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A New Synthesis of (±)-Myodesmone

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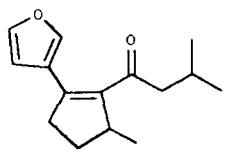
(±)-Myodesmone was synthesized, starting from 2-cyclopentenone. The key reaction involved α-dimethoxymethylation of 2-cyclopentenone and organocopper conjugate addition reaction.

Key words: (±)-Myodesmone, Furanosesquiterpene, Three consecutively substituted cyclopentane ring, α-dimethoxymethylation of 2-cyclopentenone, Organocopper conjugate addition reaction

INTRODUCTION

The toxic furanosesquiterpene, (±)-myodesmone (**1**) was first isolated from *Myoporum deserti* and Myoporum acuminatum and have been shown to be toxic to mice, rats and sheep (Blackburne *et al.*, 1971). This rather simple molecule presents the synthetic challenge of constructing three consecutively substituted cyclopentane ring. The only synthesis published successfully resolved this problem, using regiospecifically substituted α-oxoketene dithioacetal(Dieter and Dieter, 1983). We report here a new synthesis of (±)-myodesmone (**1**), which involves α-dimethoxymethylation of 2-cyclopentenone as a key reaction. The organocopper conjugate addition reaction in combination with α-dimethoxymethylation of 2-cyclopentenone was used for constructing three consecutively substituted cyclopentane ring.

Our synthetic route to (±)-myodesmone is outlined in Scheme 1.



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MATERIALS AND METHODS

General

Reactions requiring anhydrous conditions were performed with precaution for rigorous exclusion of air and moisture. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography(TLC) was performed on precoated silica gel 60 F254 plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammonium molybdate-sulfuric acid spray. The ^{1}H NMR spectra were recorded on Varian EM-360 spectrometer. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane. IR spectra were obtained on Perkin-Elmer Model 337 spetrometer. Chemicals were purified, when necessary, according to the reported procedure (Perrin *et al.*, 1980).

2-Dimethoxymethyl-2-cyclopentenone (2)

To a solution of TMSOTf (889 mg, 4 mmol) in dry dichloromethane(10 ml) were successively added the dimethyl sulfide (248 mg, 4 mmol) and 2-cyclopentenone (328 mg, 4 mmol) at −78℃ under nitrogen atmosphere. After the mixture was stirred at −78℃ for 40 min, trimethyl orthoformate (425 mg, 4 mmol) was added at this temperature. Then the mixture was warmed at −23℃ and kept for 1 h. 1,8-Diazabicyclo [5,4,0]undec-7-one (DBU, 609 mg, 4 mmol) was added to the mixture and stirred at this temperature for 1h. The mixture was allowed to warm to room temperature and quenched with water. The reaction mixture was subjected to extractive workup with dichloromethane (25 mL×3). Chromatography of the crude product on a silica gel column (1:40 ethyl acetate/hexane) gave 2-dimethoxymethyl-2-cyclopentenone (324 mg, 52%) as a colorless oil: IR (neat, NaCl disc) 1690 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 2.40(m, 2H), 2.70(m, 2H), 3.30(s, 6H), 5.70(s, 1H), 6.80(m, 1H).

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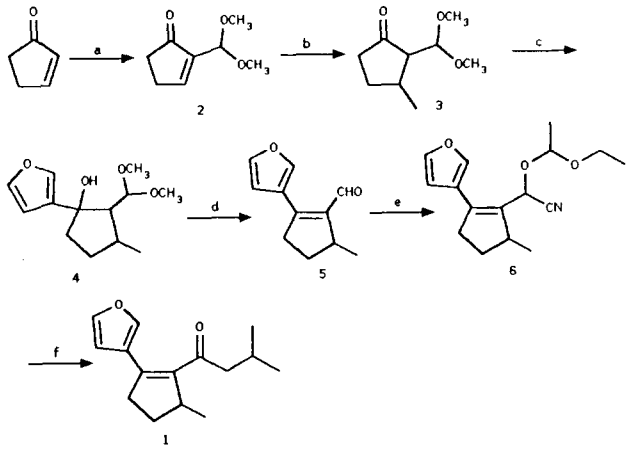


Scheme 1

a. $TMSOT_f$, $(CH_3)_2S$, $CH(OCH_3)_3$, DBU; b. CH3Li, CuI; c. 3-Bromofuran, n-BuLi; d. $FeCl_3/SiO_2$; e. NaCN, HAc; Ethyl vinyl Ether, p-TsOH; f. LDA, 1-Bromo-2-methyl propane.

