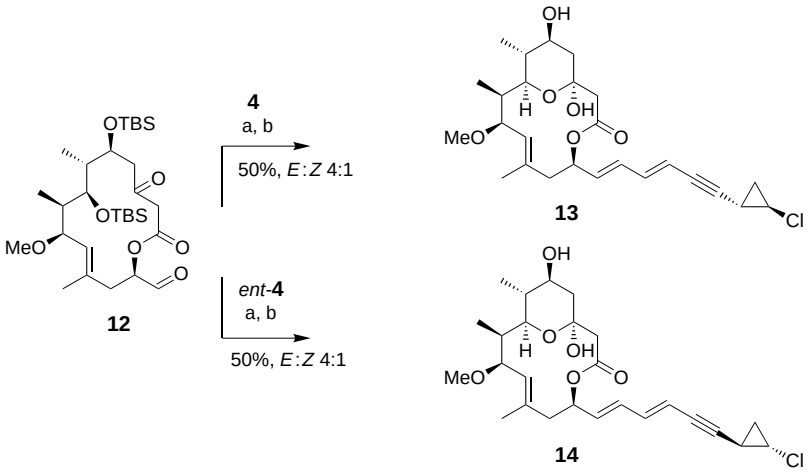
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



Scheme 2. Synthesis of the side chain. a) LiTMP, $BrCH_2Cl$, THF, $-78\,^{\circ}C$. b) NaOH (5 M), *i*PrOH, $70\,^{\circ}C$. c) $SOCl_2$, room temperature. d) DMAP, nBu_4NI, CCl_4 (0.02 M), 1 h, room temperature, then AIBN, 5 h, $80\,^{\circ}C$. e) $CH_3NHOCH_3 \cdot HCl$, *i*PrMgCl, THF, $-10\,^{\circ}C$. f) DIBAH, CH_2Cl_2, $-78\,^{\circ}C$. g) CBr_4, PPh_3, CH_2Cl_2, room temperature. h) $[Pd_2(dba)_3] \cdot CHCl_3$, $(4\text{-}CH_3OPh)_3P$, DIPEA, DMF, $80\,^{\circ}C$. i) CBr_4, PPh_3, CH_2Cl_2, $-40\,^{\circ}C$. j) $P(OC_2H_5)_3$, $100\,^{\circ}C$. LiTMP = lithium 2,2,6,6-tetramethylpiperidine, DMAP = 4-dimethylaminopyridine, AIBN = azobisisobutyronitrile, DIBAH = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, dba = *trans*,*trans*-dibenzylideneacetone.

yielded *trans*-chlorocyclopropane **8** in a reproducible 60 % yield (9 mmol scale, 33:1 diastereomeric ratio).[12] This reaction can be performed in 10 min (instead of 6 h) under microwave[13] irradiation ($150\,^{\circ}C$) in 52 % yield, and needs to be performed under dilute conditions (0.02 M). Chloride **8** was then converted in three steps into known dibromoolefin **9**[4c,d] via a Weinreb amide in excellent yield.[14, 15] We then used the Stille conditions developed by Shen and used by Olivo for this reaction to produce known enyne **10**[4c,d] in moderate yield. Enne **10** is easily transformed into phosphonate **4** via the corresponding bromide **11** in good yield.[8a, 16] The side chain **4** was synthesized over ten linear steps from the commercially available dimenthyl succinate in an overall yield of 20 %. By using the enantiomeric starting succinate ester, *ent*-**4** was obtained in similar overall yield.



Scheme 3. Synthesis of the callipeltoside aglycons. a) LiHMDS, THF, $-78\,^{\circ}C$, then $-40\,^{\circ}C$, then room temperature; b) HF · pyridine, MeOH, $0\,^{\circ}C$. LiHMDS = lithium

The side chains **4** and *ent*-**4** were coupled to macrolactone **12** by using an Emmons–Wadsworth–Horner,[2] and proceeded in modest yields (52 %; *E*:*Z* 4:1). The callipeltoside A aglycons **13** (prepared from **4**) and **14** (prepared from *ent*-**4**) were obtained in 96 % yield after deprotection with HF · pyridine in methanol (Scheme 3).[17] Comparison of the analytical data of our synthetic aglycons with those of the enantiomeric aglycons reported by Paterson et al. shows a perfect match.[18] The glycosidation and final deprotection gave a single diastereoisomer. Two diastereoisomers of callipeltoside A, **15** (prepared from **4**) and **16** (prepared from *ent*-**4**), have been synthesized in a 22-step longest linear sequence, and 50 total steps in 0.47 % overall yield. The ^{1}H and ^{13}C NMR spectroscopic data shows, as expected, no difference between **15**, **16**, and the natural sample (Scheme 4).[19]

The unambiguous assignment of the absolute and relative configuration comes from the rotation values. Indeed, **15** has a rotation of $[\alpha]_D^{22} = -19.2$ ($c = 1.0$, CH_3OH), very close in absolute value to and with the same sign as the natural sample $[\alpha]_D = -17.6$ ($c = 0.04$, CH_3OH), whereas **16** has a rotation of $[\alpha]_D^{22} = +156.3$ ($c = 0.55$, CH_3OH). This significant difference allows us to assign the absolute and relative configuration of callipeltoside A (**1**) as **15**.

