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An Aldol-Based Approach to the Asymmetric Synthesis of L-Callipeltose, the Deoxyamino Sugar of L-Callipeltoside A

David A. Evans,* Essa Hu, and Jason S. Tedrow

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

evans@chemistry.harvard.edu

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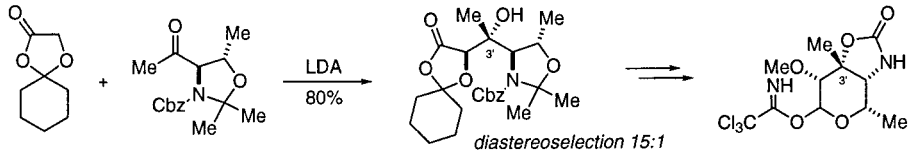
ABSTRACT



The L-callipeltose subunit of L-callipeltoside A has been synthesized in 10 steps and 13% overall yield from D-threonine. The key steps are a highly diastereoselective Felkin anti aldol addition to a methyl ketone and a selective methylation of a secondary alcohol in the presence of a secondary carbamate.

Isolated from the lithistid sponge *Callipelta* sp. by Minale and co-workers in 1996, the callipeltosides A−C (**1a**−**c**, Figure 1) became the first members of a new class of marine natural products with unique structural complexity and biological activity.[1] While all three callipeltosides share the same dienyne-*trans*-chlorocyclopropane side chain appended to the 14-membered aglycon, they are differentiated by their appended sugar subunits. In particular, callipeltoside A (**1a**) contains a highly functionalized deoxyamino sugar (callipeltose). Callipeltoside A exhibits cytotoxic activity against the NSCLC-N6 human bronchopulmonary non-small-cell lung carcinoma and P388 cell lines.[1a] The relative stereochemical relationships of callipeltose to the macrolactone have been proposed on the basis of extensive 2D-NMR spectroscopic studies; however, the relative stereochemical relationships of the chlorocyclopropane side chain to the macrolactone and the absolute stereochemistry of callipeltoside A remain to be determined. In our effort to synthesize callipeltoside A and to elucidate its stereochemical ambiguities, the macrolide was divided into three subunits: the sugar **2**, the side chain **3**[2], and the macrolactone **4** (Scheme 1). Practical synthetic routes have been designed in order to

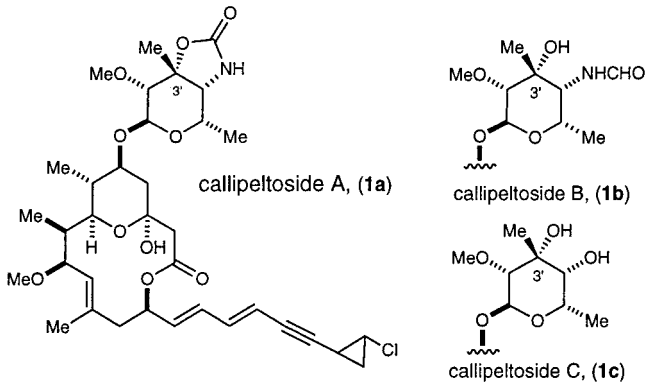


Figure 1. Proposed structures of callipeltosides A−C.

(1) (a) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085−11088. (b) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C. *Tetrahedron* **1997**, *53*, 3243−3248.

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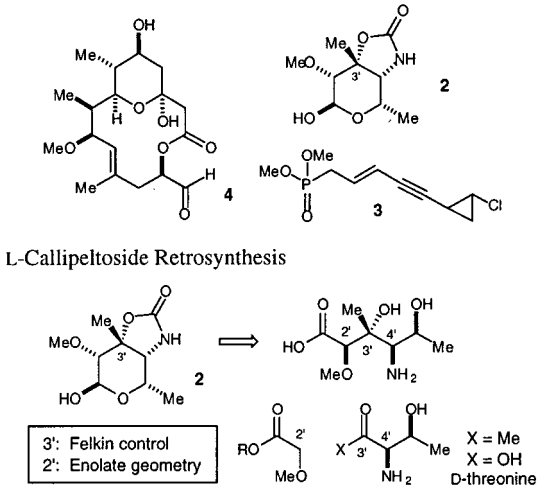
Scheme 1. Callipeltoside Subunits and Retrosynthesis