2-Dimethoxymethyl-3-methylcyclopentanone (3)

To a suspension of cuprous iodide (457 mg, 2.4 mmol) in dry ether (10 mL) was added 1.37 M methyllithium in ether (3.5 mL, 4.8 mmol) at −78℃ under nitrogen atomsphere. The mixture was stirred at this temperature for 40 min. Then a solution of 2-dimethoxymethyl-2-cyclopentenone (312 mg, 2 mmol) in dry ether(6 mL) was added at −78℃ under vigorous stirring. After the mixture was stirred at this temperature for 1.5h, it was warmed to −25℃ over a period of 3h, and quenched with a saturated ammonium chloride solution with vigorous stirring at this temperature. The reaction mixture was subjected to extractive workup with ether (20 mL×3). Chromatography of the crude product on a silica gel column (1:120 ethyl acetate/hexane) gave 2-dimethoxymethyl-3-methylcyclopentanone (200 mg, 58%) as a colorless oil: IR (neat, NaCl disc) 1745, 1380 cm^{-1}; ^1H NMR(CDCl3) δ 1.23(d, J=7Hz,3H), 1.5~2.3(m, 2H), 2.45~2.72(m, 3H), 3.31(s, 6H), 3.4(m, 1H), 4.95(d, J=5.5Hz, 1H).

2-Dimethoxymethyl-1-(3-furyl)-3-methylcyclopentanol (4)

To a sloution of 3-bromofuran (676 mg, 4.6 mmol) in dry ether (10 mL) was added 2.28 M n-butyl lithium in hexane (2 mL, 4.6 mmol) at −78℃ under nitrogen atmosphere. The mixture was stirred at this temperature for 1 h. Then a solution of 2-dimethoxymethyl-3-methylcyclopentanone (516 mg, 3 mmol) in dry ether (5 mL) was added at −78℃ and stirred for 30 min. The mixture was allowed to warm to 0℃ and quenched with a saturated ammonium chloride solution. The reaction mixture was subjected to extractive workup with ether (30 mL×3). Chromatography of the crude product on a silica gel column (1:7 ethyl acetate/hexane) gave 2-dimethoxymethyl-1-(3-furyl)-3-methylcyclopentanol (518 mg, 72%) as a colorless liquid: IR (neat, NaCl disc) 3500~2800, 3030, 2920 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.10(d, J=7Hz,3H), 1.10~2.40(m, 5H), 2.40~2.75(m, 1H), 3.31(s, 6H), 4.05(br. s, 1H), 5.05(d, J=5.5Hz, 1H), 6.40(m, 1H), 7.30(s, 1H), 7.35(m, 1H).

2-(3-Furyl)-5-methyl-1-cyclopentenecarbaldehyde (5)

2-Dimethoxymethyl-1-(3-furyl)-3-methylcyclopentanol (720 mg, 3 mmol) and the anhydrous $FeCl_3/SiO_2$ reagent (3.6 g) were stirred at room temperature for 1h. The reaction mixture was stirred with ether (25 mL×4), filtered through celite and the filtrate was concentrated in vacuo to give a crude product. This crude product was chromatographed on the silica gel column using ethyl acetate/hexane(1:5) as eluent to give 2-(3-furyl)-5-methyl-1-cyclopentenecarb-aldehyde (343 mg, 65%) as an oil: IR (neat, NaCl disc) 1685, 1385 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.13(d, J=7Hz, 3H), 1.50~2.33(m, 2H), 2.40~2.70(m, 2H), 3.10(m, 1H), 6.40(m, 1H), 7.36(m, 1H), 7.70(br. s, 1H), 9.70(s, 1H).

2-(Cyanohydroxymethyl)-1-(3-furyl)-3-methylcyclopentene

Sodium cyanide (225 mg, 4.6 mmol) dissoled in a minimum quantity of water (1 mL) was added THF (1 mL). The resulting solution was cooled with ice bath. A solution of 2-(3-furyl)-5-methylcyclopentenal (546 mg, 3.1 mmol) in THF and HAC (276 mg, 4.6 mmol) were added succesively and stirred vigorously for 3 hr. After elimination of THF in the reaction mixture in vacuo, the residue was subjected to extractive workup with ether (15 mL×3). The crude product was used for the protection of hydroxyl group without purification (630 mg, 100%) as an oil: IR (neat, NaCl disc) 3400, 2250 cm^{-1}.

α-Ethoxyethyl ether of 2-(cyanohydroxymethyl)-1-(3-furyl)-3-methylcyclopentene (6)

To a neat 2-(cyanohydroxymethyl)-1-(3-furyl)-3-methylcyclopentene (528 mg, 3 mmol) and a catalytic amount of p-TsOH was added ethyl vinyl ether portionwise with vigorous stirring manually for 25 min. The completion of reaction was monitored by TLC. To the reaction mixture was added a saturated solution of $NaHCO_3$. Extractive workup with ether (20 mL×3), gave a crude product. The crude product was chromatographed on the silica gel column using ethyl acetate/hexane (1:7) as eluent to give α-ethoxyethyl ether of 2-(cyanohydroxymethyl)-1-(3-furyl)-3-methylcyclopentene (594 mg, 72%) as a colorless oil: IR (neat, NaCl disc) 3100, 2950, 1140~1020 cm^{-1}; 1H NMR

($CDCl_3$) δ 1.07(t, J=6.5Hz, 3H), 1.18(t, J=7.5Hz, 3H), 1.30 and 1.34(2d, J=5.5Hz, 3H), 1.80~2.20(m, 1H), 2.20~ 2.40(m, 3H), 3.30~3.50(broad q, J=7Hz, 1H), 3.30~3.65(complex singal, 2H), 4.65~4.87(complex signal, 2H), 6.43(m, 1H), 7.20(brs, 1H), 7.40(t, J=1.5Hz, 1H).

