Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 337-340, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00007-0

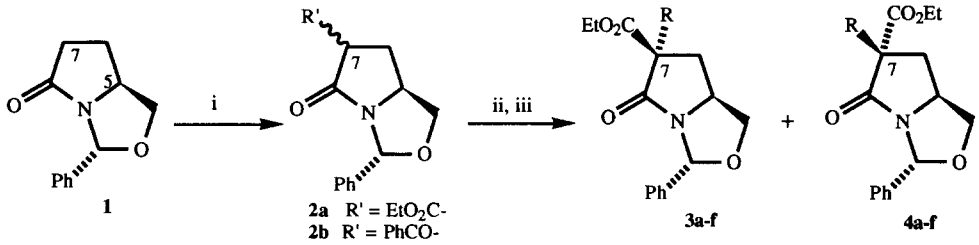
A CONCISE APPROACH TO FUNCTIONALISED, HOMOCHIRAL PYRROLIDINONES

Mark J. Bamford†, Mark Beard¶, David T. Cherry¶, and Mark G. Moloney¶*

¶ The Dyson Perrins Laboratory, University of Oxford, South Parks Rd, Oxford. OX1 3QY.
† Glaxo Research and Development, Greenford. Middlesex. UB6 0HE.

Abstract: Acylation of *O,N*-acetal **1** gives excellent yields of the C-7 substituted products **2a,b**. Alkylation of **2a** under mild conditions gives high yields of the *exo*- **3** and *endo*- **4** substituted products in varying ratios, depending on the alkylating agent. The unsaturated derivative **8** reacts in high yields under mild conditions with dienes and 1,3-dipoles to give the corresponding cycloadducts. Elaboration of these compounds by acidic deprotection to substituted pyroglutaminols, and oxidation to the corresponding pyroglutamates, can be readily achieved.

The elaboration of homochiral amino acids, obtained from the chiral pool, is an important method for the preparation of a wide range of chiral products. Our interest in this area is to develop simple and efficient routes to highly functionalised pyrrolidines, with substitution at any or all positions around the ring. Such compounds are of considerable pharmaceutical and biochemical importance because of their antibiotic, antibacterial, antifungal and cytotoxic effects, e.g pramanicin,[1] preussin,[2] anisomycin,[3, 4] TAN-950[5] and the kainoids,[6] the cytochalasans,[7] the echinocandins[8] and manzamines.[9, 10] The application of bicyclic lactam **1** to the preparation of a variety of products with C-6 and C-7 substitution, has been described.[11-19] We report herein that lactam **1** can be conveniently acylated at C-7 to give derivatives **2**. Lactam **2a** provides a convenient precursor for efficient alkylation and cycloaddition reactions to give a variety of highly functionalised intermediates, which can be conveniently elaborated to the corresponding pyrrolidinones. In particular, the cycloaddition reactions give direct access to 6,7-difunctionalised derivatives in a highly stereocontrolled manner. Similar activation has been recently reported[20, 21] in a related bicyclic lactam in which preferential *endo*- diastereoselectivity in alkylation reactions was observed.



(i) NaH, $(EtO)_2CO$ or $PhCO_2Me$, reflux; (ii) NaH, THF, 0°C then r.t.; (iii) RX (see table), THF, r.t. or reflux

Scheme 1

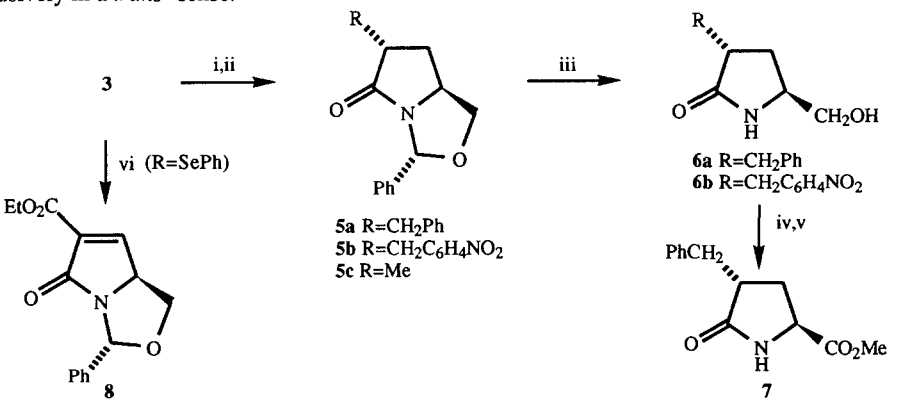
Pyroglutaminol[22] (of e.e >95% as determined from n.m.r. spectroscopic analysis of the Mosher's derivative[23]) was converted to lactam **1** according to the literature method.[17] Reaction of **1** with sodium hydride and diethylcarbonate at reflux in toluene,[24-26] gave the product **2a** in good yield (72%) as an inseparable 1:1 mixture of epimers at the new chiral centre at C-7. When this reaction was repeated using methyl benzoate, the product **2b** was obtained in 83% yield, as a mixture of *exo*- and *endo*- isomers, although the *exo*-isomer predominated in solution as shown by n.O.e. spectroscopic investigations. Functionalisation of dicarbonyl **2a**, by treatment with sodium hydride in THF, followed by any of a variety of electrophiles,

