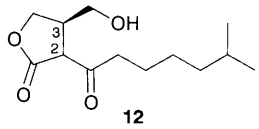
Synthesis of Optically Active A-Factor

Philip J. Parsons,*[a] Pierre Lacrouts[a] and A. D. Buss[b]

[a] *Department of Chemistry, University of Reading, Reading, Berkshire, UK RG6 2AD*
[b] *Glaxo Group Research and Development Ltd., Greenford Road, Greenford, Middlesex, UK UB6 0HE*

(3*R*)-(−)-A-factor and (3*S*)-(+)-A-factor are synthesised *via* the same chiral intermediate **6**, the synthesis of which proceeds through a Johnson–Claisen rearrangement key step.

Isolated from *Streptomyces griseus* in 1976 by Khokhlov *et al*,[1] (3*R*)-(−)-A-factor **12** is an autoregulator of cytodifferentiation, which induces the production of streptomycin in these strains of bacteria. The stereochemistry of this natural product was elucidated in 1983 by Mori[2] as being 3*R*, position C-2 readily epimerising by enolisation. Mori also completed the synthesis of optically active A-factor, introducing the chirality by an enzymatic method.[3]



12

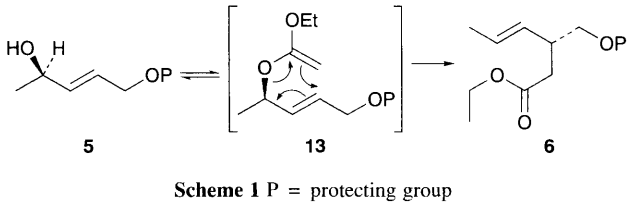
We report here an efficient and straightforward chemical synthesis of optically active A-factor starting with very simple reagents. We have developed a novel strategy which allows access to both enantiomers through the same chiral intermediate **6**, obtained by a high yielding Johnson–Claisen rearrangement[4] of the chiral ketene acetal **13** derived from the corresponding chiral allylic alcohol **5**, Scheme 1.

Both enantiomers were then obtained in a three step process from this common chiral intermediate. Special care was required to achieve the last step under neutral conditions to avoid racemisation at C-3 by facile intramolecular *trans*-esterification, Scheme 2.

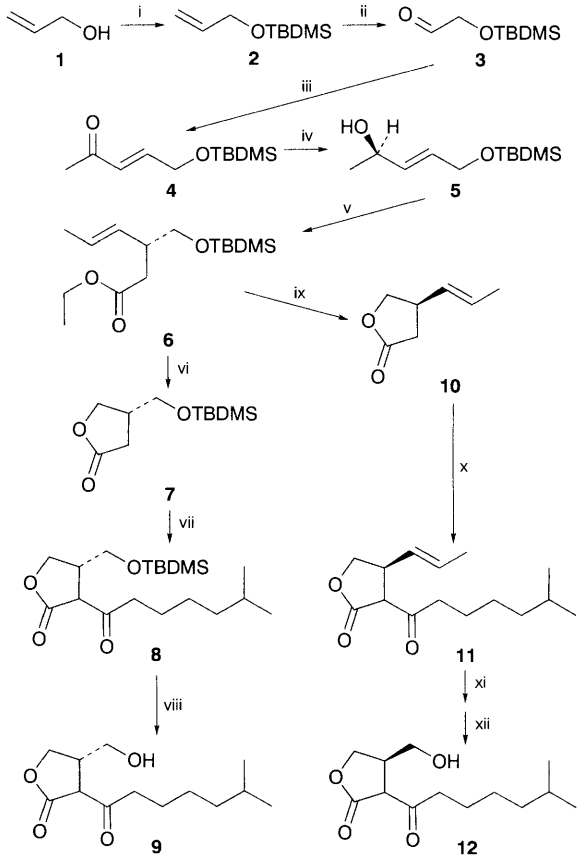
O-silylation of allyl alcohol **1** with *tert*-butyldimethylsilyl chloride, followed by ozonolysis with a triphenylphosphine work up[5] afforded the aldehyde **3** in an overall yield of 90%. A stabilised Horner–Emmons reaction using diethyl(2-oxopropyl)phosphonate afforded the *trans* α,β-unsaturated ketone **4** (80% yield). Enantioselective reduction of **4** using CBS conditions[6] afforded the allylic alcohol **5** in 80% yield with 84% ee.† Refluxing **5** with triethyl orthoacetate in the presence of an acid catalyst allowed the key Johnson–Claisen rearrangement to occur, yielding the chiral intermediate **6** in 75% yield. Ozonolysis of **6** followed by reductive cleavage of the ozonide with sodium borohydride afforded the first monosubstituted five-membered lactone **7** in 60% yield. The side chain was introduced by treatment of **7** with lithium hexamethyldisilazane and 6-methylheptanoyl chloride to give the protected A-factor **8**. Removal of the silyl protecting group under neutral conditions with tetrabutylammonium fluoride afforded (3*S*)-(+)-A-factor **9**, $[\alpha]_D^{25}$ = +9.8 (*c* = 0.05, $CHCl_3$). (lit.,[7] $[\alpha]_D$ = +12.7).

