Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 547–550

TETRAHEDRON: *ASYMMETRY*

Synthesis of (*R*)-(−)-argentilactone

Trond Vidar Hansen*

School of Pharmacy, Department of Medicinal Chemistry, University of Oslo, PO Box 1185, N-0316 Blindern, Oslo, Norway

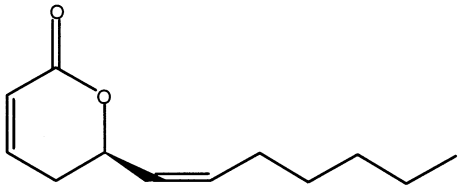
Received 27 February 2002; accepted 14 March 2002

Abstract—A synthesis of (*R*)-(−)-argentilactone is reported starting from the (*S*)-enantiomer of glycidol. The synthesis is based on ring closing metathesis of the acrylic ester of (*R*)-1-*O*-(*tert*-butyldiphenylsilyl)-4-penten-1,2-diol **4**.

1. Introduction

Argentilactone **1** was first isolated in 1977 from the rhizomes of *Aristolochia argentia*,[1] and exhibits both antileishmanial activity[2] and cytotoxic activity against mouse leukemia cells.[3] Its structure contains an α,β-unsaturated δ-lactone moiety with (*R*)-configuration at the stereogenic center. This structural feature is also present in several other biologically active natural products that have been targets for syntheses.[4,6c] There are a few syntheses of (−)-argentilactone[5] and its non-natural enantiomer[6] reported in the literature, as well as one of the racemic compound.[7] Usually, the (*R*)-stereogenic center has been introduced with carbohydrate building blocks,[5a,b] or the chirality has its origin from asymmetric reductions using enzymes.[6b]

We wish to report a facile synthesis of (−)-argentilactone **1**, starting from the commercially available (*S*)-glycidol, that utilizes a ring closing metathesis reaction as the key step.



