Pergamon

Tetrahedron Letters, Vol 35, No. 27, pp. 4861-4864, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00896-5

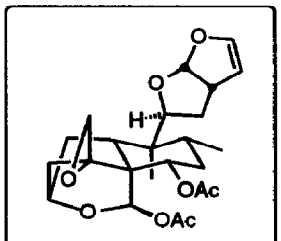
Model Studies towards the Insect Antifeedant Jodrellin A using an Organoselenium Mediated Cyclization Reaction.

Wally M. Blaney,[a] Ana C. Cuñat,[b] Steven V. Ley,*[b] Francis J. Montgomery[b] and Monique S.J. Simmonds[c]

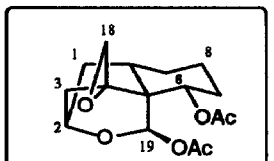
a) Department of Biology, Birkbeck College, London, WC1E 7HX, UK.
b) Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK.
c) Jodrell Laboratory, Royal Botanic Gardens, Kew, Richmond, Surrey, TW9 3AE, UK.

Abstract: An organoselenium mediated cyclization reaction of a ß-ketolactone (**5**), was used as the key step in an efficient synthesis of the molecular skeleton of the insect antifeedant Jodrellin A (**1**). The model compound (**2**) shows significant activity against the African leaf worm *Spodoptera littoralis*, at 1000 ppm.

For some years we have studied natural products which disrupt the feeding of insect pests.[1] During the course of this work we have characterized potent clerodane antifeedants isolated from *Scutellaria woronowii* (*Juz*).[2,3] One of the active compounds from this series, Jodrellin A (**1**), encompasses a rigid molecular framework which we believe to be important for its biological activity compared with similar clerodanes.[2] Here we report an approach to the preparation of a model compound (**2**) using a selenium mediated cyclization reaction to set up much of the required skeleton and functionality of the natural product. We also believe this approach may be adapted to the synthesis of (**1**) itself.



(**1**)

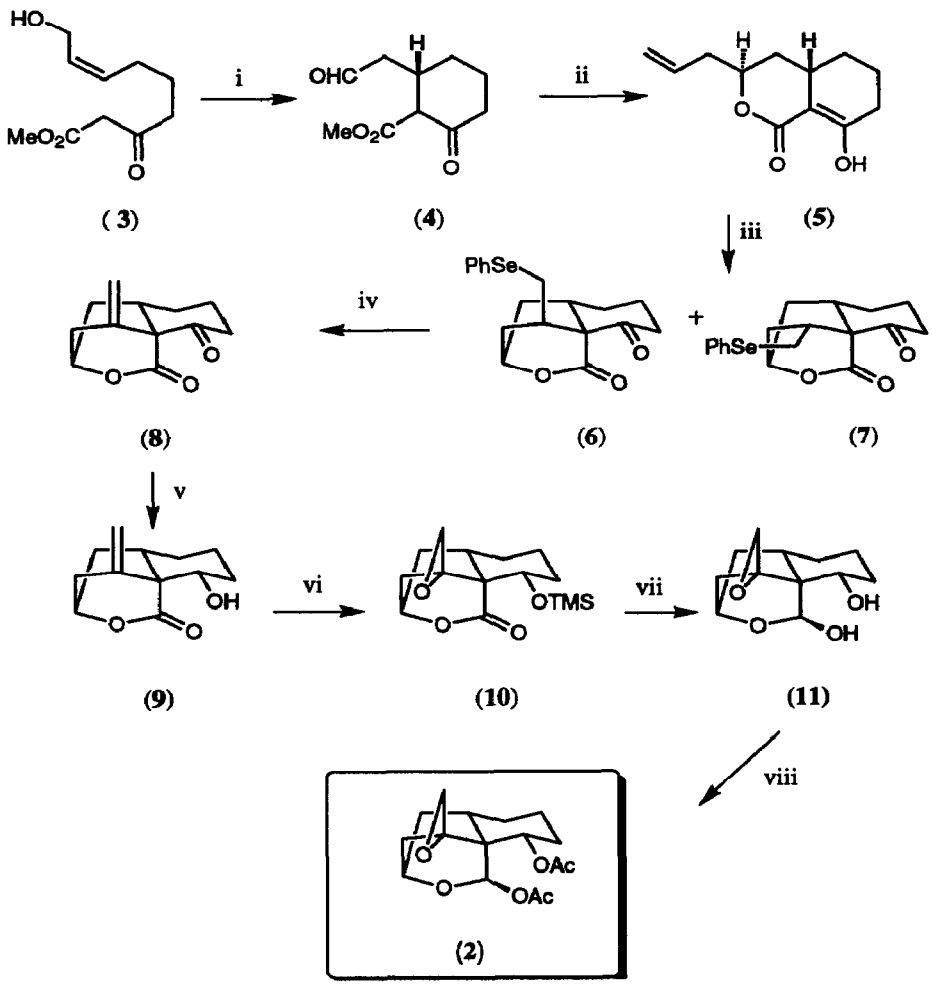


(**2**)

