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Enantioselective Total Synthesis of Callipeltoside A

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Callipeltoside A (**1**) was isolated from the lithistid sponge *Callipelta* sp. by Minale and co-workers in 1996.[1] Preliminary biological assays indicated that this marine natural product exhibits cytotoxic activity against NSCLC-N6 human bronchopulmonary nonsmall-cell lung carcinoma and P388 cell lines.[1] At the time this project was undertaken, the relative stereochemical relationships between the sugar and the macrolactone had been proposed on the basis of 2D-NMR studies. However, the relative stereochemistry of the chlorocyclopropyl side chain to the rest of the molecule and the absolute stereochemistry of callipeltoside A remained unassigned. Recently, both Paterson[2a] and Trost[2b] have found that enantiomeric *trans*-chlorocyclopropane side chains were too remote to induce visible differences in the ^{1}H- or ^{13}C-NMR spectra of either the aglycons or the glycosylated macrolactones. However, the optical rotations of the two side chain stereoisomers were dramatically different. These values enabled Trost to determine the relative and absolute stereochemistry of callipeltoside A through his recently disclosed total synthesis. In this Communication, we wish to report a convergent asymmetric synthesis of callipeltoside A from the illustrated subunits (Scheme 1).

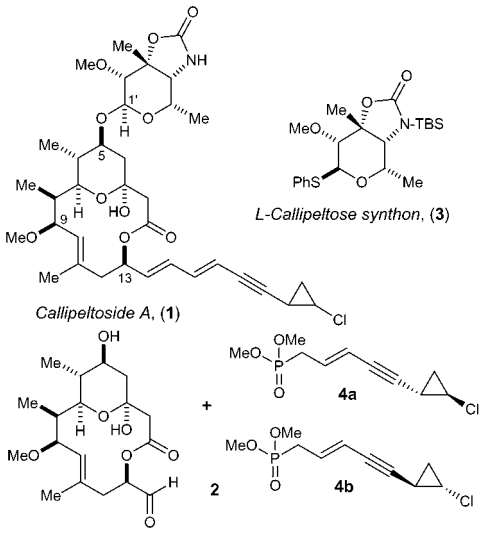
In prior communications, we have described approaches to the syntheses of L-callipeltose and the enantiopure chlorocyclopropane-containing side chain fragments **4**.[3] On the basis of Celmer's model for macrolide stereochemical relationships,[4] we selected the illustrated macrolactone enantiomer as the synthesis objective.

The synthesis began with the development of the illustrated [Cu((*R*,*R*)PhPyBox)](SbF$_6$)$_2$·2H$_2$O (**5**)[5,6] catalyzed vinylogous aldol addition reaction[7] between enolsilane **6**[8] and *p*-methoxy benyzloxyacetaldehyde (**7**), which afforded the desired aldol adduct **8** in excellent yield (93%) and enantioselectivity (95%) as a single olefin isomer.[9] This ester was then converted to aldehyde **9** in good overall yield. With aldehyde **9**-(*R*) in hand, the anti-aldol reaction with *β*-ketoimide **10** was then investigated (Scheme 2, eq 1).[10] In contrast to prior precedent, this aldol reaction proceeded with poor facial selectivity, yielding a 55:45 mixture of the two anti-aldol adducts, favoring the desired isomer **11a**.[11] On the other hand, the analogous reaction with aldehyde **9**-(*S*) afforded the aldol adduct **11b** with excellent diastereochemical control (92:8). *Taken together, these two reactions (eqs 1 and 2) document an unanticipated facial bias resulting from the remote secondary silyloxy stereocenter on the aldehyde reaction partner*. This result forced us to reconsider the eventual macrocyclization strategy where the C13 center would have to be inverted.[12]

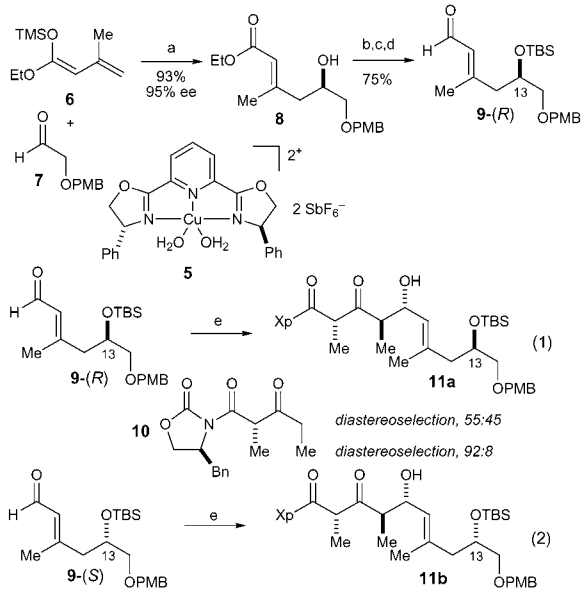
The assemblage of the seco acid continued with a hydroxyl-directed anti-reduction of **11b**,[13] followed by ring closure to lactone **12** (Scheme 3), a convenient point for purification. Following a routine series of transformations, Chan's diene[14] was added to aldehyde **13** with excellent Felkin control (>95:5).[15] Silylation, methanolysis, and methylation of **14** then produced the lactol methyl ether **15**.

