

A Formal Synthesis of the Callipeltoside  
Aglycone

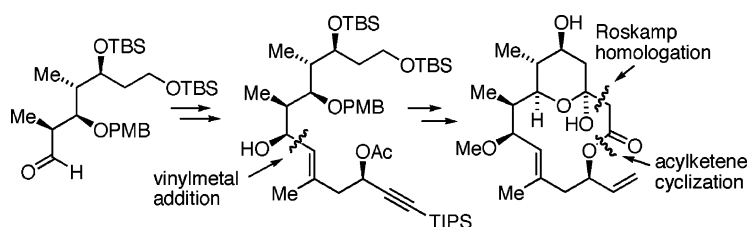
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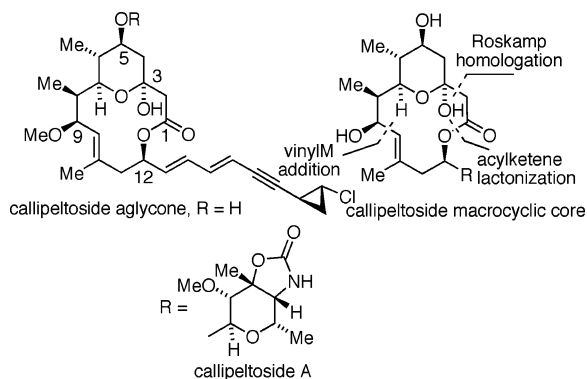
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## ABSTRACT



A synthesis of the macrocyclic core structure of callipeltoside A and a C9 epimer has been achieved by applications of chiral vinylzinc or Kishi–Nozaki–Hiyama (K–N–H) additions, Roskamp homologations, and acylketene or intramolecular K–N–H macrolactonizations as key bond-forming steps.

The lithistid sponge metabolite callipeltoside A and its aglycone (Figure 1) have attracted the attention of synthetic



**Figure 1.** Structure of callipeltoside A and retrosynthesis of the aglycone core.

groups since its reported isolation in 1996 by Minale and co-workers.<sup>1</sup> Initial synthetic work by Paterson,<sup>2</sup> Trost,<sup>3</sup> and Evans<sup>4</sup> led to the correct assignment of relative and absolute

stereochemistry, culminating in total syntheses of the natural product. In these efforts aldol methodology played an important role in construction of the polyketide segments. More recently, Huang and Panek synthesized this array by means of allylsilane reactions.<sup>5</sup> In the present report, we describe a formal total synthesis of the callipeltoside aglycone and its C9 epimer from aldehyde **1**, the enantiomer of which was previously employed in our synthesis of discodermolide.<sup>6</sup>

We have recently shown that the vinylzinc bromide-*N*-methylephedrine complex, prepared from vinyl iodide **2** by the procedure of Oppolzer, reacts with aldehyde **1** to afford the *anti* adduct **3** with >90:10 diastereoselectivity (Scheme 1).<sup>7</sup> This addition efficiently introduces the key C9 stereo-center of the callipeltoside aglycone. Our present studies were

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

(2) (a) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603. Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 4477.

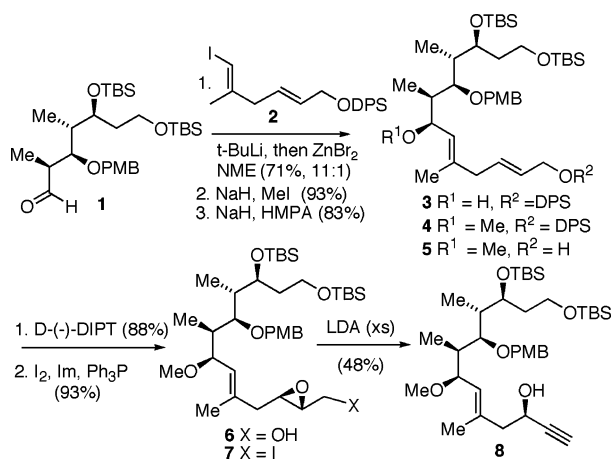
(3) (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

(4) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654.

(5) Huang, H.; Panek, J. S. *Org. Lett.* **2004**, *6*, 4383.

(6) Marshall, J. A.; Lu, Z.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.

