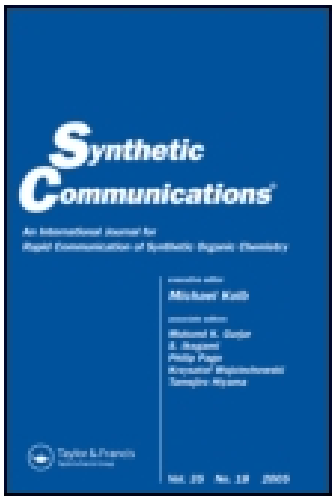

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Short and Efficient Synthesis of (±)-A-Factor

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Short and Efficient Synthesis of (±)-A-Factor

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ABSTRACT

An efficient synthesis of (±)-A-factor *via* ring opening of electrophilic cyclopropane **2** with KOAc/AcOH, DMSO, as a key step is described.

Key Words: A-factor; Cyclopropane; Ring opening.

A-factor is a pleiotropic regulator which triggers the production of streptomycin and sporulation in *S. griseus.*[1] It was first isolated, synthesized and characterized by Khoklov and co-workers. They proposed the structure of A-factor as (2*S*)-(6′-methylheptanoyl)-(*3S*)-hydroxymethylbutyrolactone.[2,3] Later in 1983 Mori et al.[4] revised the stereochemistry of A-factor as (*2R*)-(6′-methylheptanoyl)-(*3R*)-hydroxymethyl-butyrolactone. The chiral centre at

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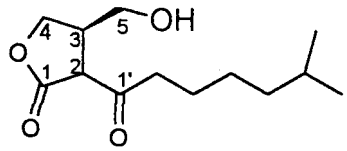
C-2 was shown to rapidly epimerize by enolization. They reported the synthesis of (−)-A-factor starting from (*S*)-(−)-paraconic acid[5,6] and also developed a synthetic route for the same by an enzymatic approach.[7]



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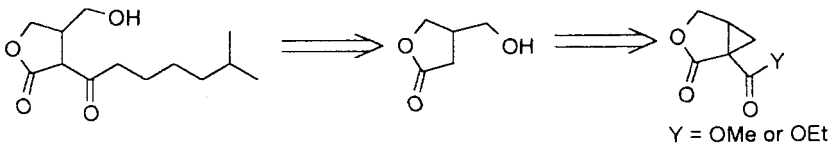
In 1994 Yadav et al.[8] accomplished the total synthesis of (±)-A-factor *via* regioselective oxidation of an acetoxy furan derivative using MnO_2-HCl. (*R*)-(−)-A-factor has also been synthesized previously using the Johnson–Claisen–Ireland rearrangement of a ketene acetal as a key step.[9] In 1998 Rawlings et al.[10] reported the asymmetric synthesis from pure (*S*)-paraconic acid based upon the diastereoselective benzyloxymethylation of (*4R*)-3-(3-phenylpropanoyl)-4-isopropyloxazolidin-2-one.

Herein we report a novel and efficient synthesis of (±)-A-factor in a minimum number of steps, which allows the use of commercially available, inexpensive, chemical reagents.

The retro synthesis delineated in Sch. 1 revealed that the target molecule could be achieved from ring opening of electrophilic cyclopropane, which can be prepared very easily from known literature procedures.[11–13]

When the cyclopropane **2** was subjected to crucial ring opening with KOAc/AcOH[14] in dry DMSO at 110°C (Sch. 2), it gave rise to ring opened as well as decarboxylated acetoxy lactone **3** in 66% yield. As per the literature protocol,[15] activated cyclopropane **2** when treated with acetic acid and H_2SO_4 failed to furnish the desired ring opened product (starting material remained intact). Deacetylation of lactone **3** with K_2CO_3/aq. MeOH furnished alcohol **4** in poor yield (27%). Improved yields during deacetylation was obtained using NaOMe (cat)/MeOH. Later the hydroxylactone **5** was efficiently converted to the *tert*-butyldimethylsilyl ether **5** in 77% overall yield starting from acetoxy lactone **3**.