(-)-argentilactone **1**

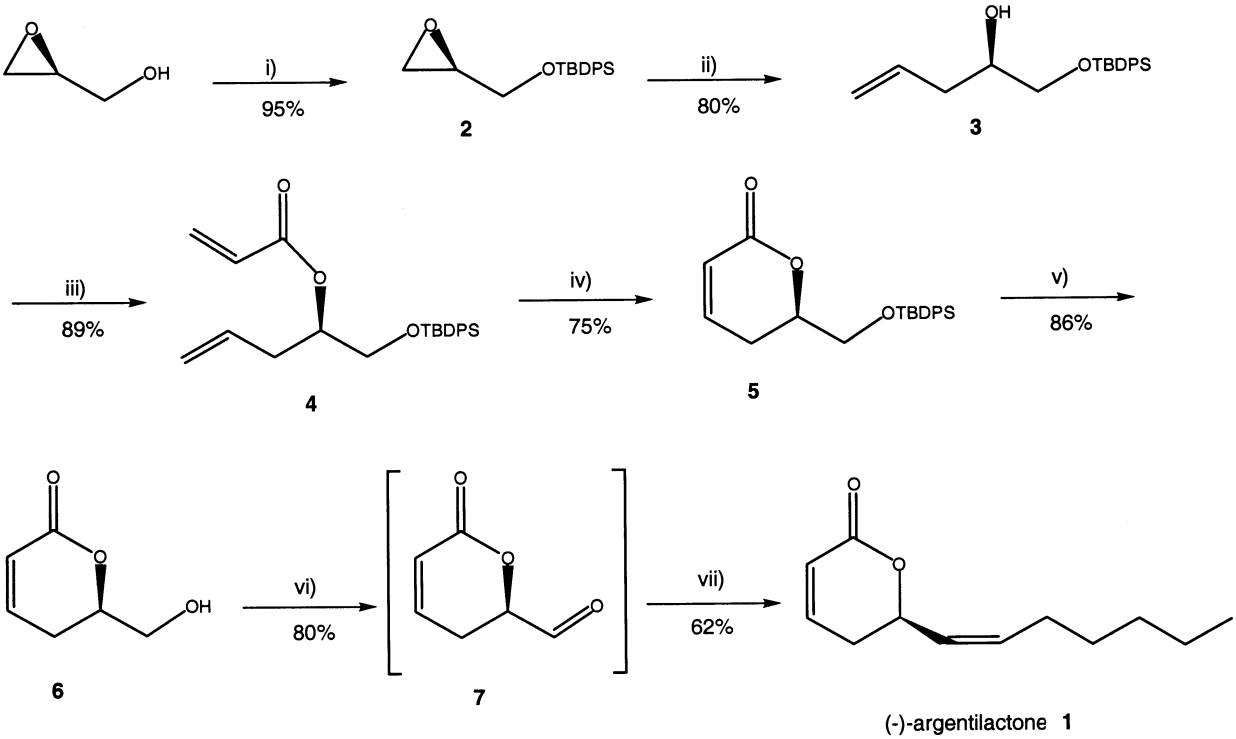
2. Results and discussions

Reaction of (*S*)-glycidol with *tert*-butyldiphenylsilylchloride (TBDPS-Cl) and imidazole in DMF afforded the silyl ether **2** in 95% yield (Scheme 1). The protected glycidol was then subjected to an ethereal solution of the organocuprate reagent $(CH_2CH)_2Cu(CN)(MgCl)_2$[8] affording the homoallyl alcohol **3**, which was then treated with acryloyl chloride in THF in the presence of Et_3N to give the ester **4** in 80% overall yield.

We envisaged that compound **4** could be transformed into the δ-lactone ring using a ring closing metathesis reaction. Treating the acryloyl ester **4** with 10% of Grubb's catalyst,[9] bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride, in refluxing CH_2Cl_2 under high dilution conditions resulted in formation of the lactone **5** in 75% yield after purification by column chromatography. The spectral data and specific rotation value of the lactone **5** were in agreement with literature values.[4] Removal of the protecting group under standard conditions with tetra-*n*-butylammonium flouride in DMF afforded the unsaturated lactone alcohol **6** in 86% yield. Swern oxidation of **6** provided the unstable aldehyde **7**, which was used directly in the Wittig reaction with hexylidenetriphenylphosporane furnishing (−)-argentilactone **1** in 50% yield over the two steps. According to the NMR data and GLC analysis, the diastereomeric ratio of the olefin formed in the Wittig reaction was >96:4 in favor of the (*Z*)-isomer, and the two isomers could be separated by column chromatography. The spectral data and specific rotation value were in good agreement with

* Corresponding author. Fax: +47 22 85 59 47; e-mail: t.v.hansen@farmasi.uio.no

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00138-6



Scheme 1. (i) TBDPSiCl, imidazole, DMF; (ii) (a) CuCN, THF, −78°C, (b) $CH_2CHMgCl$, −78 to −20°C, (c) **2**, THF, −78°C; (iii) Et_3N, acryloyl chloride, THF, 0°C; (iv) $Ru{=}CHPhCl_2(PCy_3)_2$, CH_2Cl_2, Δ; (v) Bu_4NF, DMF; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; (vii) $C_5H_{11}CH{=}PPh_3$, THF, 0°C.

those published for (−)-argentilactone **1**, $[\alpha]_D^{25} = -20.5$ (*c* 0.5, EtOH) (as compared to the reported $[\alpha]_D = -21.1$ (*c* 0.5 EtOH) for natural (−)-argentilactone).[1]

In conclusion, we have reported an efficient seven-step synthesis of (−)-argentilactone **1** in 22% overall yield. Our synthetic route compares favorably with those already published with respect to both overall yield and simplicity.[5]

3. Experimental

3.1. General

NMR spectra were recorded on a VARIAN MERCURY 300 instrument using $CDCl_3$ as solvent. ^1H and ^{13}C spectra were recorded at 300 and 75 MHz, respectively. IR spectra were recorded on a Perkin–Elmer Paragon 500 FT Spectrometer. Analytical GLC was performed on a 25 M SP2100 capillary column on a Varian GC 3300 instrument. Optical rotations were measured on an Optical Activity Ltd. AA-10 Automatic Polarimeter. All reactions were carried out under an atmosphere of nitrogen. Where the term purified by column chromatography is used this refers to flash chromatography using silica gel (230–400 mesh).

3.2. (*R*)-(*tert*-Butyldiphenylsilyloxy)methyloxirane 2

A solution of *tert*-butyldiphenylsilyl chloride (18.15 g, 66 mmol) and imidazole (4.5 g, 66 mmol) in DMF (100 mL) at 0°C was treated by dropwise addition of a solution of (*S*)-glycidol (4.07 g, 55 mmol) in CH_2Cl_2 (10 mL) over a period of 20 min. The solution was stirred for a further 15 h at ambient temperature and the reaction was worked up in the usual manner. Purification by column chromatography (5% EtOAc in hexanes) afforded the silyl ether (16.3 g, 95%). $[\alpha]_D^{23} = +2.3$ (*c* 2.0, $CHCl_3$); IR (film) 2955, 1470, 1110, 825, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.65 (dd $J = 5.1$, 3.2 Hz, 1H), 2.76 (dd $J = 5.1$, 4.0 Hz, 1H), 3.18–3.10 (m, 1H), 3.74 (dd, $J = 12.0$, 4.5 Hz, 1H), 3.85 (dd, $J = 12.0$, 3.2 Hz, 1H), 7.30–7.45 (m, 6H), 7.67–7.73 (m, 4H); 19.12, 26.53, 44.25, 52.23, 64.26, 127.61, 127.66, 129.71, 129.78, 133.20, 135.51.