including alkylating, acylating and selenating agents, gave the separable products **3** and **4** in good to excellent yield (Table)[27, 28]; isomer **3**, which arose by attack of the electrophile on the *exo*- face of the bicyclic system,

Table: Yields of derivatives **3** and **4** prepared according to Scheme 1

COMPOUND	ELECTROPHILE	R	YIELD (%)	RATIO (3:4)
3a,4a	PhSeBr	PhSe-	73	1.5 : 1.0
3b,4b	MeI	Me-	67	1.7 : 1.0
3c,4c	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$-	68	4.7 : 1.0
3d,4d	$PhCH_2Br$	$PhCH_2$-	75	7.5 : 1.0
3e,4e	$pNO_2C_6H_4CH_2Br$	$pNO_2C_6H_4CH_2$-	94	10.0 : 1.0
3f,4f	CH_3COCl	CH_3CO-	72	10.0 : 1.0

was obtained as the major product in all cases. Both the yields and the diastereofacial selectivity obtained in this reaction were generally superior, particularly for the more sterically demanding electrophiles, to direct alkylations of the parent lactam **1**.[11,13-15] The stereochemistries of these compounds were readily determined by n.O.e. spectroscopic studies, and confirmed in the case of compound **3e** by single-crystal X-ray structure determination. The stereoselectivity in these reactions would appear to be controlled by a preference for addition of the electrophile from the least hindered face of the lactam enolate, but the presence of a relatively high proportion of the *endo*-isomer in nearly all cases suggests that the relative bulk of the C-7 ethoxycarbonyl substituent and the incoming electrophile may also be important. The favoured *exo*-diastereofacial selectivity of this process is similar to that recently reported for sequential double alkylation at C-4 of protected pyroglutamates, in which bulky electrophiles have been reported to add preferentially or exclusively in a *trans*- sense.[29]



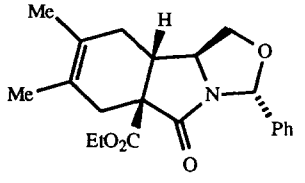
(i) NaOH(1M), MeCN, r.t., 24h ; (ii) 130-150°C, vacuum; (iii) TFA, CH_2Cl_2, r.t., 2h; (iv) $NaIO_4$, RuO_2, H_2O, CCl_4, MeCN, r.t., 2h; (v) CH_2N_2, CH_2Cl_2, r.t., 30min (vi) H_2O_2, CH_2Cl_2, 30°C, 30min

Scheme 2

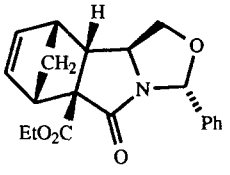
Hydrolysis and decarboxylation of **3d** and **3e** gave respectively the lactams **5a** and **5b** in yields of 67 and 41% respectively; under the same conditions, a mixture of **3b/4b** (in a ratio of 1:3.5) gave **5c** exclusively in 77% yield (Scheme 2). Deprotection of **5a** and **5b** with trifluoroacetic acid/dichloromethane gave the alcohols **6a** and **6b**, and conversion of **6a** to the benzyl substituted pyroglutamate **7** was readily achieved in

88% yield over the two steps, with no trace of the *cis*-substituted product. This approach therefore represents a convenient route to diastereomerically pure C-4 substituted pyroglutaminols and pyroglutamates in good yield from a conveniently prepared homochiral precursor.

