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Progress toward the Total Synthesis of Callipeltin A (I): Asymmetric Synthesis of (3*S*,4*R*)-3,4-Dimethylglutamine

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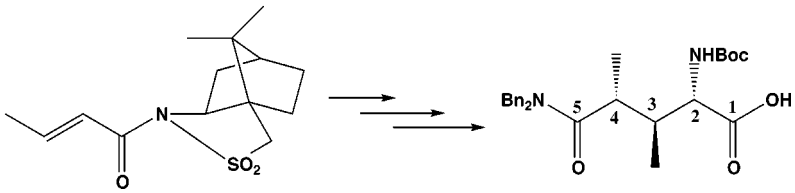
ABSTRACT



During the total synthesis of the novel cyclic depsipeptide callipeltin A (1), the unit (3*S*,4*R*)-3,4-dimethylglutamine, was successfully synthesized by asymmetric Michael addition and subsequent electrophilic azidation. The key feature of this approach is the generation of three adjacent stereogenic centers using the same camphorsultam chiral auxiliary.

Cyclic depsipeptides have emerged as a very important class of bioactive compounds from marine natural products.[1] In 1996, Minale et al. reported the isolation of three new cyclic depsipeptides, callipeltins A (**1**), B (**2**), and C[2] (Figure 1), from a shallow water sponge *Callipeltin* sp. These compounds showed marked activity in cytotoxic assays against KB and P388 cells and in anti-HIV and antifungal tests. The structures of the callipeltins were determined by interpretation of spectral data, chemical degradation, and evaluation of the amino acids obtained by acid hydrolysis. In our efforts to synthesize a series of bioactive cyclic depsipeptides, we chose callipeltin A (**1**) as a target due to its interesting anti-HIV properties and its novel amino acid residues: β-methoxytyrosine (β-OMeTyr), (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxy heptanoic acid (AGDHE), and (3*S*,4*R*)-3,4-dimethyl-L-glutamine. En route to a total synthesis of callipeltin A (**1**), we developed a novel chiral auxiliary-controlled asymmetric synthesis of (3*S*,4*R*)-3,4-dimethylglutamine.

We envisioned that the *erythro*-3,4-dimethyl groups of 3,4-dimethylglutamine would arise from an asymmetric Michael addition,[3−5,6h] to give stereocontrolled substitution at C(β) and C(γ), followed by an electrophilic azidation[6a,b] or amination[6c−h] which would generate the α-amino group. The retrosynthetic analysis of the protected 3,4-dimethylglutamine (**3**) is shown in Figure 2.

Camphor derivatives have been shown to be very useful auxiliaries in organic synthesis.[7] According to the procedure reported by Capet,[8] the chiral auxiliary (−)-camphorsultam (**6**) was synthesized in high yield (Scheme 1). Reaction with *trans*-crotonyl chloride provided compound **7**,[9] which was

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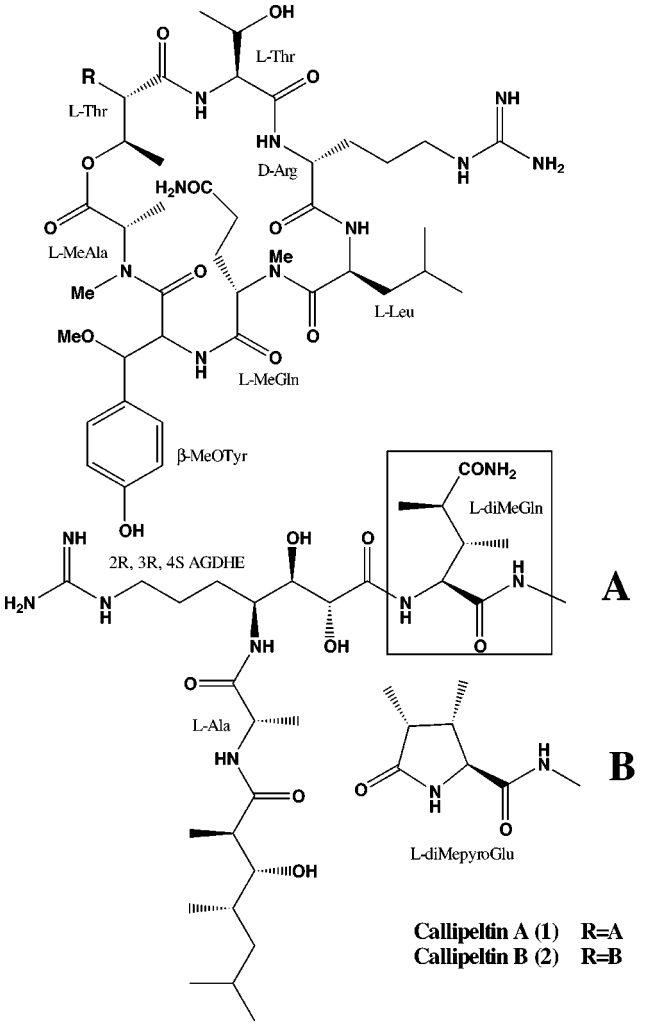