Scheme 1

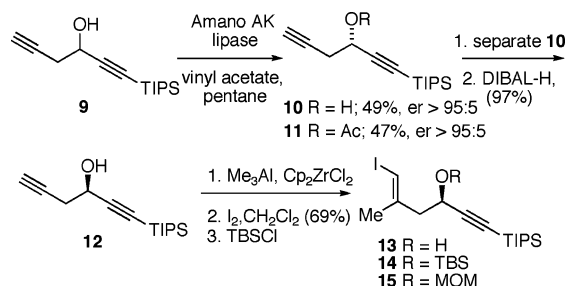


directed toward further elaboration of this intermediate to the macrocyclic lactone core of the natural product.

Methylation of alcohol **3** and then cleavage of the primary DPS ether<sup>8</sup> and Sharpless asymmetric epoxidation of the liberated allylic alcohol **5** with the D-(-)-tartrate reagent gave the epoxy alcohol **6**.<sup>9</sup> Upon treatment with LDA, the derived epoxy iodide **7** underwent double elimination to afford the alkynol **8**.<sup>10</sup>

We also explored a more convergent synthesis of this intermediate by employing the vinyl iodide **14** in which the propargylic alcohol moiety is already present in protected form (Scheme 2). The synthesis of this iodide commenced

Scheme 2



with the kinetic resolution of the racemic alcohol **9** with Amano AK lipase and vinyl acetate in pentane,<sup>11</sup> which afforded a 49:47 mixture of the (*S*)-alcohol **10** and (*R*)-acetate **11** of *er* > 95:5, as measured by Mosher ester analysis.<sup>12</sup> Reductive cleavage of the acetate **11** and selective carboalumination and iodinolysis<sup>13</sup> of the terminal alkyne afforded the iodo alcohol **13** in 69% yield.

(7) Marshall, J. A.; Eidam, P. M. *Org. Lett.* **2004**, *6*, 445.

(8) Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

(9) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(10) (a) Yadav, J. S.; Chander, M. C.; Joshi, B. V. *Tetrahedron Lett.* **1988**, *29*, 2737. (b) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455.

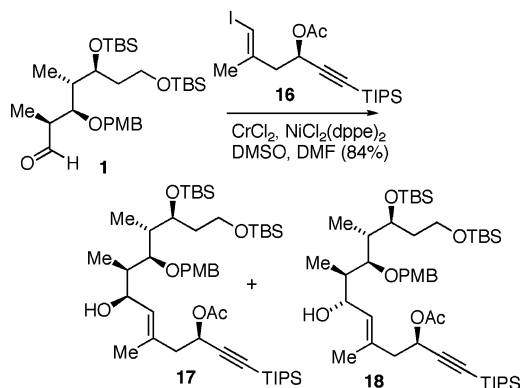
(11) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129.

Surprisingly, our efforts to convert vinyl iodide **14**, the TBS ether of alcohol **13**, to the zinc reagent needed for the Oppolzer addition to aldehyde **1** were not successful. Attempted lithiation of iodide **14** with *t*-BuLi, *s*-BuLi, or BuLi, or by direct lithiation afforded only recovered iodide and decomposition products.

The free alcohol **13** also failed to lithiate. When the MOM ether **15** was treated with *t*-BuLi, a mixture of recovered **15** and its (*Z*) isomer was isolated, suggestive of an OMOM-assisted deprotonation of the vinylic hydrogen.<sup>14</sup> This assumption was verified by lithiation and subsequent D<sub>2</sub>O quench. In separate experiments with vinyl iodide **2** we attempted to generate the Oppolzer zinc complex by reaction with Rieke zinc<sup>15</sup> and subsequent addition of the lithio *N*-methylephedrine followed by cyclohexane carboxaldehyde. None of the desired adduct was produced in these experiments, but we did isolate the protonolysis product derived from the vinylzinc intermediate. Evidently the reactive zinc–NME complex is not formed under these conditions.