3.3. (2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-4-penten-2-ol 3

CuCN (6.73 g, 75 mmol) was placed in a flask under argon and dried by gentle heating with a heat gun under vacuum. After cooling to room temperature, ether (100 mL) was added and the mixture cooled to −78°C. The resulting slurry was treated by dropwise addition of vinylmagnesium chloride (87 mL, 147 mmol) over a period of 15 min. The mixture was warmed to −20°C until the CuCN dissolved completely, and then the solution was cooled again to −78°C. A solution of **2** (10.0 g, 32 mmol) in ether (125 mL) was added dropwise and the reaction mixture was allowed to warm to −60°C and stirred for 6 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (50 mL) and warmed to ambient temperature, the aqueous phase was extracted with ether (2×50 mL),

the combined organic solutions were washed with brine and then dried ($MgSO_4$). Removal of the solvents yielded a yellow oil of the alcohol **3** (8.71 g, 80%), which was used directly in the next step. $[\alpha]_D^{23}=+2.9$ (*c* 0.9, $CHCl_3$); IR (film) 3078, 2930, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.08 (s, 9H), 2.15 (bs 1H), 2.20–2.25 (m, 2H), 3.55 (dd, $J=10.5$, 7.2 Hz, 1H), 3.65 (dd, $J=10.5$, 3.5 Hz, 1H), 3.75–3.84 (m, 1H), 5.05–5.12 (m, 2H), 5.75–5.82 (m 1H), 7.38–7.44 (m, 6H), 7.66–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 19.26, 26.77, 37.54, 67.22, 71.22, 117.42, 127.61, 127.66, 129.71, 129.78, 133.20, 134.37, 135.51.

3.4. (6*R*)-6-(*tert*-Butyldiphenylsilyloxy)methyl-5,6-dihydro-2*H*-pyran-2-one 5

To a solution of the alcohol (8.5 g, 25 mmol) in dry THF was added Et_3N (126 mg, 1.25 mmol) at 0°C. A solution of acryloyl acid chloride (2.49 g, 27.5 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to the mixture over a period of 30 min and stirring was continued for a further 3 h. Brine (50 mL) was added and the aqueous phase extracted with ether (2×30 mL), the combined organic solutions were washed with brine and then dried ($MgSO_4$). Removal of the solvent afforded the ester **4** (8.77 g, 89%) which was used as such in the next step.

Grubb's catalyst (0.16 g, 0.02 mmol, 10 mol%) was dissolved in dry CH_2Cl_2 (5 mL) and was added dropwise to a refluxing solution of the above ester **4** (0.79 g, 2 mmol) in dry CH_2Cl_2 (200 mL). The mixture was heated under reflux for 6 h by which time all of the starting material was consumed (TLC). The solvent was removed and the reaction mixture was purified by column chromatography (25% EtOAc in hexane) to obtain **5** as an oil (0.55 g, 75%). $[\alpha]_D^{23}=+34.2$ (*c* 1.5, $CHCl_3$); IR (film) 3078, 2930, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.08 (s, 9H), 2.45 (dddd, 18.5, 5.5, 4.5, 1.1 Hz, 1H), 2.60 (dddd, 18.5 Hz, 11.0, 9.5, 2.5, 2.5 Hz, 1H), 3.85 (d, $J=5.0$ Hz, 2H), 3.65 (dd, $J=10.5$, 3.5 Hz, 1H), 4.50 (dddd, $J=11.0$ Hz, 9.5, 5.0, 5.0 Hz, 1H), 6.05 (ddd, $J=10.0$ Hz, 6.0, 2.5 Hz, 1H), 6.90 (ddd, $J=10.0$ Hz, 2.5, 1.2 Hz, 1H), 7.38–7.50 (m, 6H), 7.65–7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 3×19.26, 25.87, 26.85, 64.71, 77.24, 121.23, 127.80, 127.86, 129.75, 129.92, 133.61, 135.54, 144.78, 163. 81.