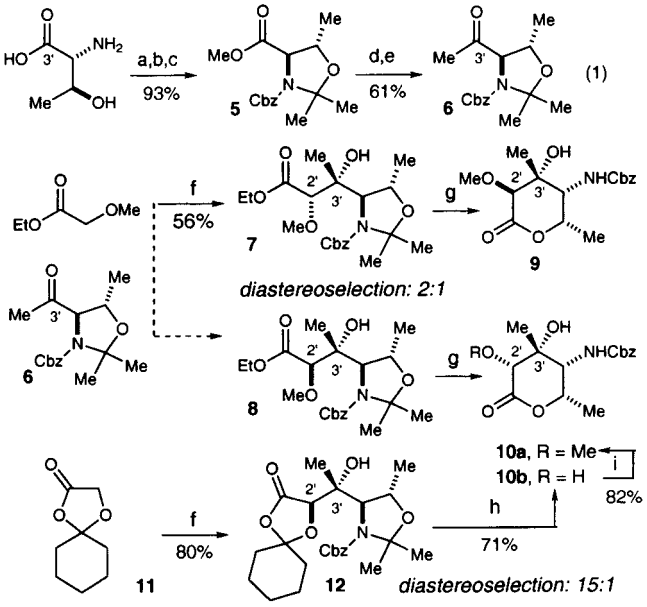
access both enantiomers of each of the three subunits. In this Letter, we describe an asymmetric synthesis of L-callipeltose.

To date, reported syntheses of callipeltose have begun with manno-pyranoside, rhamno-pyranoside, or D-glucal.[3] The need to synthesize both enantiomers of callipeltose prompted us to design a synthesis plan around the utilization of either of the readily available D- or L-threonine enantiomers. Using both enolate geometry and Felkin control elements, we planned to use a diastereoselective aldol addition to threonine methyl ketone to establish both the C2′ and C3′ stereocenters of callipeltose **2** (Scheme 1).

The synthesis began with the well-established protection procedure for D-threonine to afford the *N*-Cbz-D-threonine methyl ester **5** in three steps and 93% yield (eq 1). The addition of the *N*,*O*-dimethylhydroxyamine-derived magnesium amide to ester **5** provided the Weinreb amide in 93% yield,[4] which was transformed to methyl ketone **6** with methylmagnesium bromide in 69% yield (eq 1).[5]

The design of a stereoselective aldol addition to methyl ketone **6** was the pivotal step to this synthesis. Due to reactivity considerations, lithium and sodium enolates were evaluated (Scheme 2). Unfortunately, aldol additions of metal enolates of α-methoxy esters and α-hydroxy esters favored the formation of the undesired syn aldol adducts such as **7**, presumably as a result of metal chelation with the α-alkoxy substituent reinforcing the formation of (*E*) enolates. For example, the lithium enolate derived from ethyl α-methoxyacetate afforded a 2:1 ratio of the Felkin aldol adducts **7** and **8**. The structure of the syn Felkin adduct **7** was un-

Scheme 2. Diastereoselective Aldol Bond Construction[a]



[a] Reaction conditions: (a) NaOH, Cbz-Cl, MeCN, H_2O; (b) MeI, K_2CO_3, DMF; (c) TsOH, dimethoxypropane, benzene; (d) *i*PrMgCl, HN(OMe)Me·HCl, THF; (e) MeMgBr, THF; (f) LDA, then **6**; (g) HF, THF; (h) AcOH, H_2O; (i) $Me_3O{\cdot}BF_4$, 2,6-di-*tert*-butyl-4-methylpyridine.

equivocally established by X-ray crystallography (Figure 2). Both aldol adducts were then individually transformed to afford lactones **9** and **10a**. NOE studies carried on these lactone diastereomers established that both aldol adducts possessed the desired absolute stereochemical relationship at the 3′ tertiary carbinol center and a diastereomeric relationship at the 2′ center. These results then directed our attention to the related aldol reactions of the lithium enolate derived from 1,4-dioxaspiro[4.5]decan-2-one **11**,[6] which would afford the complementary (*Z*) enolate geometry. In the event, the aldol addition with methyl ketone **6** afforded the Felkin anti aldol adduct **12** with a 15:1 diastereomeric ratio and 80% yield (Scheme 2). The stereochemical assign-

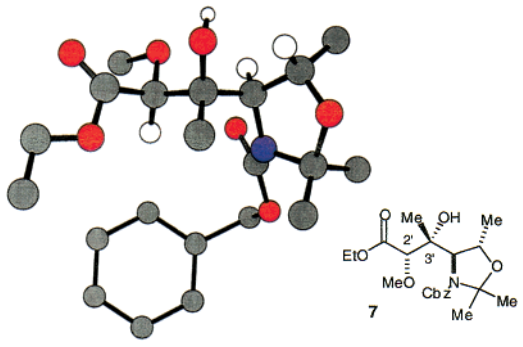


Figure 2. X-ray structure of aldol adduct **7**.

(2) Our synthesis of the side chain has been published: Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503−505.

(3) (a) Smith, G. R.; Finley, J. J. IV; Giuliano, R. M. *Carbohydr. Res.* **1998**, *308*, 223−237. (b) Gurjar, M. K.; Reddy, R. *Carbohydrate Lett.* **1998**, *3*, 169−172. (c) Pihko, A. J.; Nicolaou, K. C.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2001**, *12*, 937−942.

