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Diastereoselective Intramolecular [4+3] Cycloaddition: Synthesis of a Versatile Precursor for Preparation of 5,7-Fused Ring Compounds

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Abstract: Compound **8** which could be used as a versatile precursor for the synthesis of 5,7-membered fused ring containing natural products was synthesized *via* tandem Pummerer rearrangement and intramolecular [4+3] cycloaddition in moderate yield and with high diastereoselectivity.

Introduction

Since there are many bioactive natural products containing a 5,7- fused ring skeleton, the studies on the synthesis of these compounds have attracted considerable attention and interest from many synthetic chemists.[1] Several approaches to this ring system have been developed. The intramolecular [4+3] cycloaddition represents an efficient and promising approach.

Although the intermolecular [4+3] cycloaddition is well known, the intramolecular process has yet to be widely applied for the construction of polycyclic skeletons. The reason is that [4+3] cycloaddition reactions usually occur to unfunctionalized allylic cations and dienes, and the stereochemical outcome is not well understood. To the best of our knowledge only one paper dealing with diastereoselective intramolecular [4+3]cycloaddition has been published to date, [2] in which a 5, 7-fused ring compound was obtained. In order to expand the scope of this reaction, we decided to investigate the stereoselectivity further.

Results and Discussions

Harmata and his co-workers reported a method to generate an allylic cation for [4+3] cycloaddition through the Pummerer rearrangement of an allylic sulfoxide.[3] We exploited this method on a highly functionalized precursor,[4] and by means of a tandem Pummerer rearrangement and intramolecular [4+3] cycloaddition, we have succeeded in a diastereoselective synthesis of a functionalized 5,7- fused

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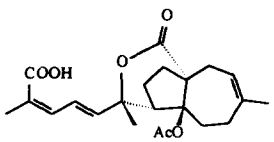
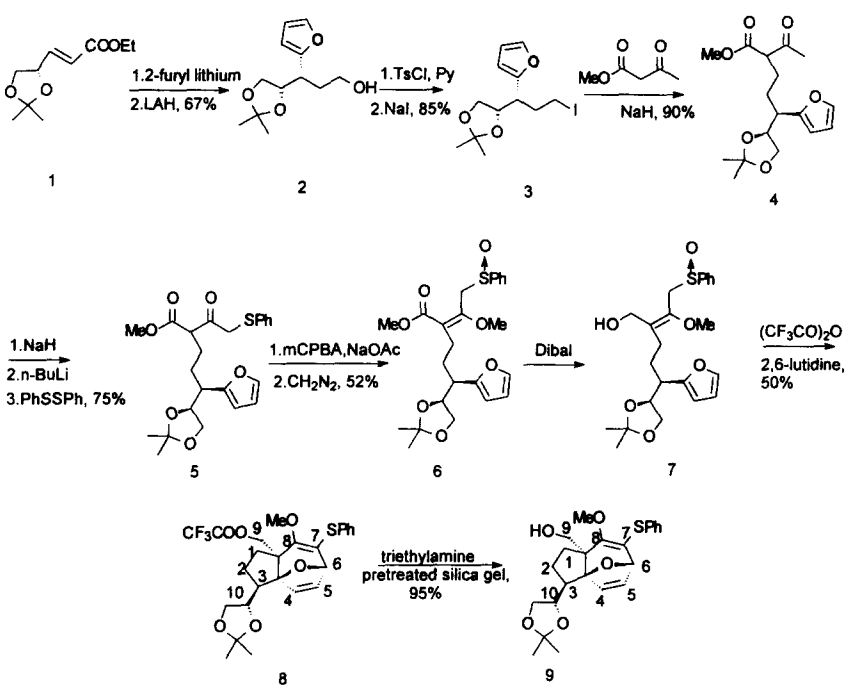
ring compound **9**, which could be used as a precursor for the preparation of pseudolaric acid A,[5] one of our target molecules, and other natural products.