Figure 1. Structures of callipeltin A (**1**) and B (**2**); callipeltin C is an acyclic callipeltin A.

subjected to Michael addition[3d,4b] with the lithium enolate of dibenzylpropionylamide to afford two diastereomeric isomers, **8** and **9**, both with *erythro*-dimethyl groups. The stereochemistries of both products were determined by X-ray

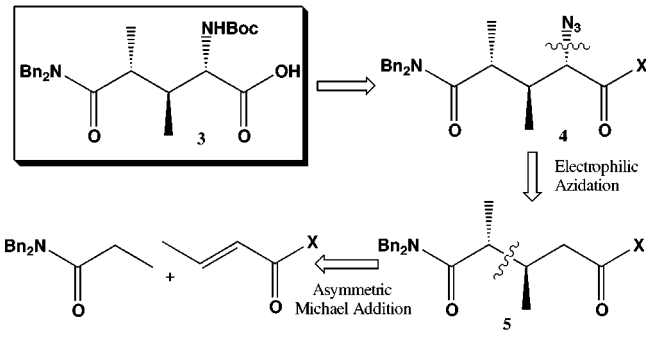
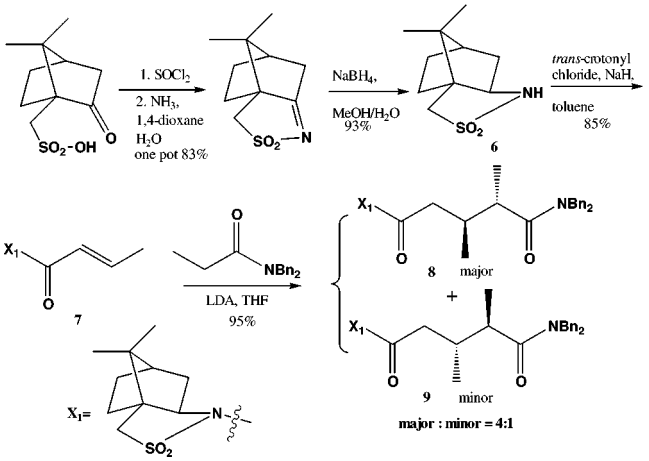


Figure 2. Retrosynthetic analysis of 3,4-dimethylglutamine.

Scheme 1



analysis (Figures 3 and 4). The ratio of the major to minor isomer was 4:1. Unfortunately, the stereochemistry of the major isomer did not match that of the desired compound.

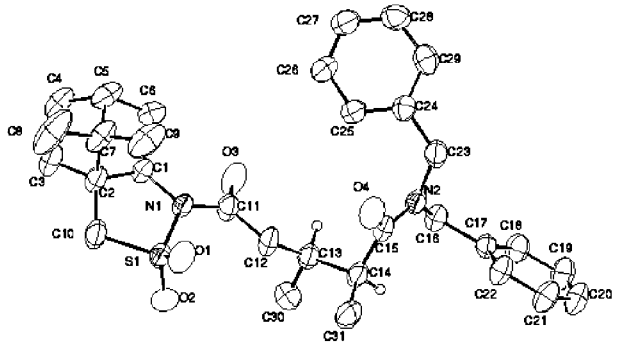
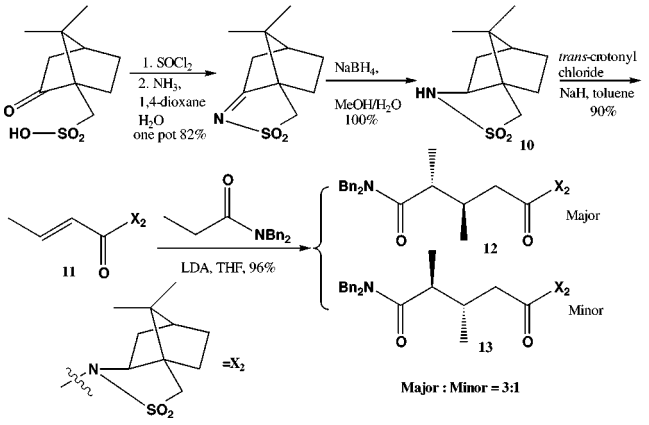


Figure 3. ORTEP drawing of compound **8**.