3.5. (6*R*)-6-(Hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-one 6

To a solution of the lactenone **5** (0.53 g, 1.45 mmol) in dry DMF (10 mL) a solution of tetra-*n*-butylammonium fluoride (2.9 mL, 1.0 M, 2.9 mmol) in THF was added dropwise at 0°C. Workup was completed in the usual manner[10] and purification by column chromatography (EtOAc:hexane, 1:1) yielded the alcohol **6** as a colorless oil (0.16 g, 86%). IR (film) 1732, 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2.30–2.36 (m, 1H), 2.52–2.70 (br m, 2H), 3.70–3.92 (m, 2H), 4.48–4.60 (m, 1H), 6.06 (dd, $J=10.0$, 3.5, Hz, 1H), 6.96 (ddd, $J=10.0$, 3.5, 1.5 Hz, 1H); $[\alpha]_D^{22}=+172.7$ (*c* 1.0, $CHCl_3$) lit. $[\alpha]_D^{26}=+174.95$ (*c* 0.92, $CHCl_3$); HRMS (*m*/*z*). Found 128.0466, calculated 128.0472 for $C_6H_8O_3$ (M^+).

3.6. (*R*)-Argentilactone 1

To a stirred solution of oxalyl chloride (0.16 mL, 1.83 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of DMSO (2 mL, 2.55 mmol) in dry CH_2Cl_2 (5 mL) at −78°C. After stirring for 20 min, the alcohol **6** (0.16 g, 1.25 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise and stirring was continued for a further 45 min at this temperature. Et_3N (0.87 mL, 6.25 mmol) was added and stirring was continued for another 30 min. Workup in the usual manner afforded the aldehyde **7** (126 mg, 80%), which was immediately dissolved in dry THF (5 mL) and added dropwise to a solution of hexylidenetriphenylphosphorane[5c,11] in THF (5 mL) at −15°C. The mixture was then stirred for 45 min. Brine (5 mL) was added followed by the addition of Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2×10 mL) and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc:hexane, 9:1) to afford (*R*)-argentilactone **1** (132 mg, 62%). $[\alpha]_D^{25}=-20.5$ (*c* 0.5 EtOH), literature: $[\alpha]_D=-21.1$ (*c* 0.5, EtOH); IR (film) 1730, 1245 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, $J=7.0$ Hz, 3H), 1.25–1.45 (m, 3H), 2.10 (m, 2H), 2.42 (m, 2H), 5.25 (ddd, $J=10.0$, 8.5, 5.0 Hz, 1H), 5.59 (dddd, $J=11.0$, 8.5, 1.5, 1.0 Hz, 1H), 5.68 (dtd, $J=11.0$, 7.5, 0.7 Hz, 1H), 6.06 (ddd, $J=10.0$, 2.5, 1.5 Hz, 1H), 6.92 (ddd, $J=10.0$, 5.2, 3.1, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.06, 22.47, 27.75, 29.08, 29.88, 31.41, 73.94, 121.53, 126.40, 135.66, 144.92, 164.28.

Acknowledgements

Financial support from the Norwegian Research Council is gratefully acknowledged.

References

1. Priestap, H. A.; Bonafede, J. D.; Ruveda, E. A. *Phytochemistry* **1977**, *16*, 1579.
2. Waechter, A. I.; Ferreira, M. E.; Fournet, A.; Rojas de Arias, A.; Nakayama, H.; Torres, S.; Hocquemiller, R.; Cave, A. *Planta Med.* **1997**, *63*, 433.
3. Matsuda, M.; Endo, Y.; Fushiya, S.; Endo, T.; Nozoe, S. *Heterocycles* **1994**, *38*, 1229.
4. Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161 and references cited therein.
5. (a) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *27*, 5201; (b) Carretero, J. C.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 2059; (c) Rahman, S. S.; Wakefield, B. J.; Roberts, S. M.; Dowle, M. D. *J. Chem. Soc., Chem. Commun.* **1989**, 303; (d) Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281; (e) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *J. Ind. Chem. Soc.* **1999**, *76*, 739; (f) Saed, M.; Ilg, T.; Abbas, M.; Voelter, W. *Tetrahedron Lett.* **2001**, *42*, 7401.
6. (a) Saed, M.; Abbas, M.; Khan, K. M.; Voelter, W. *Z. Naturforsch.* **2001**, *56b*, 325; (b) Job, A.; Wolberg, M.; Muller, M.; Enders, D. *Synlett* **2001**, 1796 and references

cited therein for other natural products with this structural feature.
7. Chidambaram, N.; Satyanarayana, K.; Chandrasekaran, S. *Tetrahedron Lett*. **1989**, *30*, 2429.
8. Lipshuzt, B. H.; Kozlowski, J. A. *J. Org. Chem*. **1984**, *32*, 404.
9. Schwab, P.; Grubbs, R. H.; Ziller, J. *J. Am. Chem. Soc*. **1996**, *118*, 100.
10. Hanessian, S.; Lavalee, P. *Can. J. Chem*. **1977**, *53*, 2975.
11. Begue, J. P.; Bonnet-Delpon, D.; Mesureur, D.; Nee, G.; Sheng, W. *J. Org. Chem*. **1992**, *57*, 3807.