pseudolaric acid A

(*S*,*E*)-α,β-Unsaturated ester **1**, prepared from D-(-)-mannitol,[6] underwent conjugate addition [7] with 2-furyllithium.[8] Reduction of the resulting ester with LAH then gave alcohol **2** with high diastereoselectivity (>20:1). Alcohol **2** was further converted to iodide **3**.[9]



Scheme 1

Condensation of iodide **3** with methyl acetoacetate formed compound **4** in 90% yield. Deprotonation with NaH and *n*-BuLi, followed by quenching with PhSSPh, next yielded sulfide **5** in 75% yield.[10] In a buffered medium, sulfide **5** was oxidized to the sulfoxide, [11] which was methylated *in situ* to the *E*-isomer of enol ether **6**. Compound **6** was then reduced with DIBAL, and the alcohol **7** thus obtained was subjected to a tandem Pummerer rearrangement and intramolecular [4+3] cycloaddition[3] in the presence of trifluoroacetyl anhydride and 2,6-lutidine to form cycloadduct **8** in high d.e. (>95%) and moderate chemical yield (50%). Filtration of the solution of trifluoroacetate **8** through a pad of

silica gel pretreated with triethylamine afforded detrifluoroacetylated product **9** in 95% yield (**Scheme 1**).

The absolute configuration of the newly formed stereogenic center in compound **2** was assigned to be *R* according to the Heiser's[7a] and Leonard's[7c] reports. The absolute configurations of the stereogenic centers in the cycloadduct **8** were determined to be 3a*R* and 8a*S* based on 1D NOE difference spectrum and 2D NOESY experiments of its detrifluoroacetylated product **9**. On irradiation of H-3, about 5% NOE enhancements of H-9 and H-4 were observed respectively, which means that these hydrogens are all on the same side of the five-membered ring. Irradiation of H-4 or H-9 gave consistent results. The NOESY experiment of compound **9** showed clearly the cross peaks between these protons.

Conclusion

In summary, we have developed a novel approach to an optically pure and highly functionalized 5, 7-fused ring compound **9** *via* intramolecular [4+3] cycloaddition. The functional groups in this molecule can undergo further manipulation, and various methods for the stereo- and regioselective cleavages of the C-O bond of the bridge oxygen have been reported.[12-14] Therefore, the cycloadduct **9** is a potential precursor for the synthesis of many natural products. The stereochemistry of C-3a and C-8a in compound **9** is in accordance with that of pseudolaric acid A, and the total synthesis of this molecule by means of the diastereoselective intramolecular [4+3] cycloaddition is underway.

Experimental Section

General Procedure All solvents were purified before use. Ether, tetrahydrofuran were distilled under nitrogen from sodium benzophenyl ketal. Methylene chloride was distilled under nitrogen from CaH_2. Infrared spectra were recorded on a Nicolet Magna IR-750 as thin films. NMR spectra were measured as $CDCl_3$ solutions unless noted otherwise and they were referenced with the resonance of $CDCl_3$ and residual $CHCl_3$. Mass spectra were measured on a Virian MAT-711 and accurate mass spectra were run in electron impact mode (at 70 eV) on a MAT-95. TLC analysis was performed on silica gel plates (0.25 mm thickness) with F_{254} indicator. Flash chromatography was performed as described by Still and co-workers on 200-300 mesh silica gel.

(3*R*, 4'*S*)-3-(2', 2'-Dimethyl-1', 3'-dioxolan-4'-yl)-3-(2-furyl)-propanol (2): Under a nitrogen atmosphere, a fresh solution of furyl lithium (80 mL, 37.5 mmol) in anhydrous ether was added to a solution of compound **1** (5.00 g, 25 mmol) in anhydrous ether (50 mL) at -78°C. The reaction mixture was stirred at this temperature for 2 h, then quenched with saturated aqueous NH_4Cl (50 mL). The organic layer was separated, washed with H_2O (50 mL x 2) and brine (50 mL) successively, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give the crude ester.

