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Stereocontrolled Total Synthesis of (−)-Callipeltoside A

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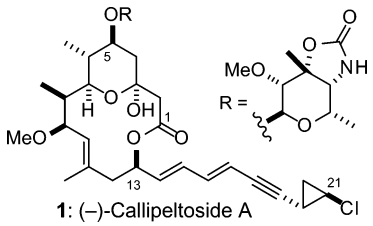
ABSTRACT



1: (−)-Callipeltoside A

A highly stereocontrolled total synthesis of the cytotoxic macrolide (−)-callipeltoside A has been achieved in 23 steps (4.8% overall). Notable features include a novel asymmetric vinylogous aldol reaction to install the C13 stereocenter and (*E*)-trisubstituted alkene, an anti-selective aldol addition, a Sonogashira coupling, and, last, a Schmidt-type glycosylation to attach the sugar unit.

Callipeltoside A (**1**) is a rare cytotoxic polyketide, isolated by Minale and co-workers[1] from the lithistida sponge *Callipelta* sp., collected off the coast of New Caledonia. Preliminary biological screening in vitro indicated marked cytotoxicity, blocking proliferation in the G1 phase, highlighting callipeltoside A as a putative mechanism-based lead. Structurally, callipeltoside A features a 14-membered macrolide, containing a six-membered hemiacetal ring, linked glycosidically through C5 to an unusual aminodeoxy sugar. The pendant dienyne side chain at C13 terminating in a *trans*-chlorocyclopropane ring constitutes a further unusual feature, where its stereochemical relationship relative to the macrolactone segment was initially undefined.

The extraordinary structure together with the stereochemical ambiguities, combined with its significant biological activity, have sparked extensive synthetic studies toward callipeltoside A,[2−6] culminating recently in its total synthesis by the Trost[2a,b] and Evans[3a] groups. These efforts served to assign the full configuration as indicated in **1**, while we had earlier established the configuration of the macrolide core by synthesis of the ent-callipeltoside aglycon.[4] Herein, we report an efficient total synthesis of (−)-callipeltoside A, corresponding to the natural antipode, that proceeds with a uniformly high level of stereocontrol.

As outlined in Scheme 1, our synthetic plan for callipeltoside A relied on the late-stage elaboration of the advanced macrolide intermediate **2** by attachment of the enantiomerically pure cyclopropyl alkyne **3** (C18−C22) and the activated sugar derivative **4**, derived from L-rhamnose.[6] It was envisaged that the iododiene **2** would be assembled, in turn, by

(1) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085.

(2) (a) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396. (b) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841. (c) Trost, B. M.; Gunzner, J. L. *J. Am. Chem. Soc.* **2002**, *123*, 9449.

(3) (a) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654. (b) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133. (c) Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503.

(4) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603.

(5) For other synthetic studies, see: (a) Huang, H. B.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991. (b) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5*, 1147. (c) Romero-Ortega, M.; Colby, D. A.; Olivo, H. F. *Tetrahedron Lett.* **2002**, *43*, 6439. (d) Pihko, A. J.; Nicolaou, K. C.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2001**, *12*, 937. (e) Olivo, H. F.; Velazquez, F.; Trevisan, H. C. *Org. Lett.* **2000**, *2*, 4055. (f) Velazquez, F.; Olivo, H. F. *Org. Lett.* **2000**, *2*, 1931. (g) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169.

(6) Smith, G. R.; Finley, J. J.; Giuliano, R. M. *Carbohydr. Res.* **1998**, *308*, 223.