This work exploits the use of a selenium mediated reaction which we developed some years ago for the preparation of new carbon-carbon bonds during the cyclization of ß-ketoesters with alkenes.[4]

Oxidative cyclization[5,6] of the substituted ß-ketoester (**3**) gave the aldehyde (**4**) in good yield using pyridinium dichromate (PDC) as the oxidant together with acetic acid and 3Å powdered molecular sieves to

Scheme 1



Reagents: (i) PDC, AcOH (cat), 3Å powdered sieves, CH_2Cl_2, (85%). (ii) a) NaH, THF, 0°C. b) [allylTi(O^iPr)$_4$]$^-$Li$^+$, -78°C, (80%, 6:1). (iii) NPSP, ZnI_2, CH_2Cl_2, (95%). (iv) TBHP, Ti(O^iPr)$_4$, Dihydropyran, CH_2Cl_2, (92%). (v) $NaBH_4$, MeOH, 0°C, (95%). (vi) a) Br_2, MeCN/NH_4Cl (1:1), (76%). b) Amberlite® IRA-420, CH_2Cl_2, then TMSOTf, Et_3N, CH_2Cl_2, -78°C, (90%). (vii) DIBAL-H, PhMe, -78°C (89%). (viii) a) AcCl, Py, DMAP, CH_2Cl_2. b) Ac_2O, Py, DMAP.

improve the rate of the reaction[7] (Scheme 1). Allylation[8] and lactonization of (**4**) was achieved on treatment with NaH at 0°C followed by $[(allyl)Ti(O^iPr)_4]^-Li^+$ [9] at -78°C. After warming the reaction mixture to room temperature the product (**5**) was isolated as a 6:1 mixture of diastereomers at the newly created chiral centre. The major isomer (**5**) is ideally substituted to effect cyclization using N-phenylselenophthalimide (NPSP) and ZnI_2.[4] Consequently selenation at the α-position of the ß-ketolactone followed by migration to the olefin and subsequent trapping of the selenonium ion by the regenerated enol tautomer of the β-keto lactone (**5**) afforded the selenides (**6**) and (**7**) in a 1:6 ratio in 95% yield. While these isomers could be separated it was found to be more convenient to oxidise the mixture and *syn*-eliminate to afford a single alkene (**8**). This selenium mediated cyclization was extremely pleasing since alternative methods for cyclization, for example using $Mn(OAc)_3$[10] failed. Highly stereoselective reduction of (**8**) with sodium borohydride gave a 95% yield of (**9**). Attempts to use the hydroxyl group in (**9**) to direct epoxidation from the required underface were unsuccessful. However, if (**9**) was treated with bromine in MeCN and saturated ammonium chloride at 0°C an intermediate bromohydrin was formed, which was immediately converted to an epoxide using Amberlite® IRA-420 ion exchange resin in CH_2Cl_2. Silylation of the alcohol provided (**10**) in 90% overall yield. Reduction of (**10**) with Dibal-H in toluene afforded the lactol (**11**) upon work-up with pyridinium tosylate (PPTS), in THF/H_2O. Presumably the stereochemistry at the lactol centre arises as a result of ring opening and reclosure to the thermodynamically and sterically most favoured arrangement. Finally, acylation of (**11**) was achieved in two stages, firstly using acetyl chloride, in pyridine containing a catalytic amount of N,N-dimethylaminopyridine (DMAP) at room temperature and secondly with acetic anhydride, pyridine and DMAP to give the epoxy diacetate model compound (**2**)[11]. The first acylation occurred selectively at the lactol hydroxyl group while the second acylation of the remaining hydroxyl substituent was slower.

Although the racemic model compound (**2**) was not as active as the natural product Jodrellin A (**1**), it did show significant antifeedant activity at 1000 ppm (Table 1). This result suggests that the constrained epoxy diacetate decalin unit in the natural product is, at least in part, responsible for the observed antifeedant activity. This is consistent with our previous studies, whereby small structural fragments of active compounds can show significant antifeedant activity.[12, 13]

Table 1 *Antifeedant activity of compounds* (**1**) *&* (**2**)

	Antifeedant index §[(C-T)/C+T)] x 100 (mean ± SEM)	
Concentration applied to disc (ppm)	Jodrellin A[2]	Compound (**2**)
1000		32* ± 8.8
100	92* ± 7.6	24 ± 4.7
10	53* ± 13.3	
1	43* ± 15.9	

§ Antifeedant index is obtained by presenting larvae of *Spodoptera littoralis* with a choice of two fibre discs.[12] Both discs were treated with phagostimulant, sucrose, and then one disc, the treatment disc, was treated with 100 µl of a known concentration of one of the test compounds. C and T represent the amount eaten by the larvae of the control and treatment disc, respectively.

* Significant at $P<0.05$ (Wilcoxon signed ranks test); 10 replications.

Acknowledgement: We thank B. P. for a Research Endowment (to SVL), Northern Ireland Education Authority (to FJM) and the EEC (to ACC) for Research Fellowships. The insect bioassays were carried out at Birkbeck College under a licence from MAFF for the Import and Export (Plant Health Great Britain) Order 1980 and Plant Pests (Great Britain) Order 1980.