The crude ester was added dropwise to a suspension of LAH (1.0 g, 26.3 mmol) in anhydrous THF (50 mL) at 0 °C. The

reaction mixture was refluxed for 6 h, cooled to r.t., and then quenched with H_2O (1 mL), 15% NaOH (3 mL) and H_2O (3 mL) successively. The slurry thus obtained was treated with anhydrous Na_2SO_4, and stirred for 1 h. The solid was filtered and washed with ether (50 mL x 2). The filtrate was concentrated *in vacuo* and chromatographed on silica gel (petroleum ether : ethyl acetate, 3 : 1) to give the product as a colorless oil (3.78 g) in 67% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34 (d, 1H, J = 1.0 Hz), 6.30 (dd, 1H, J = 1.0, 2.0 Hz), 6.14 (d, 1H, J = 2.0 Hz), 4.35 (m, 1H), 4.00 (dd, 1H, J = 6.4, 12.3 Hz), 3.75 (dd, 1H, J = 7.4, 8.3 Hz), 3.65 (m, 1H), 3.50 (m, 1H), 3.15 (m, 1H), 1.93 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H). MS (m/z): 226 (M^+, 15), 211 (30), 151 (10), 101 (100). $[\alpha]_D^{20}$ = -1.42 (c 0.71, ethanol). IR (film): 3500, 1564, 1371, 1217, 1054 cm^{-1}. HRMS Calcd for $C_{12}H_{18}O_4$: 226.1203. Found: 226.1196.

(3′*R*, 4″*S*)-Methyl 2-[3′-(2″, 2″-dimethyl-1″, 3″-dioxolan-4″-yl)-3′-(2‴-furyl)]propyl acetoacetate (4): Methyl acetoacetate (0.60 mL, 4.25 mmol) was added dropwise to a suspension of NaH (0.18 g, 60% in mineral oil, 4.5 mmol) in anhydrous THF (10 mL) at 0°C. The mixture was stirred for 1 h, and a solution of compound **3** (1.35 g, 4 mmol) in anhydrous THF (20 mL) was added through a syringe. The mixture was refluxed for 27 h, cooled to r.t. and then quenched with saturated aqueous NH_4Cl (15 mL). The organic layer was separated and the aqueous layer was extracted with ether(30 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4 and then filtered. The filtrate was concentrated *in vacuo* and chromatographed on silica gel (petroleum ether : ethyl acetate, 6 : 1) to give the product as a colorless oil (1.17 g) in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (d, 1H, J = 1.8 Hz), 6.30 (dd, 1H, J = 1.8, 3.0 Hz), 6.15 (d, 1H, J = 3.0 Hz), 4.27 (m, 1H), 3.98 (m, 1H), 3.70 (m, 4H), 3.40 (m, 1H), 2.90 (m, 1H), 2.18 (d, 3H, J = 4.0 Hz), 1.60-1.80 (m, 4H), 1.36 (brs, 6H). IR (film): 1745, 1716, 1369, 1217, 1155, 1058, 860, 789 cm^{-1}. MS (m/z): 324 (M^+, 5), 309 (14), 277 (3), 248 (30), 133 (30), 101 (100). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.96; H, 7.41. Found: C, 62.56; H, 7.23.