Using the same procedure,[8] we synthesized the (+)-camphorsultam (**10**) (Scheme 2) and treated it with *trans*-

Scheme 2



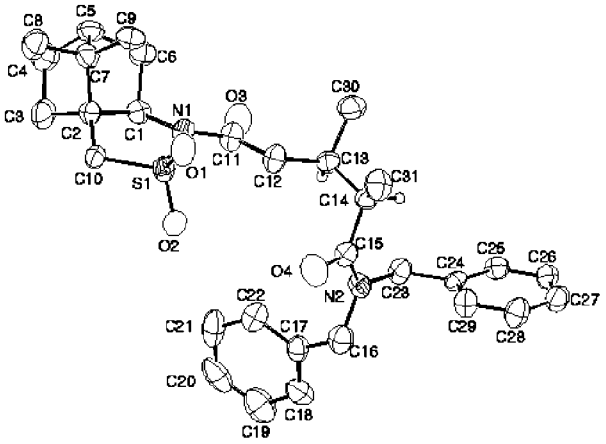


Figure 4. ORTEP drawing of compound **9**.

crotonyl chloride to provide compound **11**.[9] By employing the same Michael addition protocol, we obtained a 3:1 major to minor isomer ratio for the Michael adducts. Their stereochemistries were also determined by X-ray analysis (Figures 5 and 6). Heathcock and co-workers have thoroughly investigated the stereochemistry of the Michael addition of *N*,*N*-disubstituted amides to α,*β*-unsaturated ketones,[4b] and the formation of *anti* products was expected.

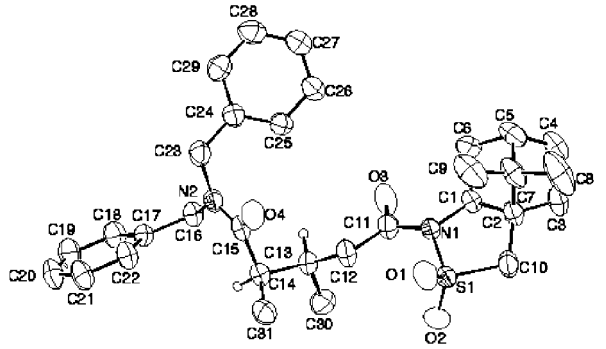


Figure 5. ORTEP drawing of compound **12**.

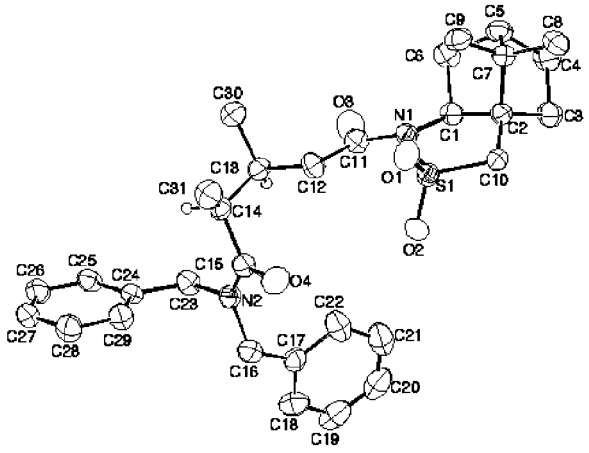
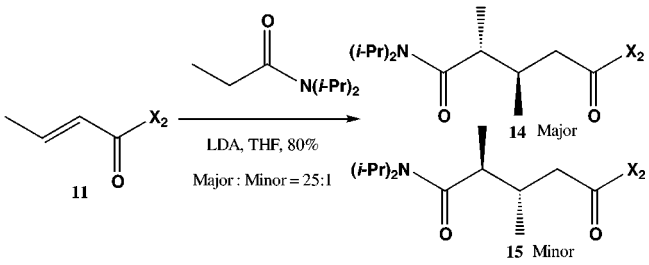


Figure 6. ORTEP drawing of compound **13**.

To improve the ratio of the major to minor isomer, we prepared *N*,*N*-diisopropylpropionyl amide (Scheme 3), which

Scheme 3



was treated with LDA and reacted with compound **11** to give a 25:1 ratio of major isomer to minor isomer.

