matography. The *Z* isomer (0.41 g, 42%; mp 92–95 °C) was recrystallized from methanol to give the analytical sample: mp 93.5–95.5 °C; IR (Nujol) 1601 cm^{-1} (s, C=N); NMR ($CDCl_3$) δ 2.24 (s, 3, CH_3), 3.86 (s, 3, $NOCH_3$), 7.64 (d, J = 9 Hz, 2, aromatic H, 8.26 (d, J = 9 Hz, 2, aromatic H).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.57; H, 5.19; N, 14.45.

Kinetic Method. The isomerizations were followed by either GLC (**1**, **5a**, and **6**) or HPLC (**4b**,**c**). The details of the techniques used for following the kinetics have been described previously.[2] The rate constant for the isomerization of **6** to **7** was calculated from the equation derived from reversible first-order kinetics and the equilibrium constant for **6** $\rightleftarrows$ **7**.[13] Since the equilibrium favored the *E* isomer (**6**), the isomerization of **7** to **6** was followed.

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Registry No. (*E*)-**1**, 41071-34-5; (*Z*)-**2**, 41071-35-6; **3b**, 2475-92-5; **3c**, 10342-64-0; (*E*)-**4a**, 15754-20-8; (*E*)-**4b**, 80965-21-5; (*E*)-**4c**, 80965-22-6; (*Z*)-**5a**, 15754-21-9; (*Z*)-**5b**, 80965-23-7; (*Z*)-**5c**, 80965-24-8; (*E*)-**6**, 41071-40-3; (*Z*)-**7**, 41071-39-0.

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Total Synthesis of Pallescensin A

Pierluigi Gariboldi,* Giancarlo Jommi, and Massimo Sisti

Laboratorio di Chimica Organica, Facoltà di Scienze, Università di Milano, Milano, Italy

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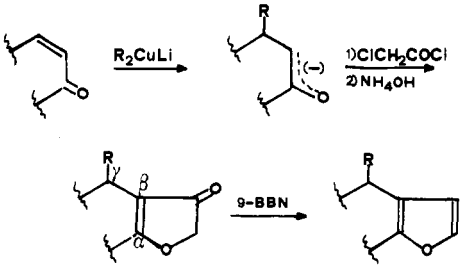
In recent papers[1,2] we have described a new method for the construction of fused furan rings and its application to the synthesis of some natural compounds.

An enolate anion was generated by conjugate addition of lithium dimethylcuprate to an α,β-unsaturated ketone and was quenched with chloroacetyl chloride. Then, base-promoted intramolecular ring closure afforded a β-furanone, which was easily reduced to the furan (Scheme I). By this route, only alkyl (R = Me or other) γ-substituted furans could be synthesized, whose occurrence in natural compounds is very limited.[3]

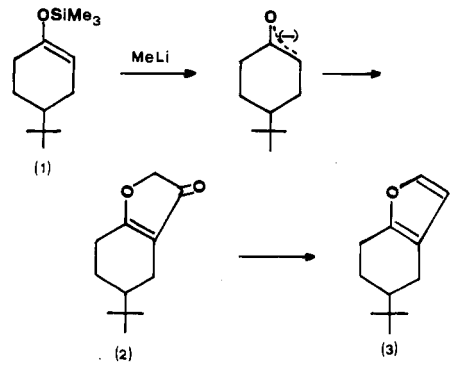
If the enolate anion had been directly generated from the corresponding saturated ketone, by the same procedure, γ-unsubstituted (R = H) furan compounds, which are more widespread in nature, should have been obtained.

A very simple substrate, i.e., 4-*tert*-butyl cyclohexanone, was first submitted to the described reaction sequence in order to check its applicability, with its trimethylsilyl enol ether[4] as a carbanion source. Compound **1** was reacted with methyllithium until disappearance of the starting material, and then the lithium enolate obtained was quenched with chloroacetyl chloride. Weak base (iced ammonia) extraction of the reaction mixture afforded **2**

Scheme I



Scheme II



in 82% yield (Scheme II). After 9-BBN reduction,[1] the furan compound **3** was isolated in excellent yield.

The same method was then applied for the synthesis of racemic pallescensin A (**4**), a furan sesquiterpenoid of unusual skeleton, which has been isolated by Cimino et al.[5] from the marine sponge *Disidea pallescens* and recently synthesized by Nasipuri and Das[6] by following a biomimetic scheme.

Ketone **5** was synthesized by starting from 2-methylcyclohexane-1,3-dione (in 38% overall yield) and following the procedure of Welch and Rao.[7]

Treatment of **5** with trimethylchlorosilane according to standard procedures[4] led to very poor yields of **6**, whereas ethyl (trimethylsilyl)acetate together with tetra-*n*-butylammonium fluoride[8] (Scheme III) successfully performed the transformation (73% yield).