(3′*R*, 4″*S*)-Methyl 2-[3′-(2″, 2″-dimethyl-1″, 3″-dioxolan-4″-yl)-3′-(2‴-furyl)]propyl -4-phenylthio-acetoacetate (5): A solution of compound **4** (652 mg, 2 mmol) in anhydrous THF (5 mL) was added dropwise to a suspension of NaH (120 mg, 60% in mineral oil, 3 mmol) in anhydrous THF (10 mL) at 0°C. The mixture was stirred at this temperature for 0.5 h and then cooled to -15°C. To this homogeneous mixture was added n-BuLi (1.4 M in hexane, 2.14 mL, 3 mmol) through a syringe. After stirring for an additional 1.5 h at -15°C, a solution of PhSSPh (436 mg, 2 mmol) in anhydrous THF (2 mL) was added. The mixture was stirred for an additional 1.5 h at this temperature, then 4 h at r.t., and 5% HCl (3 mL) was added to quench the reaction. After separation, the organic layer was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and chromatographed on silica gel (petroleum ether : ethyl acetate, 6 : 1) to give the product as a colorless oil (650 mg) in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 7.20-7.45 (m, 6H), 6.32 (dd, 1H, J = 1.8, 3.0 Hz), 6.15 (d, 1H, J = 3.0 Hz), 4.10-4.32 (m, 1H), 3.60 (s, 3H), 3.37-3.50 (m, 5H), 2.70-2.82 (m, 1H), 1.45-1.82 (m, 4H), 1.38 (s, 3H), 1.32 (s, 3H). IR (film): 1745, 1752, 1564, 1438, 1371, 1244, 1217, 1157, 1057, 858, 787, 742 cm^{-1}.Anal. Calcd for $C_{23}H_{28}O_6S$: C, 63.87; H, 6.52. Found: C, 63.46; H, 6.43.

(3′*R*, 4″*S*)-Methyl 2-[3′-(2″, 2″-dimethyl-1″, 3″-dioxolan-4″-yl)-3′-(2‴-furyl)]propyl-3-methoxy -4-methylsulfinyl-2-butenoate (6): A solution of m-CPBA (180 mg, 75%, 1 mmol) in $CHCl_3$ (10 mL) was added slowly to a solution of compound **5** (432 mg, 1 mmol) in $CHCl_3$ (10 mL) over a period of 1.5 h by a motor driven syringe at 0°C. $CHCl_3$ (50 mL) and half saturated aqueous $Na_2S_2O_3$ (6 mL) were then added. After separation, the organic layer was washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure to

give the crude sulfoxide.

To a solution of the crude sulfoxide in ether (20 mL) was added an ethereal solution of CH_2N_2 (6.8 mmol) at 0°C. The mixture was stirred at this temperature for 2 h, and then concentrated. The residue was chromatographed on silica gel (petroleum ether : ether, 2 : 1) to give the product as a colorless oil (240 mg) in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (m, 2H), 7.50 (m, 3H), 7.33 (brs, 1H), 6.30 (brs, 1H),6.14 (d, 1H, J = 2.7 Hz), 4.62 (dd, 1H, J = 6.0, 7.0 Hz), 4.38 (m, 1H), 4.14 (d, 1H, 13.1 Hz), 3.97 (t, 1H, J = 6.0 Hz), 3.60-3.70 (m, 7H), 2.87 (m, 1H), 2.26 (m, 2H), 1.60 (m, 2H), 1.3 (brs, 6H). IR (film): 2885, 1693, 1602, 1444, 1368, 1275, 1047, 862, 750, 692 cm^{-1}. MS (m/z): 462 (1), 447 (350, 431 (6), 279 (26), 247 (56), 101 (100). Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.34; H, 6.49. Found: C, 62.10; H, 6.46. $[\alpha]_D^{20}$ = -14.06 (c 0.27, ethanol).

(3*R*, 3a*R*, 6*R*, 8a*R*, 4′*S*)-3-(2′, 2′-Dimethyl-1′, 3′-dioxan-4′-yl)-8-methoxy-8a-trifluoroacetoxymethyl-7-phenylthio-1,2,3,6-tetrahydro-3a,6-epoxyazulene (8): Dibal (1 M in hexane, 0.2 mL) was added to a solution of compound **6** (20 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (2 mL) at -78°C. The mixture was stirred at this temperature for 2 h, and CH_3OH (23 μL) was added. After the mixture was warmed up to r.t., brine (46 μL), ether (20 mL) and anhydrous Na_2SO_4 (1 g) were added successively. The slurry was stirred for an additional 1 h and filtered. The solid was washed with ether (10 mL x 2) and the filtrate was concentrated *in vacuo* to give the crude alcohol **7** (17 mg).