While attempts to induce macrolactonization under Mitsunobu conditions did not afford any desired product, it was found that exposure of mesylate **16** to cesium carbonate, and 18-crown-6 in

Scheme 1



Scheme 2 [a]



[a] Reagents: (a) 2.5 mol% [Cu((*R*,*R*)-PhPyBox)](SbF$_6$)$_2$·2H$_2$O (**5**), CH$_2$Cl$_2$, −78 °C; HCl (aq), EtOAc, rt. (b) TBSCl, imid., DMF, rt. (c) LiAlH$_4$, Et$_2$O, rt. (d) SO$_3$·pyr, DMSO, Et$_3$N, CH$_2$Cl$_2$, 0 °C. (e) **10**, Cy$_2$BCl, EtNMe$_2$, Et$_2$O, 0 → −78 °C then RCHO, −78 → −20 °C.

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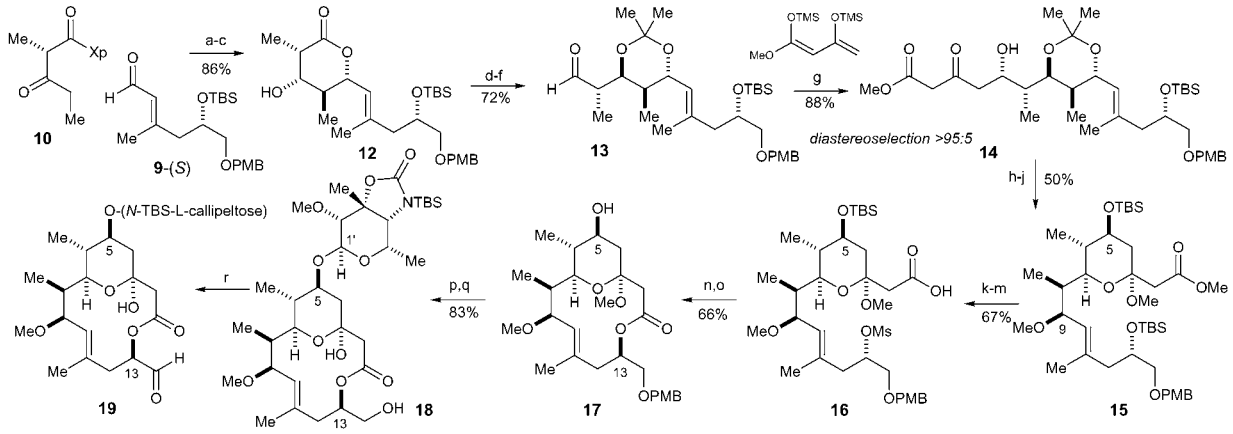
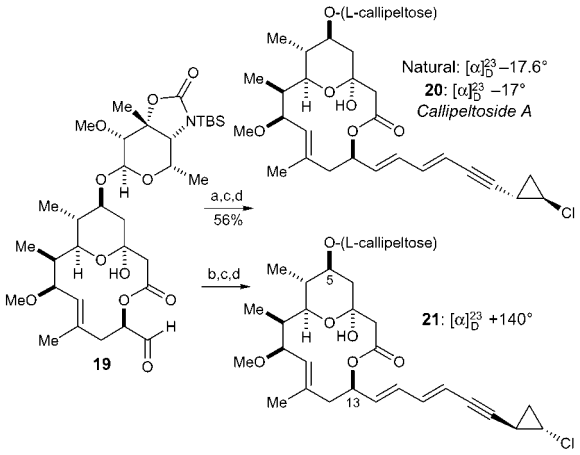
Scheme 3 [a]