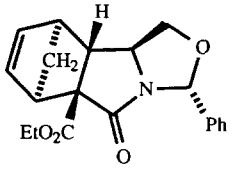
The selenenyl derivative **3a** could be readily converted to the unsaturated lactam **8** by oxidation and elimination with hydrogen peroxide in dichloromethane. Reaction of **8** with a variety of electron-rich dienes (2,3-dimethylbutadiene, cyclopentadiene, or Danishefsky's diene) or a dipolarophile (N-α-diphenylnitrone) in refluxing toluene gave moderate to good yields of the expected cycloadducts **9** (72%), **10a** (36%) and **10b** (18%), **11** (45%), and **12a** (64%) and **12b** (32%), respectively.[30] These reactions proceeded with excellent *exo*-facial selectivity to the least hindered face of the bicyclic lactam and, in the case of the reaction with cyclopentadiene, with predominant *endo*- diene addition. The structures of **12a,b** have been established by n.O.e. and COSY analysis; structure **12a** has been confirmed by single crystal X-ray analysis. The regiochemistry of the addition of the nitrone to **8** is consistent with that reported for other highly electron deficient alkenes,[31] and similar diastereofacial selectivity has been observed in related systems.[32,33] However, adduct **12b** arose by *endo*-facial selectivity, which has not been previously observed in the reactions of **8**, and this product could be easily converted to the corresponding isomer **12a** by refluxing in toluene, indicating that **12b** is the kinetic product of cycloaddition.



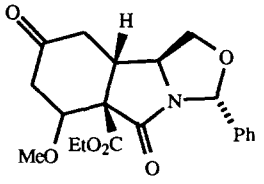
9



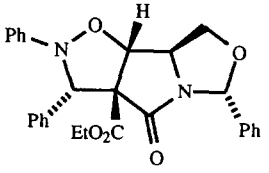
10a



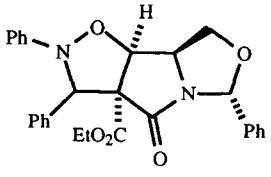
10b



11

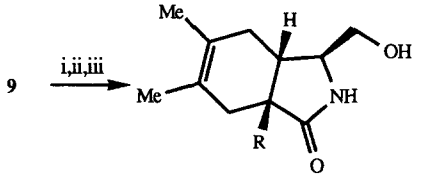


12a



12b

Hydrolysis and decarboxylation of **9** followed by acid deprotection gave the highly functionalised pyroglutaminol derivative **13** (R=H) in 52% overall yield(Scheme 3). However, the oxazolidine adduct **12a** did not survive this treatment, consistent with the known instability under thermal conditions of some cycloadducts derived from nitrones.[34] Alternatively, treatment of **9** with TFA in dichloromethane gave **13** (R=CO_2Et) in 82% yield.



13

(i) NaOH(1M), MeCN, r.t., 24h ; (ii) 130-150°C, vacuum; (iii) TFA, CH_2Cl_2, r.t., 2h

Scheme 3

The facile reaction of the activated lactams **2a** and **8** with a variety of electrophiles and dienes respectively demonstrates their versatility, providing convenient access to a range of substituted pyrrolidinones. The application of this approach to the preparation of a range of homochiral products is under active investigation.

Acknowledgements: DTC gratefully acknowledges SERC and Glaxo Research and Development for a CASE award.