1 **4** **2**

Scheme 1.

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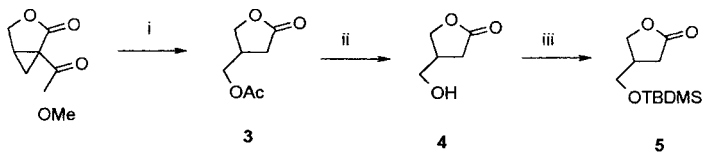
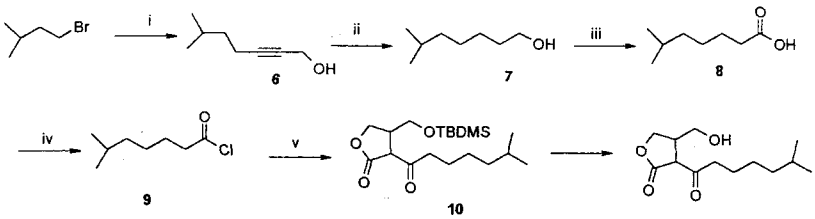


Scheme 2. Reagents and conditions: (i), a) KOAc/AcOH, DMSO, 6 h, 110°C; (ii) NaOMe (cat)/MeOH, 1 h, r.t.; and (iii) TBDMSCI, imidazole, CH_2Cl_2, 3 h, r.t.

The 4 steps preparation of the acid chloride **9** reported in the literature produces an overall yield of 32% only.[10] In this paper we describe a successful preparation of 6-methylheptanoyl chloride (**9**) in 40% overall yield. As shown in the Sch. 3, 1-bromo-3-methylbutane was condensed with propargyl alcohol using $LiNH_2$/liqNH_3 to furnish 6-methyl-2-heptyne-1-ol (**6**) in 61% yield. The acetylenic alcohol was subjected to hydrogenation using 10% Pd/C (40 psi) as well as with Raney nickel under normal pressure. It was observed that hydrogenation under Raney nickel gave consistent and higher yields (81%) of completely saturated alcohol as compared to Pd/C catalyzed hydrogenation (61% yield). The saturated alcohol **7** was subjected to Jones oxidation to give 6-methylheptanoic acid (**8**) in 96% yield. The acid thus obtained was converted to 6-methylheptanoyl chloride using $SOCl_2$ in 85% yield.

Gratifyingly, condensation of silylether **5** and 6-methylheptanoyl chloride with lithium hexamethyldisilazane (LHMDS) provided the silyl protected A-factor in 85% yield (Scheme 3), whose conversion to (±)-A-factor can be obtained from the established protocol.[9,10] It is pertinent to mention that similar acylation reaction reported in literature[10,17] either using lithium diisopropylamide or LHMDS furnished the corresponding acylated products in poor yields.

In conclusion a new synthetic route to (±)-A-factor has been demonstrated by use of a homoconjugate addition of KOAc/AcOH to doubly



Scheme 3. Reagents and conditions: (i) propargyl alcohol, $LiNH_2$/liq NH_3, overnight, −33°C; (ii) Raney nickel, H_2, MeOH, overnight, r.t.; (iii) Jones reagent, 8 h, 0°C to r.t.; (iv) $SOCl_2$, DMF (cat), 24 h, r.t.; and (v) **5**, LHMDS, THF, 1 h, −78°C.

activated cyclopropane **2**. The notable feature of this synthetic route is that (±)-A-factor is synthesized from simple and readily available starting materials. Extension of this strategy to the synthesis of biologically active (*S*)-(−)-A-factor is currently underway in our laboratory.

EXPERIMENTAL

Materials and General Methods

All solvents were distilled before use. DCM and DMSO were dried over calcium hydride. Methanol was dried over magnesium methoxide cake and THF was dried over sodium metal. Petroleum ether refers to boiling range of 60–80°C.

TLC analysis was carried out on glass plates using silica gel GF-254 and the plates were analyzed by keeping in iodine. In case were chromatographic purification was done silica gel (60–120 mesh) was used as the stationary phase.