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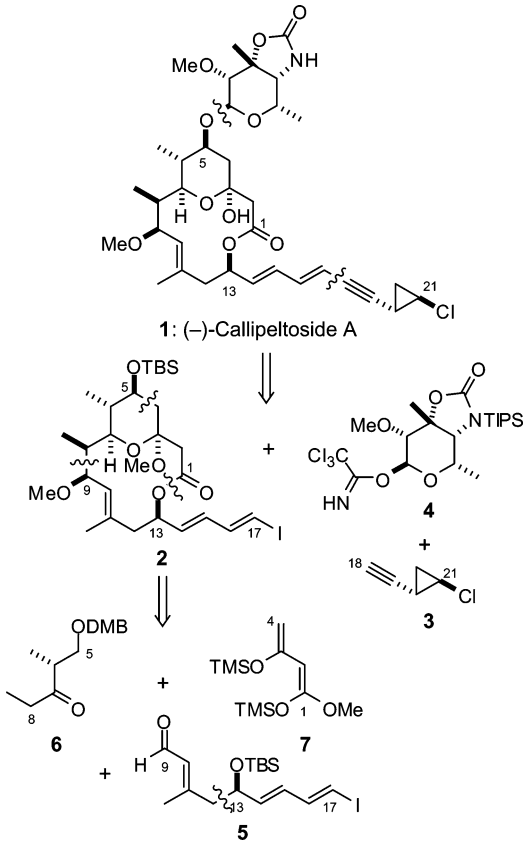
Scheme 1. Retrosynthetic Analysis of Callipeltoside A

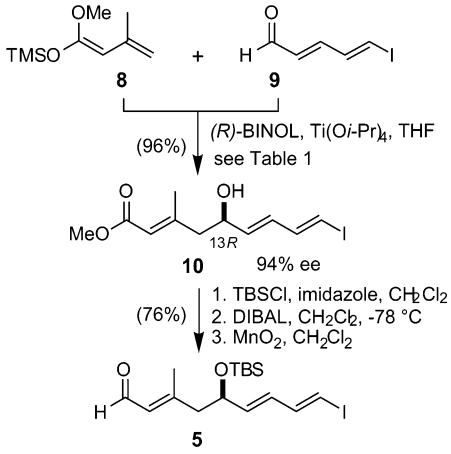


sequential aldol coupling of three building blocks, **5** (C9−C17), **6** (C5−C8), and **7** (C1−C4), followed by a suitable macrolactonization reaction. A key objective for preparing the pivotal C9−C17 subunit **5** was to set up the desired (13*R*)-configuration along with the (10*E*,14*E*,16*E*)-triene geometry in a concise manner.[7]

We reasoned that an asymmetric vinylogous Mukaiyama (AVM) aldol reaction between the silyl dienolate **8**[8] and the readily available[4,9] iododienal **9** (Scheme 2) might be realized using a suitable chiral Lewis acid promoter. Initial exploratory studies identified the (*R*)-BINOL-Ti(O*i*-Pr)$_2$ system, formed in situ from (*R*)-BINOL and Ti(O*i*-Pr)$_4$ in the presence of 4 Å molecular sieves, as a promising catalyst for this AVM reaction.[10,11]

In optimizing this reaction (Table 1), high catalyst loadings and low temperatures were found to be necessary. Notably, this procedure resulted in exclusive reaction of the silyl dienolate **8** through the γ-position with the iododienal **9**, generating aldol adduct **10** in up to 98% ee,[12] incorporating

Scheme 2



the required (*E*)-trisubstituted alkene, albeit in moderate yield initially (entries1−4).

Table 1. Optimization of the AVM Reaction to Give **10**

entry	catalyst (equiv)	temp (°C)	time (h)	additive	yield (%)	ee (%)
1	0.5	−78	4.5	4 Å MS	45	98
2	0.5	−20	14	4 Å MS	52	98
3	0.5	0	18	4 Å MS	41	89
4	0.2	−20	20	4 Å MS	36	26
5	0.5	−78	70	CaH_2	96	94

Replacement of the 4 Å molecular sieves with CaH_2 powder achieved much higher conversions (entry 5), preventing both competing hydrolysis of the silyl ketene acetal **8** and acid-promoted isomerization of the vinyl iodide. Gratifyingly, under these improved conditions (THF, −78 °C, 70 h) using 0.5 equiv each of Ti(O*i*-Pr)$_4$ and (*R*)-BINOL in the presence of CaH_2, aldol adduct **10** was obtained cleanly in 96% yield with 94% ee on a multigram scale.