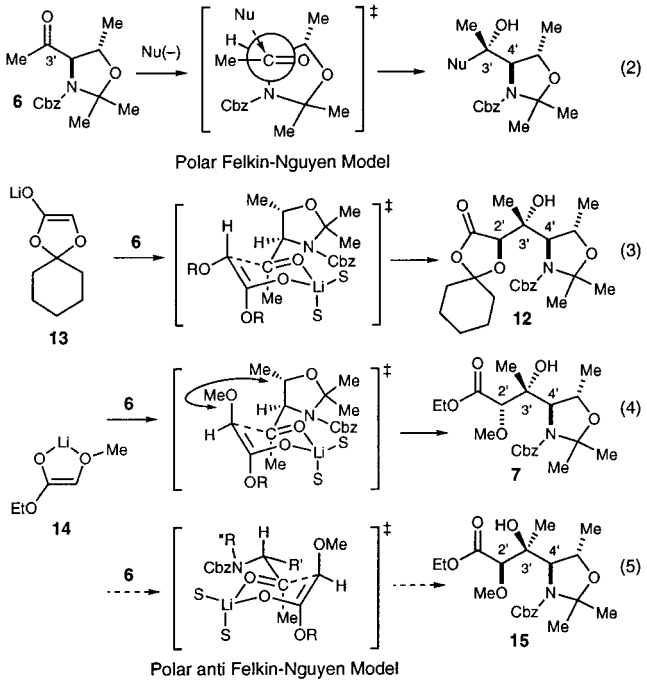
(4) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

(5) Other conditions and nucleophiles, such as methyllithium, lead to lower yields.

ment of **12** was made through the lactone **10b**, which was directly correlated with its methylated counterpart **10a**.

Scheme 3 illustrates the transition state model proposed

Scheme 3. Asymmetric Induction and Felkin−Nguyen Model



to explain the stereochemical outcome. The polar Felkin−Nguyen model[7] predicts that nucleophilic addition to the *si* face of the methyl ketone **6** should be expected (eq 2). The Zimmerman−Traxler transition state model[8] suggests that (*Z*) enolate addition to the methyl ketone should afford the anti aldol adduct **12** (eq 3). Accordingly, the stereochemical outcome of this transformation is in full accord with the indicated models.

Rationalization of the stereochemical outcome of the aldol addition of (*E*) enolate **14** to methyl ketone **6** is less straightforward. On the basis of the polar Felkin−Nguyen model, (*E*) enolate **14** should experience steric repulsion from the threonine side chain in the Zimmerman−Traxler transition state (eq 4). Minimization of this unfavorable interaction should have resulted in an anti Felkin addition of the (*E*) enolate to the *re* face of methyl ketone **6** (eq 5). However, the X-ray structure of syn aldol adduct **7** (Figure 2) reveals that the (*E*) enolate still exhibits a preferred addition to the *si* face of methyl ketone **6**. This suggests that either the steric repulsion predicted by the polar Felkin−Nguyen model was not sufficiently significant for the (*E*) enolate to reverse its *si* face preference or that there exists another low energy pathway that can accommodate the α-methoxy substituent on the (*E*) enolate while still favoring *si* face addition to the ketone. It is also worth noting that the assertion that there should be a reversal in carbonyl face selectivity for enolate **14** is based on trends established for α-methyl substituted aldehydes.[9] Aldol addition studies to α-alkoxy aldehydes reported by Heathcock[10] also suggest that carbonyl face reversal with enolates such as **14** may not be general for all chiral aldehyde substrates.

The conversion of α-hydroxy lactone **10b** to lactone methyl ether **10a** required methylation conditions that would differentiate the 2′-secondary alcohol from the 4′ secondary carbamate. Strongly basic conditions, such as sodium hydride or sodium *tert*-butoxide, either epimerized the C2′ alcohol stereocenter or opened the lactone ring. The addition of silver oxide and methyl iodide to lactone **10b** afforded only 40% of the desired product at room temperature, and elevated temperatures induced *N*-methylation of the carbamate. The use of methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine resulted in decomposition of the lactone. Meerwein's reagent ($Me_3O{\cdot}BF_4$) and proton sponge (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine) afforded less than 50% of the desired product, and separation of the base from the polar product was tedious. Fortunately, a combination of Meerwein's reagent and 2,6-di-*tert*-butyl-4-methylpyridine in dichloromethane provided the desired product **10a** in 82% yield (Scheme 2).[11]

Two transformations remained to complete the synthesis of callipeltose: formation of the cyclic carbamate and reduction of the lactone to lactol (Scheme 4). Initial attempts to form the cyclic carbamate followed by reduction of the lactone resulted in preferential opening of the more reactive cyclic carbamate. Thus, our attention turned toward lactone reduction followed by formation of a stable glycoside intermediate prior to carbamate cyclization. Diisobutylaluminum hydride reduction of lactone **10b** to lactol **19** followed by acidic methanolysis, however, did not provide the desired pyranoside **20a** but yielded the pyrrolidine derivative **20b** instead. (eq 6).