[a] Reagents: (a) **10**, Cy_2BCl, $EtNMe_2$ 0 → −78 °C then **9**-(*S*). (b) $Me_4NBH(OAc)_3$, MeCN, AcOH, 0 °C. (c) $HN(CH_2CH_2OH)_2$, EtOAc, rt. (d) HNMe(OMe)·HCl, $AlMe_3$, CH_2Cl_2, 0 °C → rt. (e) $Me_2C(OMe)_2$, PPTS, acetone, rt. (f) $LiAlH_4$, Et_2O, rt. (g) $BF_3{\cdot}OEt_2$, toluene, −90 °C. (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C. (i) PPTS, MeOH, rt. (j) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, rt. (k) TBAF, THF, rt. (l) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C. (m) LiOH, H_2O, MeOH, THF, rt. (n) 1.5 mM, Cs_2CO_3, 18-crown-6, toluene, 110 °C. (o) TBAF, THF, rt. (p) **3**, NIS, TfOH, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −15 °C → rt. (q) DDQ, MeOH, CH_2Cl_2, H_2O, rt. (r) $SO_2{\cdot}$pyr, Et_2N, DMSO, CH_2Cl_2, 0 °C.

Scheme 4 [a]



[a] Reagents: (a) LiHMDS, **4a**, THF, −78 °C → rt. (b) LiHMDS, **4b**, THF, −78 °C → rt. (c) I_2, CH_2Cl_2, rt. (d) TBAF, AcOH, THF, rt.

refluxing toluene effected the desired macrocyclization to produce macrolactone **17** in 66% yield after $Bu_4N^+F^-$ (TBAF) deprotection. NIS-mediated glycosidation[16] of thioglycoside **3** with alcohol acceptor **17** formed the glycoside bond in 95% yield as a single anomer.

Consecutive deprotection of the C14 *p*-methoxybenzyl (PMB) ether and hydrolysis of the C3 ketal to lactol with DDQ afforded **18** in 83% yield, which was oxidized to **19** under Parikh−Doering conditions.[17] Although olefination of phosphonate **4** was only moderately selective (E:Z = 3:1), this mixture could be cleanly isomerized to the trans olefin (E:Z >11:1) by using a catalytic amount of iodine (Scheme 4). Finally, desilylation with TBAF/AcOH furnished **20** in 56% overall yield from alcohol **18**. The other *trans*-chlorocyclopropane side chain isomer **21** was prepared in a similar manner. Indeed, while the spectral data of the diastereomers **20** and **21** were both completely consistent with natural callipeltoside, the optical rotations of the two diastereomers differed in both sign and magnitude: diastereomer **20** exhibited a rotation of −17° (*c* 0.19, MeOH) while diastereomer **21** registered a rotation of +140° (*c* 0.05, MeOH). Since natural callipeltoside A has a reported optical rotation of −17.6° (*c* 0.04, MeOH),[1] we conclude that **20** is the structure of callipeltoside A, in full agreement with the conclusions drawn by Trost.

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Supporting Information Available: Full characterization data of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085−11088.
(2) (a) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603−607. (b) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841−843.
(3) (a) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133−3136. (b) Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503−505.
(4) Celmer, W. D. *Ann. N.Y. Acad. Sci.* **1986**, *471*, 299−303.
(5) Evans, D. A.; Kozlowski, M. C.; Murray, J. A.; Burgey, C. S.; Connell, B. *J. Am. Chem. Soc.* **1999**, *121*, 669−685.
(6) Concurrent with this work, the Paterson group published a route to the callipeltoside aglycon that utilizes a racemic vinylogous aldol reaction to set the C10−C11 olefin geometry, ref 2a.
(7) For a review of the vinylogous aldol reaction see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972.
(8) Hoffmann, R. V.; Kim, H.-O. *J. Org. Chem.* **1991**, *56*, 1014−1019.
(9) The absolute stereochemistry of **8**, established by Mosher ester analysis, is consistent with prior precedent for these reactions, ref 5.
(10) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127−2142.
(11) (a) Due to the chromatographic instability of ketones **11a** and **11b**, diastereoselectivity was deteremined by HPLC analysis (Zorbax SiO_2 column) of lactones **12**. Relative stereochemistry of all lactones was verified by NOESY analysis, indicating that in all cases the reduction step proceeded with complete diastereocontrol. (b) As a reference, the sterically and electronically similar senecialdehyde exhibited a 5:1 diastereoselectivity in this reaction.
(12) For a successful Mitsunobu cyclization on a similar system see: Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467.
(13) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.
(14) (a) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534−3538. (b) For a review of the chemistry of Chan's diene see: Langer, P. *Synthesis* **2002**, *4*, 441−459.
(15) Felkin selectivity in this substrate is expected to be high due to the reinforcing stereochemical relationships of the α-methyl and *β*-OR relationships: Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *J. Am. Chem. Soc.* **1996,** *37*, 1957−1960.
(16) (a) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313−4316. (b) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 270−272. (c) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331−1334.
(17) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

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