This key step served not only to incorporate the terminal iododiene functionality, enabling the later attachment of the full callipeltoside side chain, and the (*E*)-trisubstituted alkene but did so with essentially complete stereocontrol at the incumbent C13 carbinol. TBS ether formation, followed by conversion to the aldehyde using DIBAL reduction and mild MnO_2 oxidation, then provided the C9−C17 subunit **5** in 76% overall yield.

At this point, the assembly of the macrolide core **2** by sequential chain extension of the nonracemic aldehyde **5**, initially employing the (*R*)-configured ethyl ketone **6**[13] in a boron-mediated anti-selective aldol coupling,[14] was required. Due to concerns over the chemoselectivity of DDQ-mediated oxidative cleavage, the 3,4-dimethoxybenzyl (DMB) ether[15]

(7) Previously, aldehyde **5** was used as its racemate, which permitted the configurational flexibility at C13 required at the time (ref 4).

(8) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.

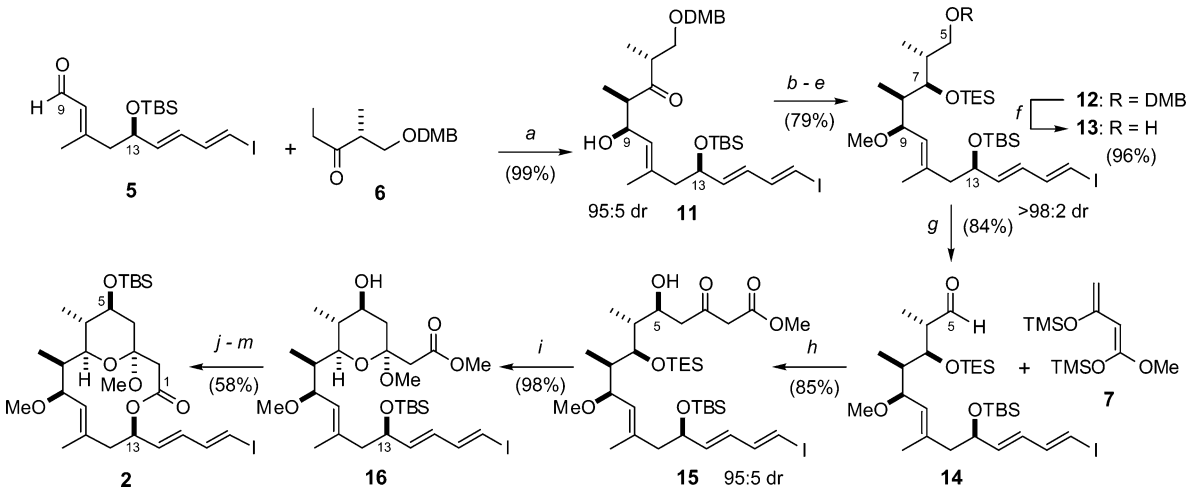
(9) Iodide **9** was prepared in two steps from pyridinium-1-sulfonate in 35% yield; see: (a) Becher *J. Synthesis* **1980**, 589. (b) Soullez, D.; Plé, G.; Duhamel, L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1639.

(10) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435.

(11) For a recent review of the vinylogous aldol reaction, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

(12) Absolute configuration of **10** was established using the advanced Mosher method, while the enantiomeric purity was determined by chiral HPLC analysis. Kusumi, T.; Hamada, T.; Ishitsuka, M. O.; Ohtani, I.; Kakisawa, H. *J. Org. Chem.* **1992**, *57*, 1033.