Treatment of **6** with a catalytic amount of concentrated hydrochloric acid in THF/H_2O 20:1 afforded the second monosubstituted five-membered lactone **10** in 80% yield. Compound **11** was obtained by treatment of **10** with lithium hexamethyldisilazane and 6-methylheptanoyl chloride. Treatment of **11** with osmium tetroxide and sodium periodate afforded the corresponding aldehyde which was immediately reduced to the alcohol under neutral conditions with zinc borohydride to yield (3*R*)-(−)-A-factor **12**, $[\alpha]_D^{25}$ = −6 (*c* = 0.018, $CHCl_3$). (lit.,[7] $[\alpha]_D$ = −13.1, *c* = 1.18). Presumably the difference in absolute value between the optical rotations of compounds **9** and **12** is due to partial racemisation *via* enolisation of the aldehyde intermediate between **11** and **12**.

A-factor in $CDCl_3$ at 25 °C was found to equilibrate with its hemiketal form **14**. The ratio between A-factor and the

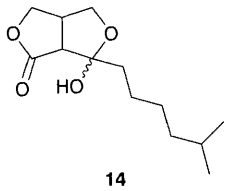


Scheme 1 P = protecting group



Scheme 2 *Reagents and conditions*: i, TBDMSCl, Et_3N, DMAP, CH_2Cl_2; ii, O_3, CH_2Cl_2, PPh_3; iii, K_2CO_3, diethyl(2-oxopropyl)phosphonate, H_2O; iv, BH_3·THF (0.6 equiv.), oxazaborolidine (0.05 equiv.), THF; v, triethyl orthoacetate, hexanoic acid (0.01 equiv.), 138 °C; vi, O_3, CH_2Cl_2, $NaBH_4$, EtOH; vii, LHMDS, 6-methylheptanoyl chloride, THF, −70 °C; viii, NBu_4F, wet THF; ix, conc. HCl (trace), THF/H_2O 20:1; x, LHMDS, 6-methylheptanoyl chloride, THF, −70 °C; xi, OsO_4 (0.04 equiv.), $NaIO_4$, dioxane/H_2O 1:1; xii, $Zn(BH_4)_2$, Et_2O/THF 1:1. TBDMS = *tert*-butyldimethylsilyl, LHMDS = lithium hexamethyldisilazane.

hemiketal form, calculated from the ^{1}H NMR spectrum, was 3 : 1. This result had never been reported.



14

Received, 9th November 1994; Com. 4/06855F

Footnotes

† The enantiomeric excess (ee) for the allylic alcohol **5** was determined from ^{19}F and ^{1}H analysis of the corresponding Mosher ester.

‡ *Spectroscopic data* for compound **6**: ^{1}H NMR ($CDCl_3$, 400 MHz) d 0.03 (s, 6H), 0.88 (s, 9H), 1.24 (t, 3H, J = 7 Hz), 1.64 (dd, 3H, J = 6.2, 1.2 Hz), 2.21 (dd, 1H, J = 15, 8.8 Hz), 2.56 (dd, 1H, J = 15, 5.5 Hz), 2.65 (m, 1H), 3.43 (dd, 1H, J = 9.9, 7.3 Hz), 3.57 (dd, 1H, J = 9.9, 5.2 Hz), 4.12 (q, 2H, J = 7 Hz), 5.3 (ddq, 1H, J = 15.4, 8, 1.5 Hz), 5.51 (dqd, 1H, J = 15.4, 6.2, 1 Hz).

For A-factor **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) d 0.86 (d, 6H, J = 6.6 Hz), 1.1–1.65 (m, 8H), 2.65 (dt, 1H, J = 18, 7.5 Hz), 3 (dt, 1H, J = 18, 7.5 Hz), 3.25 (m, 1H), 3.67 (d, 1H, J = 7 Hz), 3.68 (dd, 1H, J = 10.6, 5.9 Hz), 3.73 (dd, 1H, J = 10.6, 5.5 Hz), 4.15 (dd, 1H, J = 9.1, 6.6 Hz), 4.44 (dd, 1H, J = 8.8, 8.4 Hz).

References

1 E. M. Kleiner, S. A. Pliner, V. S. Soifer, V. V. Onoprienko, T. A. Balasheva, B. V. Rozynov and S. A. Khokhlov, *Bioorg. Khim.*, 1976, **2**, 1142.
2 K. Mori, *Tetrahedron*, 1983, **39**, 3107.
3 K. Mori and N. Chiba, *Liebigs Ann. Chem.*, 1989, 957; K. Mori and N. Chiba, *Liebigs Ann. Chem.*, 1990, 31.
4 W. S. Johnson, L. Werthemann, W. Bartlett, T. Brockson and T. Li, *J. Am. Chem., Soc.*, 1970, **92**, 741.
5 O. Lorenz and C. R. Parks, *J. Org. Chem.*, 1965, **30**, 1976.
6 E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.
7 K. Mori and K. Yamane, *Tetrahedron*, 1982, **38**, 2919.