Infra red spectra were recorded on a Perkin–Elmer 68B or 1615 FT as solution in the specified solvent, neat as films between salt disks and IR absorbance is expressed in cm^{-1}. The following abbreviations were used: s = strong, m = medium, w = weak and br = broad. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 (50 MHz). Figures in parenthesis refer to ^{13}C frequencies. Mass spectra were recorded at an ionization energy 70 eV on Finnigan MAT-1020; automated GC/MS instrument and mass values are expressed as m/z.

2-Oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylic acid methyl ester (2). Sodium (1.8 g, 75 mmol), was dissolved in dry MeOH (80 mL), and to it was added diethyl malonate (14.5 g, 90 mmol). To this solution epichlorohydrin (7.8 g, 84 mmol) in MeOH (10 mL) was added dropwise at room temperature over 1 h, and the mixture was stirred at 75°C for 20 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and chromatography on silica gel (eluting with Pet. ether-EtOAc = 6 : 4) afforded **1** as a colourless oil (5.5 g, 50%).

IR ($CHCl_3$, cm^{-1}): 1778 s, 1730 s. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.39 (m, 1H), 2.07(m, 1H), 2.75 (m, 1H), 3.79 (s, 3H), 4.2(m, 1H), 4.36 (dd, J = 9.37 Hz and 4.9 Hz) Mass: m/z (%): 156 (M^+, 17), 126 (100), 100 (45), 97 (45), 83 (76), 69 (79), 59 (41), 53 (69).

Acetic acid 5-oxo-tetrahydro-furan-3-ylmethyl ester (3). A mixture of **2** (2 g, 15.625 mmol), potassium acetate (6.3 g, 64 mmol), and acetic acid

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(4.62 g, 76 mmol) in dry DMSO (20 mL) was heated at 110°C for 6 h. After cooling, the reaction mixture was diluted with EtOAc, and the organic phase was washed with water brine and dried over anhydrous Na_2SO_4, and concentrated *in vacuo.* Chromatography on silica gel (eluting with Pet. ether-EtOAc = 6 : 4) afforded **3** (1.33 g, 66%) as a colourless oil.

IR (neat, cm^{-1}): 1780 s, 1737 s. ^1H NMR ($CDCl_3$, 200 MHz): 4.38 (1H, dd, $J = 7.32$ Hz, 9.32 Hz), 4.07 (3H, m), 2.87 (1H, m), 2.62 (1H, dd, $J = 9.04$ Hz, 17.58), 2.33 (1H, dd, $J = 6.34$ Hz, 17.58), 2.1 (3H, s). Mass: m/z (%): 159 ($M + 1^+$, 2), 128 (10), 98 (100), 85 (60), 70 (20).

4-(tert-Butyl-dimethyl-silanyloxymethyl)-dihydro-furan-2-one (5). To a solution of acetoxy lactone **3** (1 g, 6.32 mmol) in dry MeOH under argon atmosphere at 0°C was added catalytic amount of NaOMe. After stirring for 1 h at 0°C, the solution was quenched with 2N HCl. After concentration *in vacuo* the residue was dissolved in CH_2Cl_2 and washed with water. The water layer was saturated with NaCl and extracetd with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the hydroxy lactone **4**.

IR (neat, cm^{-1}): 3409 br s, 1774 s. ^1H NMR ($CDCl_3$, 200 MHz): 4.38 (1H, dd, $J = 7.33$ Hz, 9.28 Hz), 4.19 (1H, dd, $J = 4.88$ Hz, 9.2 Hz), 3.63 (2H, m), 2.73 (1H, m), 2.58 (1H, dd, $J = 8.79$ Hz, 17.09 Hz), 2.35 (1H, dd, $J = 5.61$ Hz, 17.09 Hz). Mass: m/z (%): 117 ($M + 1^+$, 20), 98 (20), 85 (30), 74 (45), 69 (20), 57 (100). IR (neat, cm^{-1}): 1781 s.