Scheme 3[a]



[a] Reagents and conditions: (a) **6**, *c*-Hex$_2$BCl, Et$_3$N, Et$_2$O, −20 °C; **5**, −78 to −30 °C. (b) SmI$_2$, EtCHO, THF, −20 °C. (c) TESOTf, lutidine, CH$_2$Cl$_2$, −78 °C. (d) DIBAL, CH$_2$Cl$_2$, −78 °C. (e) Me$_3$OBF$_4$, proton sponge, CH$_2$Cl$_2$, 0 °C. (f) DDQ, CH$_2$Cl$_2$, pH 7 buffer, reflux. (g) Dess−Martin periodinane, CH$_2$Cl$_2$. (h) BF$_3$·Et$_2$O, CH$_2$Cl$_2$, −100 °C. (i) PPTS, (MeO)$_3$CH, MeOH. (j) TBSOTf, lutidine, CH$_2$Cl$_2$, −78 °C. (k) TBAF, THF; (l) Ba(OH)$_2$·8H$_2$O, MeOH. (m) 2,4,6-Cl$_3$(C$_6$H$_2$)COCl, Et$_3$N; DMAP, PhMe, 80 °C.

was used here in place of the standard 4-methoxybenzyl (PMB) variant. Aldol coupling of the (*E*)-enolate generated from **6** with aldehyde **5** gave adduct **11** in 99% yield and 20:1 dr, where the remote silyloxy-bearing stereocenter at C13 had minimal influence on the stereoinduction. An Evans−Tishchenko 1,3-anti reduction[16] of *β*-hydroxy ketone **11** and formation of the TES ether from the resulting C7 hydroxyl group (obtained with 98:2 dr) was followed by reductive cleavage of the C9 ester and O-methylation to afford **12** in 79% overall yield.

Our choice of the DMB protecting group was precipitated by concerns over unwanted oxidation of the allylic TBS ether at C13 in **12** under the agency of DDQ. Indeed, this increased electron density led to enhanced chemoselectivity in comparison with the PMB group.[4] Treating DMB ether **12** with a slight excess of DDQ in moist CH$_2$Cl$_2$ for 15 min provided the alcohol **13** in 67% yield (96% based on recovered **12**), with none of the C13 ketone observed. Dess−Martin oxidation then gave the aldehyde **14** (84%) in readiness for a Mukaiyama-type aldol reaction. Addition of the 1,3-bis(silyloxy)diene **7**[17] to the aldehyde **14**, in the presence of BF$_3$·OEt$_2$ at −100 °C, provided the Felkin−Anh product **15** in 85% yield and 95:5 dr. Cleavage of the TES ether and concomitant methyl acetal formation (PPTS, (MeO)$_3$CH, MeOH) then gave **16**. Formation of the TBS ether at C5, followed by selective deprotection of the allylic TBS ether at C13 with TBAF and saponification with Ba(OH)$_2$, then provided the corresponding seco-acid (90%), which underwent the crucial Yamaguchi macrolactonization reaction[18] to give macrocycle **2** in 64% yield.

At this stage, it still remained to build out the chlorocyclopropyl-containing side chain and glycosylate the C5 alcohol with an appropriate sugar derivative (Scheme 4). First, the fully elaborated side chain was introduced by a Sonogashira-type[19] sp^2−sp cross-coupling between the vinyl iodide **2** and the (20*S*,21*R*)-alkyne **3**,[4] obtained on treatment of an Et$_2$O solution of dibromoalkene **17** with *n*-BuLi. Under optimized coupling conditions (PdCl$_2$(PPh$_3$)$_2$, CuI, *i*-Pr$_2$NH, EtOAc), this provided the protected aglycon **18** cleanly in 83% yield. Deprotection of the TBS ether and concomitant hydrolysis to the methyl acetal with TFA in aqueous THF then gave the callipeltoside aglycon **19** (98%). Final completion of the total synthesis of callipeltoside A relied on coupling of this aglycon with the activated sugar **4** (obtained from L-rhamnose by adaptation of the sequence reported by Guiliano and co-workers[6]) via a Schmidt-type glycosylation.[2a,20] Treatment of a mixture of the C5 alcohol **19** and the trichloroacetimidate **4** with a catalytic amount of TMSOTf in CH$_2$Cl$_2$ at −30 °C, followed by desilylation with TBAF/AcOH, then gave (−)-callipeltoside A (**1**) in 76% yield. The ^{1}H and ^{13}C NMR data and, importantly, the specific rotation value,[21] $[\alpha]^{20}_D = -17.0$ (*c* 0.34, MeOH) cf. $[\alpha]^{23}_D = -17.6$