References and Notes

1. Ley, S.V. in *Recent Advances in the Chemistry of Insect Control II*; Ed. by L. Crombie; Royal Society of Chemistry: Cambridge, **1990**, p. 90-98.
2. Anderson, J.A.; Blaney, W.M.; Cole, M.C.; Fellows, L.L.; Ley, S.V.; Sheppard, R.N. and Simmonds, M.S.J. *Tetrahedron Lett.*, **1989**, *30*, 4737-4740.
3. Merritt, A.T. and Ley, S.V. *Nat. Prod. Reports*, **1992**, *9*, 243-287.
4. (a) Jackson, W.P.; Ley, S.V. and Morton, A.J. *J. Chem. Soc., Chem. Commun.*, **1980**, 1028-1029. (b) Jackson, W.P.; Ley, S.V. and Morton, A.J. *J. Chem. Soc. Chem., Commun.*, **1980**, 1173-1174. (c) Jackson, W.P.; Ley, S.V. and Morton, A.J. *Tetrahedron Lett.*, **1981**, *22*, 2601-2604.
5. Ley, S.V. and Madin, A. in *Comprehensive Organic Synthesis*; Ed. by Trost, B.M. and Fleming, I.; Pergamon Press: Oxford, **1991**, vol. 7, p. 251-289.
6. Ihara, M. and Fukumoto, K. *Angew. Chem., Int. Ed. Engl.*, **1993**, *32*, 1010-1022.
7. Herscovici, J.; Egron, M.-J. and Antonakis, K. *J. Chem. Soc., Perkin Trans. I*, **1982**, 1967-1973.
8. Roush, W.R. in *Comprehensive Organic Synthesis*; Ed. by Trost, B.M. and Fleming, I.; Pergamon Press: Oxford, **1991**, vol. 2, p. 1-53.
9. Reetz, M.T. and Wenderoth, B. *Tetrahedron Lett.*, **1982**, *23*, 5259-5262 and references cited therein.
10. (a) Dombroski, M.A.; Snider, B.B. *Tetrahedron*, **1992**, *48*, 1417-1426. (b) Snider, B.B. and Merritt, J.E. *Tetrahedron*, **1991**, *47*, 8663-8678.
11. Compound (2): ^{1}H-nmr (Natural Product numbering) (400 MHz, $CDCl_3$) δ 0.88-1.01 (2H, m, 8-H_{ax}, 9-H_{ax}), 1.23-1.92 (8H, m, 1-H_{ax}, 1-H_{eq}, 3-H_{ax}, 7-H_{ax}, 7-H_{eq}, 8-H_{eq}, 9-H_{eq}, and 10-H), 1.97 (3H, s, 6-OAc), 2.14 (3H, s, 19-OAc), 2.39 (1H, d, J 4.4 Hz, 18-H), 2.54 (1H, dt, J 14.4, 2.6 Hz, 3-H_{eq}), 2.98 (1H, d, J 4.4 Hz, 18-H'), 4.18 (1H, m, 2-H), 4.73 (1H, dd, J 11.2, 5.2 Hz, 6-H), 6.80 (1H, s, 19-H); υ_{max} (film) 2931, 2863, 1738, 1731, 1433, 1376, 1254, 1203, 1168, 1087, 1069, 1038, 1022, 994, 949 cm^{-1}; Found: [M$^+$-OAc] (EI) 251.1285. $C_{14}H_{19}O_4$ requires 251.1283.
12. Blaney, W.M.; Simmonds, M.S.J.; Ley, S.V. and Jones, P.S. *Entomol. exp. appl.*, **1988**, *46*, 267-274.
13. (a) Ley, S.V.; Anderson, J.C.; Blaney, W.M.; Morgan, E.D.; Sheppard, R.N.; Simmonds, M.S.J.; Slawin, A.M.Z.; Smith, S.C.; Williams, D.J. and Wood, A. *Tetrahedron*, **1991**, *47*, 9231-9246. (b) Blaney, W.M.; Simmonds, M.S.J.; Ley, S.V.; Anderson, J.C. and Toogood, P.L. *Entomol. exp. appl.*, **1990**, *55*, 149-160. (c) Blaney, W.M.; Simmonds, M.S.J.; Ley, S.V.; Anderson, J.C.; Smith, S.C. and Wood, A. *Pestic. Sci.*, **1994**, *40*, 169-173. (d) Simmonds, M.S.J.; Blaney, W.M.; Ley, S.V.; Savona, G.; Bruno, M. and Rodriguez, B. *Phytochemistry*, **1989**, *28*, 1069-1071. (e) Cole, M.D.; Anderson, J.C.; Blaney, W.M.; Fellows, L.E.; Ley, S.V.; Sheppard, R.N. and Simmonds, M.S.J. *Phytochemistry*, **1990**, *29*, 1793-1796.

(*Received in UK* 12 *April* 1994; *revised* 5 *May* 1994; *accepted* 6 *May* 1994)