This synthesis of callipeltoside A (**1**) is highly convergent: the three main pieces of the molecule, that is, the macrolactone, the side chain, and the sugar, are assembled within the last four steps of the synthesis. This convergent approach is perfectly suited to pursue structure–activity studies, and enabled us to synthesize two isomers of **1**. The synthesis of the

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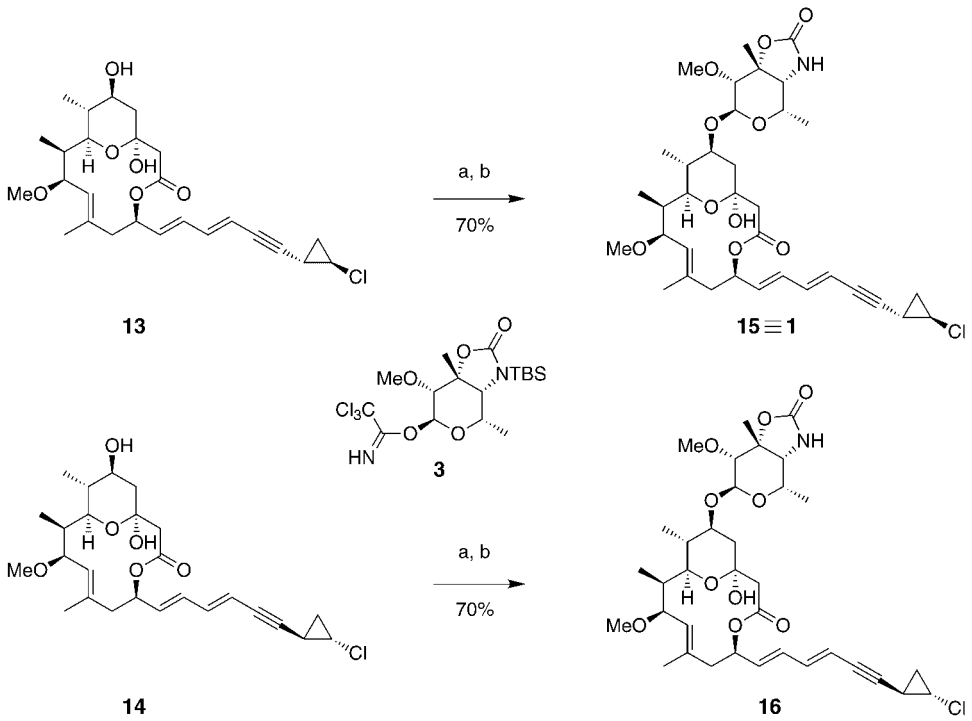

Scheme 4. Completion of the synthesis. a) **3**, TMSOTf, 4-Å molecular sieves, 1,2-dichloroethane, $-30\,^{\circ}C$. b) TBAF, AcOH, THF, room temperature. TMSOTf = trimethylsilyl trifluoromethanesulfonate, TBAF = tetrabutylammonium fluoride.

analogues as well as their biological evaluation is underway and will be reported in due course.

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[7] US$ 3.1 per mmol for both enantiomers (Aldrich), but easily accessible from the inexpensive menthol and succinyl chloride.

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[12] The first step of the process is performed at room temperature in the dark in the presence of a phase-transfer catalyst to facilitate the formation of the Barton ester. The second step of the process is performed at reflux in the presence of light and a radical initiator to favor the radical chain over thermal degradation.

[13] Microwave heating was carried out in a Smith Workstation US manufactured by Personal Chemistry AB.

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[15] All the spectroscopic data as well as the rotation of **9**/*ent*-**9** are identical to the reported values (ref. [4d]); rotation of **9**: $[\alpha]_D^{27} = -80.3$ ($c = 0.77$, CH_2Cl_2); rotation of *ent*-**9**: $[\alpha]_D^{27} = +80.1$ ($c = 1.40$, CH_2Cl_2), literature value (ref. [4d]): $[\alpha]_D^{25} = -80.5$ ($c = 0.71$, CH_2Cl_2).

[16] All spectroscopic data, with the exception of the rotation of **10**/*ent*-**10**, are identical to those reported (ref. [4d]); rotation of **10**: $[\alpha]_D^{26} = -222.7$ ($c = 0.70$, CH_2Cl_2); rotation of *ent*-**10**: $[\alpha]_D^{26} = +225.5$ ($c = 0.70$, CH_2Cl_2), literature value (ref. [4d]): $[\alpha]_D^{25} = -78.9$ ($c = 0.705$, CH_2Cl_2).

[17] The transketalization (pyridinium *p*-toluenesulfonate, MeCN, H_2O) used in our synthesis of deschlorocallipeltoside A was not necessary upon modification of the workup conditions, that is, adding a solution of sodium bicarbonate to the reaction mixture instead of adding the reaction mixture to a solution of sodium bicarbonate.

[18] For ^1H and ^{13}C NMR spectra of **13** and **14**, see: Supporting Information; rotation of **13**: $[\alpha]_D^{23} = -39.4$ ($c = 1.00$, $CHCl_3$), to be compared with the reported value for *ent*-**13** (ref. [3]): $[\alpha]_D^{20} = +45.8$ ($c = 0.28$, $CHCl_3$); rotation of **14**: $[\alpha]_D^{25} = +125.0$ ($c = 1.00$, $CHCl_3$), to be compared with the reported value for *ent*-**14** (ref. [3]): $[\alpha]_D^{20} = -97.8$ ($c = 0.19$, $CHCl_3$).

[19] For ^1H and ^{13}C NMR spectra of **15** and **16**, see Supporting Information.

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