After the above-described procedure, compound **6** afforded the β-furanone **7** in 81% yield. Smooth reduction of **7** gave pure racemic **4** in almost quantitative yield which proved to be identical with natural pallescensin A.[5]

Other classical methods for direct enolate formation by strong bases from **5** (e.g., LDA in THF) always failed, producing insignificant amounts of **7**.

Taking into account the well-known regioselectivity in trimethylsilyl enol ether formation[9] and the good yields of the subsequent steps, the above described method would seem to be promising in the field of the synthesis of natural furan compounds.

Experimental Section

^1H and ^{13}C NMR were recorded with a Varian XL-100 instrument (tetramethylsilane as an internal standard). IR spectra were registered on a Perkin-Elmer 257 spectrophotometer. Mass spectra were taken on a Varian Mat 112 spectrometer (DIS, 71-eV acceleration potential).

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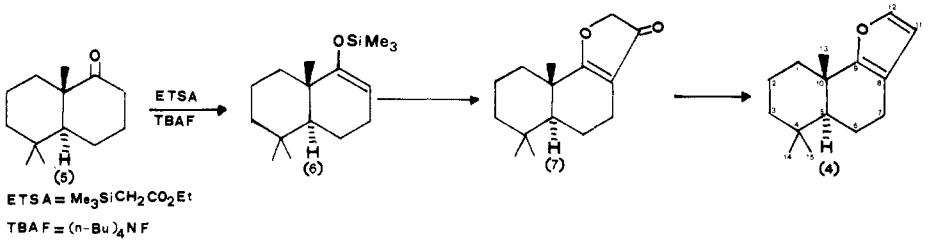
Scheme III



Synthesis of β-Furanone 2. Compound 1 (226 mg, 1 mmol) was dissolved in 8 mL of anhydrous diethyl ether, placed in a flask equipped with a dry argon inlet, and cooled at −15 °C. To the stirred solution was added 0.63 mL (1 mmol) of a 1.60 M ethereal solution of methyllithium. After 1.30 h at −15 °C, 1.5 mL of anhydrous hexamethylphosphoric triamide and 0.7 mL (8.8 mmol) of freshly distilled chloroacetyl chloride were added. The mixture was reacted 30 min at −15 °C and 1 h at room temperature.

The reaction mixture was poured into a slurry of ammonia and crushed ice, stirred for 20 min, and then extracted three times with 20 mL of diethyl ether. The combined extracts were washed with water and dried (Na_2SO_4). After evaporation at reduced pressure, 200 mg of product was obtained which was chromatographed on a Florisil (6 g) column. By elution with *n*-pentane–ethyl acetate (95:5 v/v) there was obtained 160 mg (82% yield) of pure **2**: oil; IR (liquid film) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (s, 2 H, OCH_2CO), 0.95 (s, 9 H, $(CH_3)_3C$). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.22; H, 9.28. Found: C, 74.18; H, 9.30.

Synthesis of Furan 3. In a 10-mL flask equipped with a dry argon inlet was added 40 mg (0.33 mmol) of 9-BBN to a stirred solution of 59 mg (0.30 mmol) of **2** in 6 mL of anhydrous THF at 0 °C. After 1 h at 0 °C, the cooling bath was removed and the reaction mixture left to react at room temperature for 5 h.

Methanol (0.18 mL) was added, and the solvents were evaporated under reduced pressure. The residue was dissolved in *n*-pentane, and 0.02 mL of ethanolamine was added. The mixture was filtered and the precipitate washed several times with *n*-pentane. On evaporation of the combined extracts, a crude product (56 mg) was obtained which was purified by silica gel (2 g) chromatography. Elution with *n*-pentane afforded pure **3**: 52 mg (97% yield); oil; IR (liquid film) 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, 1 H, J = 2 Hz, OCH=CH), 6.23 (d, 1 H, J = 2 Hz, OCH=CH), 0.95 (s, 9 H, $(CH_3)_3C$). Anal. Calcd for $C_{12}H_{18}O$: C, 80.90; H, 10.12. Found: C, 80.85; H, 10.15.

Synthesis of the Trimethylsilyl Enol Ether 6. In a 10-mL flask equipped with a dry argon inlet and reflux condenser was dissolved 210 mg (1.08 mmol) of **5** in 3 mL of anhydrous THF, and 173 (1.08 mg) of ethyl (trimethylsilyl)acetate was added together with a catalytic amount of tetra-*n*-butylammonium fluoride. The reaction mixture was refluxed for 4 h.