This undesired lactol rearrangement was circumvented using Rychnovsky's one-pot lactone reduction−acylation procedure.[12] Lactone **10a** was treated with diisobutylaluminum hydride, and the resulting reduction product, without isolation, was treated with acetic anhydride, pyridine, and DMAP to give the six-membered anomeric acetate **16** in 93% yield and 9:1 anomeric ratio (Scheme 4). Addition of sodium hydride transformed the *N*-Cbz group on acetate **16** into the cyclic carbamate, while the benzyl alkoxide byproduct

(6) (a) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1987**, *52*, 1353−1355. (b) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1987**, *52*, 3176−3178. (c) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235−4237. (c) Comins, D. L.; Kuethe, J. T.; Lakner, F. J. *J. Am. Chem. Soc.* **1999,** *121*, 2651−2652.

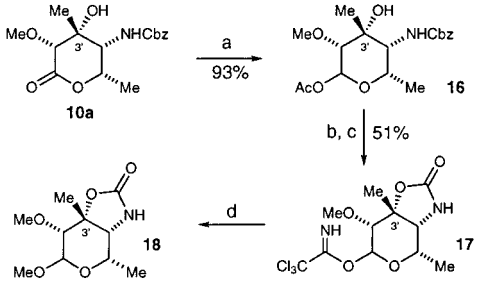
(7) One of our referees pointed out that the surname of author "Nguyen Trong Anh" is actually Nguyen because surnames are listed first according to Vietnamese custom. Therefore, we will refer to the polar model as the Felkin−Nguyen model instead of the Felkin−Anh model. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Nguyen, T. A.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70. (c) Nguyen, T. A. *Top. Curr. Chem.* **1980,** *88*, 146−162.

(8) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.

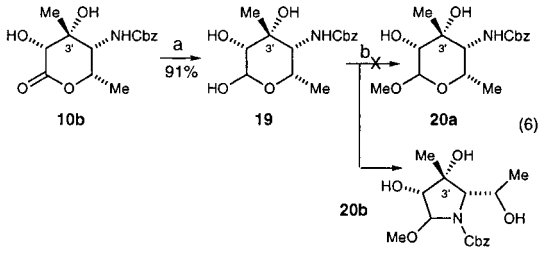
(9) For a discussion of (*Z*) enolate additions to chiral substituted aldehydes, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157.

(10) Heathcock, C. H.; Young, S. D.; Hagan, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846−3856.

Scheme 4. Assembly of L-Callipeltose[a]



Reaction conditions: a) DIBAL-H then Ac_2O, pyr, DMAP. b) NaH, THF. c) DBU, Cl_3CCN. d) MeOH, TMS-OTf, CH_2Cl_2.



Reaction conditions: a) DIBAL-H. b) MeOH, TsOH.

cleaved the anomeric acetate in situ to give the callipeltose lactol **2**.[13] The NMR spectrum of the lactol matched that reported by Nicolaou and co-workers.[3c] Treatment of the lactol with a catalytic amount of DBU and trichloroacetonitrile afforded callipeltose glycosyl donor **17** in 51% yield for the three transformations.[14] The addition of methanol and TMS-OTf transformed the glycosyl donor to callipeltose methyl glycoside **18**, whose NMR spectrum matched that reported by Giuliano and co-workers.[3a]

In summary, an asymmetric synthesis of L-callipeltose has been completed in 10 steps and 13% overall yield from commercially available D-threonine. Both enantiomers of callipeltose can be accessed by the use of either D- or L-threonine. This synthetic route is also ideal for investigation of glycosidation of sugar **2** to macrolactone **4**, since the callipeltose lactol formed can be readily converted into various kinds of glycosyl donors. The total synthesis of callipeltoside A and the elucidation of its absolute stereochemical structure will be reported in due course.

Acknowledgment. Support has been provided by the National Institutes of Health (GM 33327-16) and Merck.

Supporting Information Available: Experimental procedures and characterization of compounds **5**, **6**, **10a**, **10b**, **12**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726.

(12) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000,** *65*, 191−198.

(13) Benzyl acetate was a major byproduct in the reaction mixture, supporting the proposed role of benzyl alkoxide in acetate cleavage.

(14) Sebesta, D. P.; Roush, W. R. *J. Org. Chem.* **1992,** *57*, 4799−4802.