An alternative route to the alcohol **17** from aldehyde **1** and vinyl iodide **16** was devised by application of the Kishi–Nozaki–Hiyama (K–N–H) methodology,<sup>16</sup> but the reaction showed little stereoselectivity, affording a disappointing, albeit separable, 60:40 mixture of alcohol adducts **17** and **18** in 84% yield (Scheme 3).<sup>17</sup>

Scheme 3



The major alcohol adduct **17** was methylated,<sup>18</sup> and the primary TBS ether of the intermediate **19** was selectively

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(13) (a) Negishi, E.-i.; VanHorn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639. (b) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

(14) Bonnet, B.; Plé, G.; Duhamel, L. *Synlett* **1996**, 221. Myers, A. I.; Spohn, R. F. *J. Org. Chem.* **1985**, *50*, 4872.

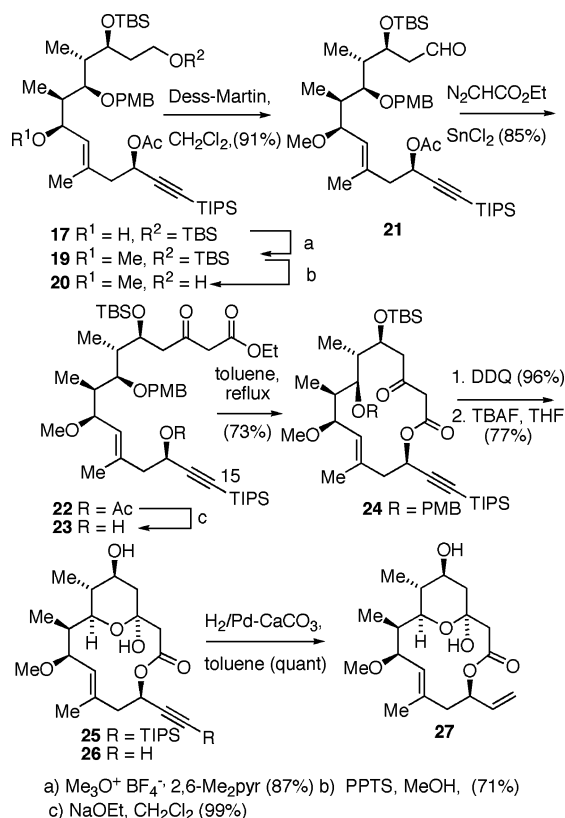
(15) Zhu, L.; Wehmeyer, R. M.; Rieke, R. R. *J. Org. Chem.* **1991**, *56*, 1445.

(16) (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431. (c) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417. (d) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421.

(17) The stereochemistry of the alcohol center was confirmed through mandelic ester analysis. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

(18) Diem, M. J.; Burrow, D. F.; Fry, J. L. *J. Org. Chem.* **1977**, *42*, 1801.

Scheme 4



desilylated to afford the primary alcohol **20** (Scheme 4). The derived aldehyde **21** was cleanly homologated to the  $\beta$ -keto ester **22** by treatment with ethyl diazoacetate and SnCl<sub>2</sub> following the Roskamp protocol.<sup>19</sup> Cleavage of the acetate with NaOEt and pyrolysis of the hydroxy ester **23** in refluxing toluene to form the acylketene<sup>20</sup> led to the macrolide **24** in 73% yield. Oxidative cleavage of the PMB ether with DDQ in CH<sub>2</sub>Cl<sub>2</sub> at pH 7 led to the pyranose **25** in 96% yield. Global desilylation with TBAF in THF gave the terminal alkyne **26** which was reduced to the vinyl compound **27** by Lindlar hydrogenation.<sup>21</sup> The spectral data of **27** were in accord with those reported by Trost.<sup>3b</sup>

The favorable results from the Roskamp homologation prompted our examination of a more elaborate version of this reaction for an alternative approach to the callipeltoside macrolide core. In this version the diazo ester homologation would be employed to prepare an extended acyclic propargylic ester **40** (Scheme 7) which would then be subjected to an intramolecular K–N–H reaction to effect cyclization. It was our hope that the intramolecular reaction would proceed

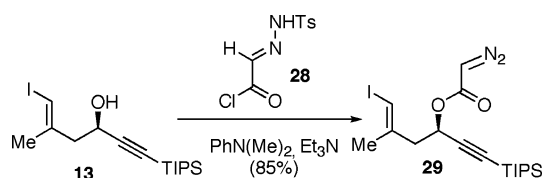
(19) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

(20) Acylketene macrolactonization methodology was first described by Boeckman and Pruitt using dimethyldioxoleneones as acylketene precursors. Boeckman, R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. The Boeckman methodology was subsequently utilized by Trost and Gunzer<sup>4</sup> in their syntheses of callipeltoside A and analogues. In the present example a  $\beta$ -keto ester is employed as the acylketene precursor along the lines of Greene and coworkers. Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380.