To a solution of alcohol **4** (0.595 mg, 5.12 mmol) in dry dichloromethane (5 mL) under argon atmosphere was added imidazole (0.768 g, 11 mmol) followed, after a 10 min delay, by TBDMSCl (0.92 g, 6.15 mmol) and the reaction was stirred at room temperature overnight. The reaction mixture was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo.* Chromatography on silica gel (eluting with Pet. ether-EtOAc = 9 : 1) afforded the title compound (1.12 g, 77%) as a colourless oil starting from **3**. ^1H NMR ($CDCl_3$, 200 MHz): 4.3 (1H, dd, $J = 4$ Hz and 6 Hz), 4.11 (1H, dd, $J = 4$ Hz and 6 Hz), 3.57 (2H, m), 2.66 (1H, m), 2.49 (1H, dd, $J = 6$ Hz and 12 Hz), 2.29 (1H, dd, $J = 4$ Hz, 12 Hz), 0.83 (9H, s), 0.00 (6H,s). Mass: m/z (%): 215 (2), 174 (47), 173 (45) 155(47), 145 (30), 115 (13), 99 (13), 75 (100), 73 (37).

6-Methyl-hept-2-yn-1-ol (6). To a stirred flask charged with 700 mL of liquid ammonia, was added 400 mg of Fe $(NO_3)_2$ with stirring. After a few seconds a small portion of the lithium (from 3.9 g, 0.561 mol) was added. As soon as the blue color of the dissolved metal has disappeared and a white greyish suspension has formed, the remaining lithium was introduced in similar manner. The entire amount of lithium was consumed in 30 min. Freshly distilled propargyl alcohol (15 g, 0.267 mol) was then added dropwise over 30 min. Ten minutes after the addition of propargyl alcohol, isoamyl

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bromide (48.5 g, 0.32 mol), was added dropwise over 30 min. Stirring was continued for additional 6 h. The ammonia was then allowed to evaporate. The resulting solid was hydrolysed by stirring with a saturated ammonium hydrochloride solution (200 mL). The solution was subjected to continuous extraction with ethyl acetate (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, and chromatography on silica gel (eluting with Pet. ether-EtOAc = 8.5 : 1.5) afforded the compound as a colourless oil (20.56 g, 61%). IR (neat, cm^{-1}): 3344 br s, 2289 w, 2223 w.

^{1}H NMR ($CDCl_3$, 200 MHz): 4.19 (2H, s), 2.59 (1H, br, s), 2.18 (2H, m), 1.65 (1H, m), 1.38 (2H, dd, J = 6 Hz, 14 Hz), 0.87(2H, d, J = 6.35 Hz). ^{13}C NMR (CDCl3, 50 MHz): 85.9 (s), 78.34 (s), 50.7 (t), 37.5 (t), 27.1 (d), 22 (2C, q), 16.6 (t). Mass: m/z (%): 111 (32), 107 (7), 95 (56), 93 (100), 83 (30), 77 (20), 70 (40), 55 (43).

6-Methyl-heptan-1-ol (7). To a solution of alcohol **6** (10 g, 79.3 mmol) in 100 mL of methanol was added 6 g of Raney nickel (washed with 3 × 10 mL methanol). Hydrogen was then admitted to the system under normal pressure and the reaction mixture was stirred at room temperature overnight. After hydrogenation was complete, the catalyst was removed by filtration of the reaction mixture through a Celite pad. Filtrate was concentrated *in vacuo*. Chromatography on silica gel (eluting with Pet. ether-EtOAc = 8:2) afforded 2 (8.25 g, 81%) as an oil. IR ($CHCl_3$, cm^{-1}): 3350 br s. ^{1}H NMR ($CDCl_3$, 200 MHz): 3.58 (2H, t, J = 6.35 Hz), 2.72 (1H, br, s), 1.52 (3H, m), 1.32 (4H, m), 1.17 (2H, m), 0.84 (6H, d, J = 6.34 Hz). Mass: m/z (%): 97 (34), 84 (24), 83 (12), 70 (31), 69(80), 56 (100), 55 (73).