References

1. Schwartz, R.E., Helms, G.L., Bolessa, E.A., Wilson, K.E., Giacobbe, R.A., Tkacz, J.S., Bills, G.F., Liesch, J.M., Zink, D.L., Curotto, J.E., Pramanik, B. and Onishi, J.C., *Tetrahedron* , 1994, **50**, 1675-1686.
2. Shimazaki, M., Okazaki, F., Nakajima, F., Ishikawa, T. and Ohta, A., *Heterocycles* , 1993, **36**, 1823-1836.
3. Tokuda, M., Fujita, H., Miyamoto, T. and Suginome, H., *Tetrahedron* , 1993, **49**, 2413-2426.
4. Takahata, H., Banba, Y., Tajima, M. and Momose, T., *J. Org. Chem.* , 1991, **56**, 240-245.
5. Tsubotani, S., Funabashi, Y., Takamoto, M., Hakoda, S. and Harada, S., *Tetrahedron* , 1991, **47**, 8079-8090.
6. McGeer, E.G., Olney, J.W. and McGeer, P.L., *Kainic Acid as a Tool in Neurobiology* (Raven Press, New York, 1978).
7. Harkin, S.A., Jones, R.H., Tapolczay, D.J. and Thomas, E.J., *J. Chem. Soc., Perkin Trans. 1.*, 1989, 489-497.
8. Morris, S.A., Schwartz, R.E., Sesin, D.F., Masurekar, P., Hallada, T.C., Schmatz, D.M., Bartizal, K., Hensens, O.D. and Zink, D.L., *J. Antiobiot.* , 1994, **47**, 755-760.
9. Martin, S.F., Liao, Y., Wong, Y. and Rein, T., *Tetrahedron Lett.* , 1994, **35**, 691-694.
10. Brands, K.M.J. and Pandit, U.K., *Heterocycles* , 1990, **30**, 257-261.
11. Herdeis, C., Hubmann, H.P. and Lotter, H., *Tetrahedron:Asymmetry* , 1994, **5**, 119-128.
12. Armstrong, R.W. and DeMattei, J.A., *Tetrahedron Lett.* , 1991, **32**, 5749-5752.
13. Baldwin, J.E., Moloney, M.G. and Shim, S.B., *Tetrahedron Lett.* , 1991, **32**, 1379-1380.
14. Hanessian, S. and Ratovelomanana, V., *Synlett.* , 1990, 501-503.
15. Hamada, Y., Kawai, A., Kohno, Y., Hara, O. and Shioiri, T., *J. Am. Chem. Soc.* , 1989, **111**, 1524-1525.
16. Allen, N.E., *Tetrahedron* , 1989, **30**, 1905-1928.
17. Thottathil, J.K., Moniot, J.M., Mueller, R.H., Wong, M.K.Y. and Kissick, T.P., *J. Org. Chem.* , 1986, **51**, 3140-3143.
18. Thottathil, J.K., Przbyla, C., Malley, M. and Gougoutas, J.Z., *Tetrahedron Lett.* , 1986, **27**, 1533-1536.
19. Griffart-Brunet, D. and Langlois, N., *Tetrahedron Lett.* , 1994, **35**, 119-122.
20. Meyers, A.I. and Snyder, L., *J. Org. Chem.* , 1993, **58**, 36-42.
21. Meyers, A.I. and Snyder, L., *J. Org. Chem.* , 1992, **57**, 3814-3819.
22. Saijo, S., Wada, M., Himizu, J.-I. and Ishida, A., *Chem. Pharm. Bull.* , 1980, **28**, 1449-1458.
23. Huang, S.-B., Nelson, J.S. and Weller, D.D., *Syn. Commun.* , 1989, **19**, 3485-3496.
24. Rueppel, M.L. and Rapoport, H., *J. Org. Chem.* , 1978, **43**, 7021-7027.
25. Haslego, M.L., Maryanoff, C.A., Scott, L. and Sorgi, K.L., *Heterocycles* , 1993, **35**, 643-647.
26. Jacob, P., *J. Org. Chem.* , 1982, **47**, 4165-4167.
27. All new compounds gave satisfactory spectroscopic and high resolution mass spectrometric or analytical data.
28. General method for the reaction of **2a**: To a stirred suspension of pre-washed NaH (1.1equiv.) in dry THF (30ml) at 0°C under a nitrogen atmosphere was added a solution of **2a** (1 equiv.) in THF (5ml) *via* syringe, and the mixture was stirred at r.t. for about 20min until the bubbling of hydrogen ceased and the suspension of NaH disappeared. A solution of electrophile (1.1equiv.) in THF (5ml) was added *via* syringe and the mixture stirred either at r.t. or at reflux for between 1h and 16h. The reaction was quenched by pouring the mixture into NH_4Cl(aq)/EtOAc (50ml, 1:1) and the aqueous portion was extracted with EtOAc (2x20ml). Organic extracts were combined, washed with water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by silica chromatography (3:1 light petroleum/EtOAc) to give the two possible diastereomeric products. Further careful silica chromatography or HPLC separation gave the individual diastereomers in homogeneous form.
29. Ezquerra, J., Pedregal, C., Rubio, A., Vaquero, J.J., Matia, M.P., Martin, J., Diaz, A. and Navio, J.L.G., *J. Org. Chem.* , 1994, **59**, 4327-4331.
30. General method for the reaction of **8**: To a solution of the dienophile **8** in toluene (60ml) was added the diene (5 equiv) and the mixture heated at reflux for 1-3days. When all of the dienophile had been consumed (tlc analysis), the mixture was cooled and the solvent removed *in vacuo* to give the crude product. Purification by silica chromatography (4:1 light petroleum/ethyl acetate) or by HPLC (9:1 cycloheptane/isopropyl alcohol) yielded the pure adducts as pale yellow oils.
31. Tufariello, J.J. in *1,3-Dipolar Cycloaddition Chemistry* (ed. Padwa, A.) 83-168 (Wiley, New York, 1984).
32. Wee, A.G.H., *J. Chem. Soc., Perkin Trans. 1* , 1989, 1363-1364.
33. Fray, A.H. and Meyers, A.I., *Tetrahedron Lett.* , 1992, **33**, 3575-3578.
34. Bianchi, G. and Gandolfi, R. in *1,3-Dipolar Cycloaddition Chemistry* (ed. Padwa, A.) 451-542 (Wiley, New York, 1984).

(*Received in UK* 8 *November* 1994)