(±)-Myodesmone (1)

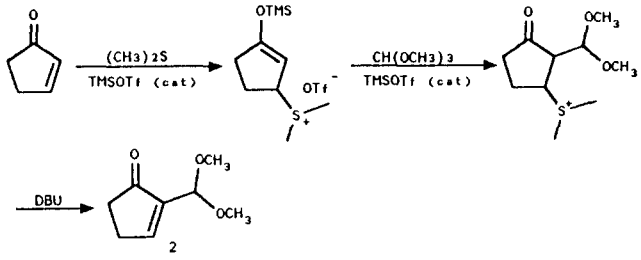
To a dry THF were successively added 15% n-BuLi in hexane (0.5 mL, 1.2 mmol) and diisopropylamine (121 mg, 1.2 mmol) in THF at −78℃ under nitrogen atomsphere. After the mixture was stirred at −78℃ for 15 min, α-ethoxyethyl ether of 2-(cyanohydroxymethyl)-1-(3-furyl)-3-methylcyclopentene (275 mg, 1 mmol) in THF was added at this temperature and stirred for 10 min. Then 1-bromo-2-methylpropane (164 mg, 1.2 mmol) in THF was added and stirred at this temperature. The reaction mixture was allowed to warm to room temperature with stirring and quenched with 5% HCl. The reaction mixture was subjected to extractive workup with ether (20 mL×3), after elimination of THF under reduced pressure. The crude product was chromatographed on a silica gel column using ethyl acetate/hexane(1:9) as an eluent to give (±)-myodesmone(120 mg, 52%) as a colorless oil: IR (neat, NaCl disc) 3100, 2950, 2860, 1670, 1600, 1460, 1360, 870, 780 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.90(d, J=7 Hz, 6H), 1.13(d, J=7Hz, 3H), 1.20~1.80(m, 1H), 1. 80~2.20(m, 1H), 2.20~2.40(m, 3H), 2.73(t, J=7Hz, 2 H) 3.50~3.00(br. q, J=7Hz, 1H), 6.59(m, 1H), 7.37(t, J=1.5Hz, 1H), 7.76(br. s, 1H).

RESULTS AND DISCUSSION

Introduction of an organic group to the α portion of α,β-enones has been intensively studied (Stork and Benaim, 1971; Corey and Enders, 1976; Branca and Smith, 1978; Shono *et al.*, 1979; Itoh *et al.*, 1980). Espesially α-alkoxyalkylation of α,β-enones (Kim *et al.*, 1991; Suzuki *et al.*, 1981) is an important process for the synthesis of natural products. Initial attempts to prepare 2-dimethoxymethyl-2-cyclopentenone (**2**) via pyridiniosilylation (Kim *et al.*, 1991) and phenylseleniosilylation(Suzuki *et al.*, 1981) were failed. However, 2-dimethoxymethyl-2-cyclopentenone (**2**) was prepared in 58% yield as indicated in Scheme 2.

The reaction of 2-dimethoxymethyl-2-cyclopentenone with lithium dimethylcuprate gave 3-dimethoxymethyl-3-methyl cyclopentanone (**3**) in 82% yield after preparative thin layer chromatography as an inseparable mixture of the stereoisomer.

The nucleophilic addition of 3-lithiofuran to **3** furnished a diastereomeric mixture of the tertiary alcohol 4 in 72% yield, which was used without purification in the next step.



Scheme 2

The transformation of dimethylacetal group of compound **4** to aldehyde **5** was carried out by using anhydrous iron (III) chloride dispersed on silica gel at room temperature in 65% yield (Fadel *et al.*, 1987). Fortunately the dehydration of tertiary alcohol of compound **4** was occurred during this transformation.

The addition of hydrocyanic acid, which was generated in situ from sodium cyanide and acetic acid, to the aldehyde **5** produced the corresponding cyanohydrin which was identified with IR and used without purification. The cyanohydrin of the aldehyde **5** was protected with ethyl vinyl ether to afford the corresponding protected cyanohydrin **6** in the usual manner (Stork and Maldonado, 1971; Stork and Maldonado, 1974). Compound **6** was obtained as a mixture of diastereomers. The lithium salt of the protected cyanohydrin **6** which was formed by LDA, was treated in THF with 1-bromo-2-methylpropane to give (±)-myodesmone in 52% yield.

The results described herein provided an efficient synthesis of (±)-myodesmone (**1**). Since the intermediate **3** could be easily prepared by sequential regioselective carbon-carbon bond constructions, our synthetic strategy appears to give a general procedure for the preparation of three consecutively substituted cyclopentane ring system.

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