In the transition state models shown in Figure 7, with a large chiral auxiliary X and large R groups, transition state A is favored over transition state B, according to the Heathcock model.[4b] A bulky amide shows *erythro*-selectivity as amide enolates are known to prefer the (*Z*)-form.[10] We only observed *anti* products in our reactions. We presume that the amide enolate approaches the enone at an angle similar to the Bürgi−Dunitz trajectory.[4b,11] The attack from the *Re* face of the enone (shown as C) is favored over that from the *Si* face (shown as D) due to the chiral auxiliary. When R is changed from benzyl to a bulkier isopropyl group, the *Si* face of the enone is more encumbered by the chiral auxiliary, making the enolate attack occur almost exclusively from the *Re* face.

Starting with the major Michael adduct **12** (Scheme 4), electrophilic azidation,[6a,b] using hexamethyldisilazide (KH-

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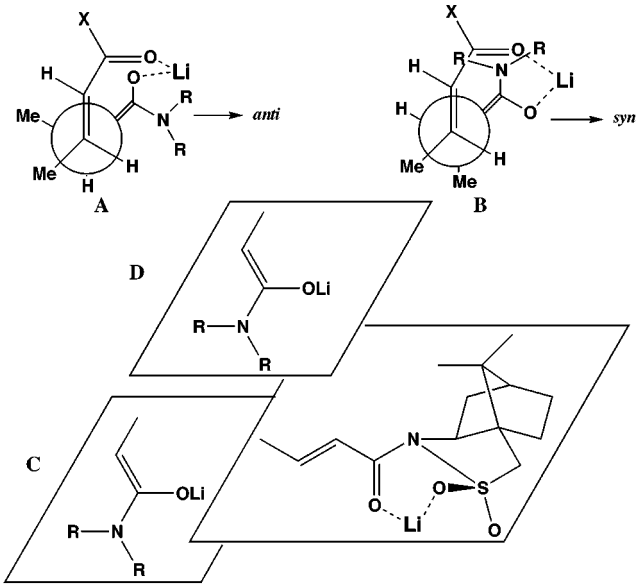
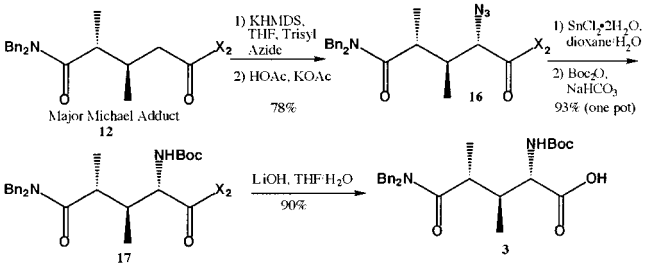


Figure 7. Transition states of Michael addition.

MDS) and 2,4,6-triisopropylbenenesulfonyl azide (trisyl azide),[12] successfully installed the azide in the α-position with the desired stereochemistry, which was confirmed in its X-ray structure (Figure 8). Reduction of the resulting azide

Scheme 4



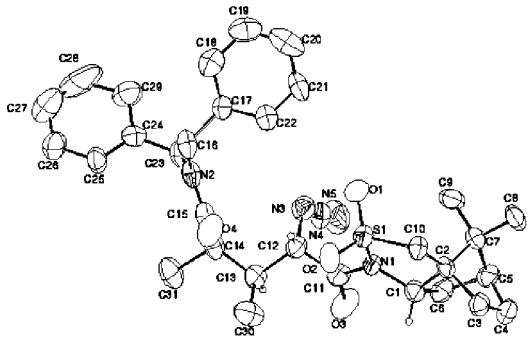


Figure 8. ORTEP drawing of compound **16**.

(**16**) with $SnCl_2$,[6b] followed by Boc protection of the resulting free amine in one pot, afforded compound **17**. Hydrolysis of the chiral auxiliary with LiOH (5 equiv) in THF:H_2O (2:1) provided the desired fragment **3**, with no epimerization of the α-amino center.[13]

In summary, we have developed a novel chiral auxiliary-controlled Michael addition and a subsequent electrophilic azidation sequence to make an unusual amino acid. It is noteworthy that three adjacent stereogenic centers were generated using the same chiral auxiliary.

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Supporting Information Available: General experimental procedures and characterizations of all new compounds including X-ray data. This material is available free of charge via Internet at http://pubs.acs.org.

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(13) After conversion of the acid to the methyl ester (MeI, K_2CO_3, Bu_4NI, DMF), Boc removal, and the formation of the (−) Mosher amide, no epimerized isomer was detected by 500 MHz ^1H NMR and ^{19}F NMR analysis.