Chinese Chemical Letters Vol. 10, No. 9, pp. 733–734, 1999

Stereoselective Synthesis of (6R)-6-(5-Methyl-2-furyl)-2-oxocyclohexanecarboxyl-10’, 2’-Sultam

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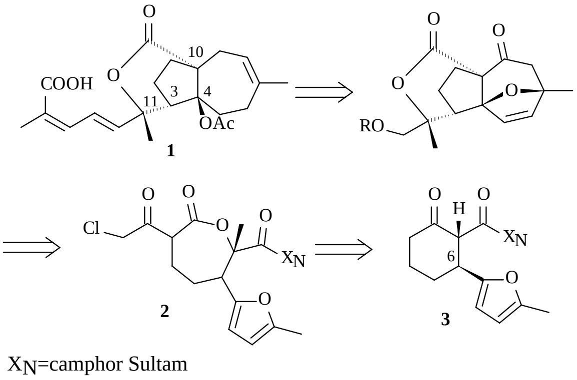
Abstract: Stereoselective synthesis of sultam **8** was reported. The overall yield in a sequence of 4 steps is 27.5%.

Keywords: Stereoselective, synthesis, sultam, conjugated addition.

Pseudolaric acid A (**1**) which exhibits antifungal and antifertility activities was isolated from *Peudolarix Kaempferi* Gord [1]. The absolute configurations of these chiral centers were assigned to be 3S, 4S, 10R and 11R respectively [2]. According to the retrosynthetic analysis, the skeleton of **1** could be constructed by intramolecular [4+3] cycloaddition from a seven-membered lactone **2** (**Scheme 1**) which could be obtained from (6S)- 6-(5-methyl-2-furyl)-2-oxocyclohexanecarboxyl acid derivative **3** by methylation and then Baeyer-Villiger oxidation.

Scheme 1

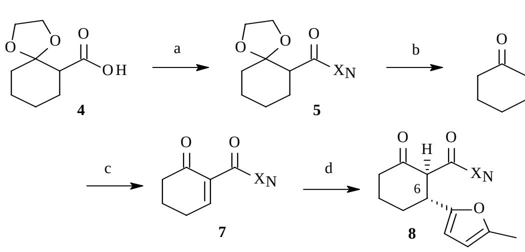


X_N=camphor Sultam

Stereoseletive 1, 4-addition of organometallic nucleophiles to conjugated carbonyl derivatives with chiral auxiliaries is the most reliable approach to enatiomerically pure β-C substituted carbonyl compounds [3]. The antipodal, camphor-derived bornane-10, 2-sultams (X_N) have proved to be versatile chiral auxiliaries for stereoselective 1, 4-addition in the last 15 years [4]. Herein, we would like to report a stereoselective synthesis of (6R)-6-(5-methyl-2-furyl)-2-oxocyclohexanecarboxyl-10’, 2’-sultam **8** [5] by means of 1, 4-addition of (5-methyl-2-furyl)$_2$CuLi to (-)-camphor sultam derivative of α, β-unsaturated acid **7** as a model test for the preparation of **3**.

The synthesis began with ketal protected β-keto acid **4**, followed by amidation with (-)-camphor sultam and DCC to obtain a pair of diastereomers **5**. The mixture **5** was directly hydrolyzed without separation to produce diastereomeric mixture **6** which was further transformed to α, β-unsaturated carbonyl compound **7** by selenium dehydrogenation. 1, 4-Addition to this compound with (5-methyl-2-furyl)$_2$CuLi stereoselectively produced (6R)-6-(5-methyl-2-furyl)-2-oxocyclohexanecarboxyl-10', 2'-sultam **8** as a sole product in 70% yield (**Scheme 2**).

Scheme 2



Reagents and conditions: a) (-)-camphor sultam, DCC, DMAP, CH_2Cl_2, r.t., 36 h, 72%; b)H_2SO_4, acetone, reflux, 2h, 91%; c)1. NaH, THF, 0°C, 15min; 2. PhSeBr, THF, 0°C, 2h; 3. H_2O_2, CH_2Cl_2, 0°C, 1 h, 60%; d) (5-methyl-2-furyl)$_2$CuLi, Me_3SiCl, -78°C to r.t., 12 h, 70%.

In literature the yields of 1,4-additon of furyllithium copuerate were reported to be less then 40% [3] and we also found the yields of 8 were fairly low in ether, DME and even lower in THF. However, we improved the yield of **8** up to 70% by adding compound **7** in toluene to the ether solution of (5-methyl-2-furyl)$_2$CuLi pretreated by 5eq of Me_3SiCl[3]. The mixture was stirred at -78°C for 2-12 h, and overnight at r.t.. The overall yield of compound **8** through a reaction sequence of 4 steps is 27.5%.

According to Oppolzer report [6] the absolute configuration of C-6 in compound **8** was deduced to be R. The coupling constant between H-1 and H-6 is 12.0Hz which indicates clearly the anti-configuration of these protons.

Acknowledgment

This work was supported by a grant of the National Natural Science Foundation of China.

References and Notes

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3. B. E. Rossiter, N. M. Swingle, *Chem. Rev.*, **1992**, *92*, 771 and references cited therein.
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5. Selected data of Compound **8**: ^{1}H NMR (400MHz, $CDCl_3$): δ 6.00 (d, 1H, J = 1.8Hz), 5.80 (d, 1H, J = 1.8Hz), 4.28 (d, 1H, J = 12.0Hz), 3.80 (m, 1H), 3.55 (m, 1H), 3.40 (dd, 2H, J = 1.0, 12.0Hz), 2.50 (m, 2H), 2.45 (m,1H), 2.20 (s, 3H), 1.40-2.20 (m, 10H), 1.15 (s, 3H), 0.98 (s, 3H). MS (m/z): 419 (M^+, 5), 273 (4), 230 (3), 214 (8), 204 (8), 177 (100), 123 (18). IR (KBr): 1720, 1698, 1332cm^{-1}. Anal Cald for $C_{22}H_{29}NO_5Si$: C, 63.03; H, 7.12; N, 3.32. Found: C, 62.98; H, 6.97; N, 3.33.
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Received 19 March 1999