6-Methyl-heptanoic acid (8). The Jones reagent was prepared by dissolving 70 g (0.70 mole) of chromium trioxide in 100 mL. of water. After it was immersed in an ice bath, 112 g (61 mL, 1.10 moles) of concentrated (18 M) sulfuric acid followed by 200 mL of water was added cautiously with manual stirring. The solution was cooled to 0°C–5°C. A solution of 10 g (1.00 mole) of alcohol **7** in 200 mL of acetone was cooled to 0°C–5°C. The cooled Jones reagent prepared above was added dropwise with vigorous stirring, at a rate to maintain the temperature of the reaction mixture at about 20°C till the solution retains the brown colour. The stirring was continued for 3 h after the addition was complete. After removing the acetone *in vacuo* the solution was subjected to continuous extraction with dichloromethane (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude acid 10.63 g (96%).

IR ($CHCl_3$, cm^{-1}): 3425 br s, 1707 s. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.35 (2H, t, J = 8 Hz), 1.63 (3H, m), 1.25–1.33 (4H, m), 0.88 (6H, d, J = 6.34 Hz). Mass: m/z (%): 145 ($M + 1^+$, 2), 129 (3), 101 (48), 85 (70), 82 (100), 72 (50), 59 (20).

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6-Methylheptanoyl chloride (9). Thionyl chloride (18.17 g, 0.15 mol), acid 11 (10 g, 0.069 mol) and a catalytic amount of dry DMF were combined and stirred at room temperature for 24 h, and the excess thionyl chloride was removed by distillation. Kughelrohr distillation furnished the title acid chloride **9** (bp110°C at 5 mmHg) as a colourless liquid (9.54 g, 85%).

IR (neat, cm^{-1}): 1806 s. ^1H NMR ($CDCl_3$, 200 MHz): 2.88 (2H, t, $J = 6.83$ Hz), 1.7 (2H, m), 1.55 (1H, m), 1.36 (2H, m), 1.2 (2H, m), 0.88 (6H, d, $J = 6.35$ Hz).

4-tert-Butylsilanyloxymethyl-3-(6-methyl-heptanoyl)-dihydro-furan-2-one (10). To a solution of protected alcohol **5** (0.5 g, 2.17 mmol) in dry THF (20 mL) under argon atmosphere at −78°C was added freshly prepared lithium bis(trimethylsilyl)amide (5.43 mmol) in THF (5 mL) dropwise. After a 20 min delay, acid chloride **9** (0.493 g, 3.03 mmol) in THF (5 mL) was added drop wise during 10 min at −78°C. After stirring for 1 h at −78°C, the reaction mixture was allowed to warm to room temperature. The mixture was poured into ice-AcOH-H_2O and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ solution (20 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo.* Chromatography on silica gel (eluting with pet. ether-EtOAc = 32 : 1) afforded the title compound **10** as a colourless oil (0.66 g, 85%). IR ($CHCl_3$, cm^{-1}): 1774 s, 1717 s. ^1H NMR ($CDCl_3$, 200 MHz): 4.36 (1H, dd, $J = 7.9$ Hz, 9.16 Hz), 4.15 (1H, dd, $J = 5.49$, 9.16 Hz), 3.59 (3H, m), 3.15 (1H, m), 2.91 (1H, m), 2.53 (1H, m), 1.21-1.55 (8H, m), 0.81 (15H, m), 0.0 (6H, s). ^{13}C NMR (CDCl3, 50 MHz): 202.33 (s), 172.16 (s), 69.23 (t), 62.43 (t), 42.62 (d), 39.53 (d), 38.98 (t), 27.07 (t), 26.08(3C, q), 23.84 (t), 22.92 (2C, q), 18.10(s), −5.24 (2C, q). Mass: m/z (%): 299 (11), 145 (21), 131 (25), 109 (42), 83 (28), 69 (21), 57 (79), 56 (100).

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