The solvent was evaporated under vacuum, and the residue, after dilution with 10 mL of water, was extracted five times with 5 mL each of diethyl ether. The organic extracts were dried over Na_2SO_4, and after evaporation at reduced pressure, 350 mg of crude product was obtained which was purified by Florisil (20 g) chromatography. By elution with pentane, 210 mg (73%) of pure **6** was obtained: oil; IR (CCl_4) 1660 cm^{-1}; ^1H NMR ($CDCl_3$; numbering of pallescensin A has been adopted) δ 4.54 (t, 1 H, J = 3.9 Hz, H_8), 2.00 (m, 2 H, H_7), 1.06 (s, 3 H, H_{13}), 0.90 (s, 3 H, H_{14} or H_{15}), 0.86 (s, 3 H, H_{14} or H_{15}), 0.17 (s, 9 H, $SiMe_3$). Anal. Calcd for $C_{16}H_{30}OSi$: C, 72.18; H, 11.28. Found: C, 72.12; H, 11.24.

Synthesis of the β-Furanone 7. The procedure described for the preparation of compound **2** was followed to synthesize the β-furanone **7**. From the compound **6** (90 mg, 0.34 mmol), after purification on a Florisil (5 g) column [*n*-pentane–ethyl acetate (95:5 vol) as eluant], was obtained pure **7**: 65 mg (81% yield); oil; IR (liquid film) 1700, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.40 (s, 2 H, H_{12}), 1.28, (s, 3 H, H_{13}), 0.96 (s, 3 H, H_{14} or H_{15}), 0.92 (s, 3 H, H_{14} or H_{15}); mass spectrum, m/e (relative intensity) 234 (M^+, 60), 123 (32), 112 (100), 111 (70), 91 (30). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.88; H, 9.42.

Synthesis of Pallescensin A (4). Pallescensin A (**4**) was synthesized by following the same procedure described for the preparation of compound **3**. From the β-furanone **7** (38 mg, 0.16 mmol), after purification on a silica gel (1.2 g) column with *n*-pentane as the eluant, was obtained pure pallescensin A: 34 mg (97% yield); oil; IR (liquid film) 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (d, 1 H, J = 2 Hz, H_{12}), 5.99 (d, 1 H, J = 2 Hz, H_{11}), 1.17 (s, 3 H, H_{13}), 0.94 (s, 3 H, H_{14} or H_{15}), 0.91 (s, 3 H, H_{14} or H_{15}); ^{13}C NMR ($CDCl_3$) δ 159.58 (s, C-9), 139.83 (d, C-12), 113.49 (s, C-8), 109.92 (d, C-11), 52.33 (d, C-5), 41.91 (t, C-7), 36.53 (s, C-10), 35.56 (t), 33.38 (q, C-13), 32.95 (s, C-4), 22.71 (t), 21.34 (2 q, C-14 and C-15), 19.54 (t), 18.60 (t); mass spectrum, m/e (relative intensity) 218 (M^+, 22), 203 (100), 147 (38), 135 (22), 69 (49). Anal. Calcd for $C_{15}H_{22}O$: C, 82.57; H, 10.09. Found: C, 82.54; H, 10.06.

Acknowledgment. We thank CNR, Rome (progetto finalizzato chimica fine e secondaria), for financial support.

Registry No. 1, 19980-19-9; 2, 80926-07-4; 3, 80926-08-5; (±)-4, 73210-04-5; (±)-5, 65556-24-3; (±)-6, 80926-09-6; (±)-7, 80926-10-9.

Esterification of N-Protected α-Amino Acids with Alcohol/Carbodiimide/4-(Dimethylamino)-pyridine. Racemization of Aspartic and Glutamic Acid Derivatives

Madhup K. Dhaon, Richard K. Olsen,* and K. Ramasamy

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322

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The carboxyl group of α-amino acids is commonly protected as an alkyl ester during peptide synthesis, for which the use of methyl, ethyl, benzyl, and *tert*-butyl esters is well-documented.[1] The preparation of esters of N-protected α-amino acids is most often effected by alkylation with an alkyl halide of the triethylammonium[2] or cesium[3] salt of the corresponding carboxylate ion. Ester formation by use of carbodiimide coupling procedures has found limited application.[4]

The method of Steglich[5] and Hassner[6] is widely used for the preparation of esters of carboxylic acids, in which esterification is effected by a carbodiimide condensation catalyzed with 4-(dimethylamino)pyridine. Application[5-7] of this method has been made for esterification of a limited number of N-protected α-amino acids. Hassner and

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