(21) Lindlar, H.; Dubuis, R. *Organic Syntheses*; John Wiley: New York, 1973; Collect. Vol. V, p 880.

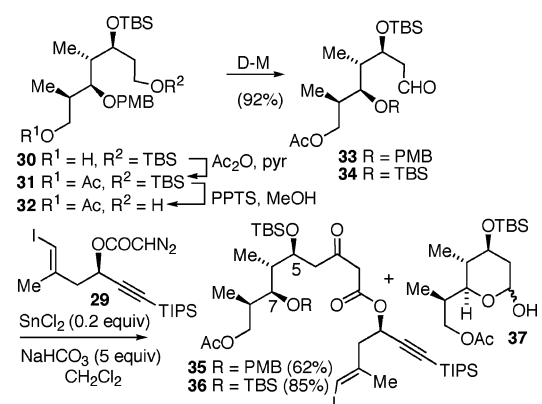
with higher diastereoselectivity than the intermolecular version depicted in Scheme 3. For this sequence alcohol **30**, the precursor of aldehyde **1**, was acetylated and selectively desilylated with PPTS in MeOH to afford alcohol **32**. Oxidation with the Dess–Martin periodinane reagent<sup>22</sup> led to aldehyde **33**, the first of our coupling partners. The second, diazo ester **29**, was secured through esterification of alcohol **13** with the tosylhydrazone **28**, which was converted to **29** in situ (Scheme 5).<sup>23</sup>

Scheme 5



Addition of diazoacetate **29** to aldehyde **33** in the presence of 20 mol % SnCl<sub>2</sub> afforded the  $\beta$ -keto ester **35** in 50% yield and the pyranoside **37** in 30% yield (Scheme 6). When the

Scheme 6



addition was conducted with added NaHCO<sub>3</sub> we obtained the  $\beta$ -keto ester **35** in 62% yield.<sup>24</sup> However, the pyranoside byproduct persisted. Evidently, pyranoside **37** is formed by intramolecular attack of the PMB ether oxygen of **33** on a SnCl<sub>2</sub>–aldehyde complex followed by cleavage of the oxonium ether by chloride.<sup>25</sup> In fact, when the above Roskamp homologation was carried out on the less basic TBS ether **34**, the  $\beta$ -keto ester product **36** was formed in 85% yield. However, as it was desirable to differentiate the C5 and C7 oxygens of **35/36**, we decided to carry on with

(22) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Ireland, R. E.; Lin, L. *J. Org. Chem.* **1993**, *58*, 2899.

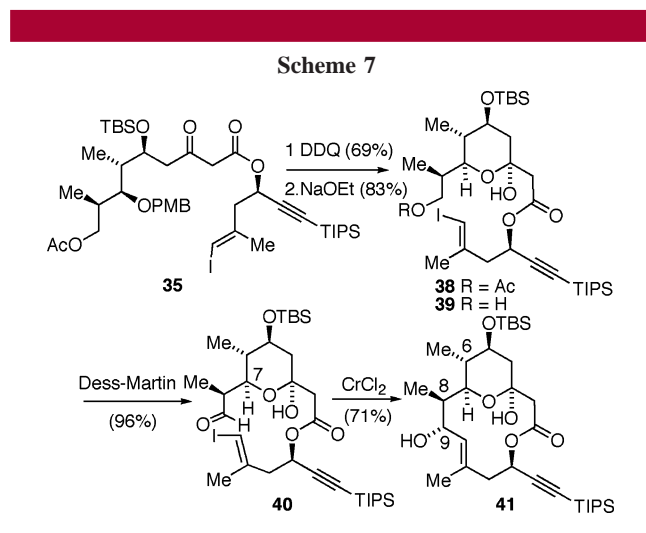
(23) (a) Corey, E. J.; Meyers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559. (b) Blankley, C. J.; Sauter, F. J.; House, H. O. *Organic Syntheses*; John Wiley: New York, 1973; Collect. Vol. V, p 258.