(13) Ethyl ketone **6** was prepared in 60% yield from methyl (*R*)-3-hydroxy-2-methylpropionate in an analogous manner to that reported previously for the PMB ether: (i) DMBO(CCl$_3$)C=NH, PPTS, CH$_2$Cl$_2$; (ii) MeONHMe·HCl, *i*-PrMgCl, THF, −20 °C; (iii) EtMgCl, THF, 0 °C. (a) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

(14) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett*. **1989**, *30*, 7121. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc*. **1994**, *116*, 11287.

(15) Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1984**, *25*, 5393.

(16) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447.

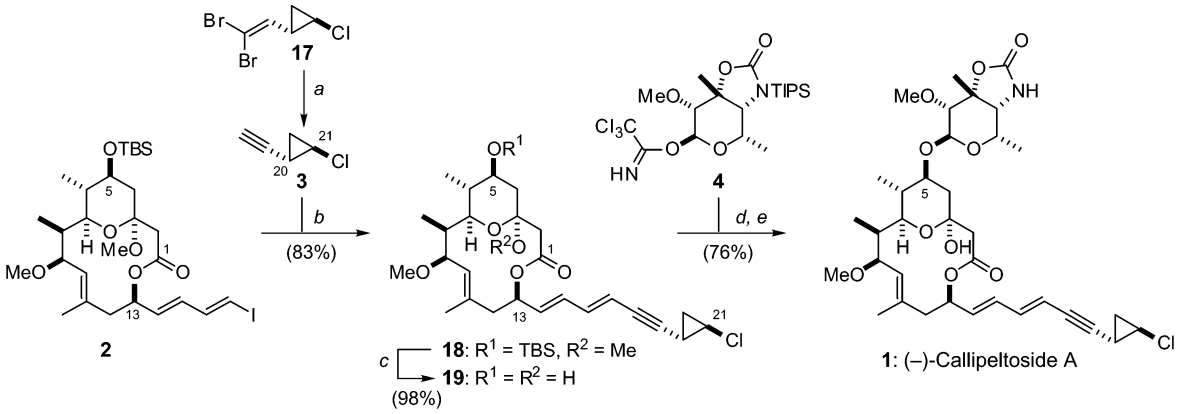
(17) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688.

(18) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989.

(19) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159.

(20) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl*. **1980**, *19*, 731.

Scheme 4[a]



[a] Reagents and conditions: (a) *n*-BuLi, Et_2O, −78 °C. (b) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, EtOAc, −20 to 0 °C. (c) TFA, aq THF. (d) TMSOTf, CH_2Cl_2, 4 Å MS, −30 °C. (e) TBAF, AcOH, THF.

(*c* 0.04, MeOH), were in agreement with that reported for natural callipeltoside A.[1]

In conclusion, a highly stereoselective synthesis of (−)-callipeltoside A has been achieved in 4.8% overall yield and 23 steps for the longest linear sequence.[22] This work highlights a novel enantioselective vinylogous Mukaiyama aldol reaction that, in tandem with our diastereoselective boron-mediated aldol methodology using the novel DMB-protected chiral ketone **6**, has provided a rapid and efficient synthetic entry into this structurally unique class of bioactive marine macrolides.

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Supporting Information Available: Full characterization of all new compounds, copies of NMR spectra for callipeltoside A, and experimental details for the preparation of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Notably, the unnatural (20*R*,21*S*)-diastereomer of callipeltoside, incorporating the antipodal chlorocyclopropane, has a distinctly different specific rotation, as reported by both Trost (ref 2a,b) and Evans (ref 3a), and as expected from our earlier findings on the aglycon (ref 4).

(22) Calculated from pyridinium-1-sulfonate as the precursor to iodide **9**.