To a stirred solution of **7** (17 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (2 mL) were added $(CF_3CO)_2O$ (27 μL) and 2,6-lutidine (41 μL) at r.t. The mixture was stirred for 2 h and then quenched with saturated aqueous $NaHCO_3$ (5 mL). After the addition of ether (20 mL), the organic layer was carefully washed with saturated aqueous solution of $CuSO_4$ and brine successively, then dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* and purified on silica gel (petroleum ether : ether, 8 : 1) to give **8** (10 mg) as a colorless oil in 50% yield. ^{1}H NMR (300 MHz, C_6D_6): 7.40 (d, 2H, J = 8.0 Hz), 7.00 (t, 2H, J = 8.0 Hz), 6.90 (t, 1H, J = 8.0 Hz), 6.28 (d, 1H, J = 5.9 Hz), 5.90 (d, 1H, J = 5.9 Hz), 4.70 (s, 1H), 4.40-4.50 (m, 1H), 4.10 (dd, 2H, J = 12 Hz), 3.90 (m, 1H), 3.70 (s, 3H), 2.55 (m, 1H), 2.10 (m, 1H), 1.60 (m, 4H), 1.40 (s, 3H), 1.10 (m, 2H). IR (film): 2980, 1786, 1412, 1261, 798 cm^{-1}. MS (m/z): 512 (M^+, 40), 497 (10), 403 (25), 327 (35), 342 (10), 101 (100). HRMS calcd for $C_{25}H_{27}F_3O_6S$: 512.1480; Found: 512.1472.

(3*R*, 3a*R*, 6*R*, 8a*R*, 4′*S*)-3-(2′,2′-Dimethyl-1′,3′-dioxan-4′-yl)-8-methoxy-8a-hydroxymethyl-7-phenylthio-1,2,3,6-tetrahydro-3a,6-epoxyazulene (9): A silica gel (5 g) column was pretreated with triethylamine and washed with ether until the pH value of the eluent was 8. Compound **8** (50 mg) was then added to the column. The column was washed with petroleum ether-ether (1:1) affording **9** (40 mg) as a white solid in 95% yield, mp: 98-100°C. ^{1}H NMR (400MHz, C_6D_6): 7.40 (d, 2H, J = 7.6 Hz), 7.10 (t, 2H, J = 7.6 Hz), 7.00 (t, 1H, J = 7.6 Hz), 6.28 (dd, 1H, J = 5.9, 1.7 Hz), 5.80 (d, 1H, J = 5.9 Hz), 4.78 (d, 1H, J = 1.7 Hz), 4.50-4.60 (q, 1H, J = 8.0 Hz), 4.00 (t, 1H, J = 8.0 Hz), 3.70-3.80 (m, 4H), 3.44-3.60 (dd, 2H, J = 12 Hz), 2.65 (m, 1H), 2.10-2.20 (m, 2H), 1.68-1.80 (m, 2H), 1.26 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (100MHz, C_6D_6): 164.6, 137.3, 132.9, 128.7, 128.5, 128.3, 126.2, 110.1, 108.9, 96.3, 80.9, 75.4, 68.4 (2C), 65.0, 60.4, 47.1, 31.4, 27.8, 26.2, 24.0. MS(m/z): 416 (M^+, 100), 384 (5), 327 (53), 311 (18), 215 (23), 182 (20), 123 (10), 59 (41). IR (film): 3525, 1602, 1581, 1479, 1371, 1210, 1066, 1049, 973, 840, 740cm^{-1}. HRMS calcd for $C_{23}H_{28}O_5S$: 416.1658; Found: 416.1658. $[\alpha]_D^{20}$ = -10.1 (c 0.015, acetone).

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