(24) In the absence of NaHCO<sub>3</sub>, ~20% of the diazo ester **29** was converted to the  $\alpha$ -chloro ester by reaction with HCl.

(25) Angle, S. R.; Wei, G. P.; Ko, Y. K.; Kubo, K. *J. Am. Chem. Soc.* **1995**, *117*, 8041.

the former, pending evaluation of the intramolecular K–N–H cyclization. As an aside, we did not observe a lactol byproduct analogous to **37** in reactions of aldehyde **21** with excess ethyl diazoacetate and SnCl<sub>2</sub> (Scheme 4).

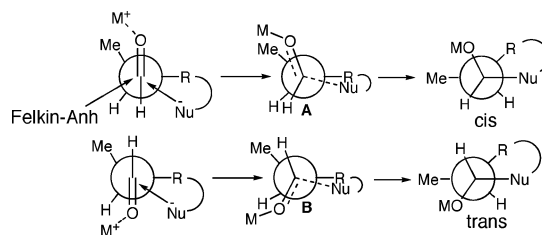
The PMB ether **35** was converted to the pyranose **38** in 69% yield with DDQ (Scheme 7). Cleavage of the acetate



with ethanolic NaOEt and oxidation of the alcohol **39** with the Dess–Martin periodinane reagent afforded aldehyde **40**. Treatment of this aldehyde with CrCl<sub>2</sub> and NiCl<sub>2</sub>(dppp)<sub>2</sub> in DMSO and DMS then afforded the macro lactone **41** as a single diastereomer in 71% yield.<sup>17</sup>

In our initial consideration of the intramolecular K–N–H reaction we carried out a molecular mechanics analysis of a truncated methyl ester analogue of the aldehyde **40**. The analysis indicated that the carbonyl oxygen is oriented anti with respect to the C7 hydrogen in a Felkin–Anh conformation (see the Supporting Information). This arrangement would afford the *cis*-adduct with the desired callipeltoside stereochemistry. However, the formation of the *trans* isomer **41** as the sole adduct must result from an *anti*-Felkin–Anh conformation. A possible explanation emerges from a consideration of the likely transition states for the two alternative additions. The 1,3-disposition of the C6 and C8 methyl groups strictly limits rotation of the C7/C8 bond to minimize a potential 1,3 eclipsing interaction, but the C8/C9 bond suffers no such constraints. While the calculated conformation of the truncated aldehyde **40** conforms to the Felkin–Anh arrangement, the intramolecular nature of the addition requires attack of the vinylic Cr moiety to be *cis* to

the larger  $\alpha$ -substituent. This mode of attack would introduce torsional strain between the C9 oxygen and the C8 methyl group in the transition state (Figure 2, **A**). If, on the other



**Figure 2.** Torsional interactions in cyclization transition states for aldehyde **40**.

hand, the aldehyde carbonyl is rotated by 180°, the corresponding transition state would involve only lower energy O/H and CH<sub>3</sub>/H interactions en route to the observed *trans*-adduct (Figure 2, **B**). Thus, although both inter- and intramolecular carbonyl additions are controlled by transition state considerations, the intramolecular nature of the latter prevents the attacking group from approaching the carbonyl syn to the smaller  $\alpha$  substituent.<sup>26</sup>

In summary, the present synthesis of the callipeltoside aglycone utilizes novel Oppolzer and Roskamp methodologies for polyketide synthesis. Our inability to lithiate vinylic iodides **13**, **14**, and **15** is noteworthy, suggesting certain limitations of this typically trivial synthetic operation. The use of the complex diazo ester **29** for the  $\beta$ -keto ester homologation represents a new application of the heretofore little used Roskamp methodology.

**Acknowledgment.** We are indebted to Martin Herold for his assistance in NMR data analysis and for helpful discussions of various experimental procedures and to Jesse Sabatini for his valuable assistance in additional studies on the zincation of vinylic iodides **13** and **15**.

**Supporting Information Available:** Experimental details, spectral data for new compounds, and a minimized structure representation for aldehyde **40**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(26) It should be noted that *anti*-Felkin–Anh attack on the non-Felkin–Anh conformation of aldehyde **40** affords the same product (*trans*) that would be produced from Felkin–Anh addition to the Felkin–Anh conformation. However, steric constraints would expectedly disfavor this latter pathway in the present case.