Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 8105-8108, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10120-4

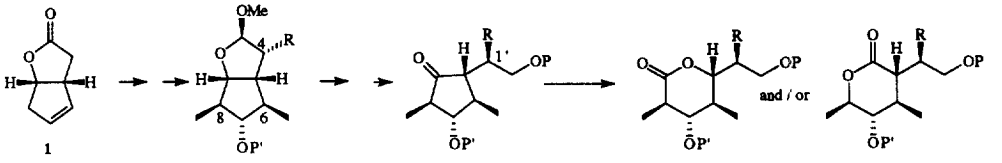
Synthesis of Tetrasubstituted δ-Lactones

Cole Clissold[a], Clare L. Kelly[a], Kenneth W. M. Lawrie[b] and Christine L. Willis[a]*

a School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS
b SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Coldharbour Road, The Pinnacles, Harlow CM19 5AD.

Abstract: A versatile route for the synthesis of δ-lactones via oxidation of tetrasubstituted cyclopentanones is described. Each step in the synthetic pathway from *cis*-2-oxabicyclo[3.3.0]oct-6-en-2-one to the ketones proceeds with excellent regio- and stereoselectivity and in good yield. Baeyer-Villiger oxidation of the cyclopentanone **21** with a further methyl substituent at C-1' of the side chain gives a single δ-lactone **22** whereas a 3:1 mixture of regioisomers **12** and **13** is obtained from the analogue **11** with no substituent at C-1'. © 1997 Elsevier Science Ltd.

The δ-lactone moiety is a common feature of many natural products including those isolated from insects, plants, fungi and marine organisms.[1] Staunton, Leadlay and co-workers have also isolated two highly substituted δ-lactones from genetically modified *Streptomyces coelicolor*.[2] In addition, δ-lactones such as Prelog-Djerassi lactone have proved valuable as intermediates in the synthesis of complex molecules.[3] Therefore a strategy giving access to variously substituted δ-lactones for the synthesis of natural products and their analogues for biological assessment and further building blocks for synthesis would be highly desirable. We now describe a general strategy for the preparation of tetrasubstituted δ-lactones from *cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** using the approach outlined in Scheme 1.



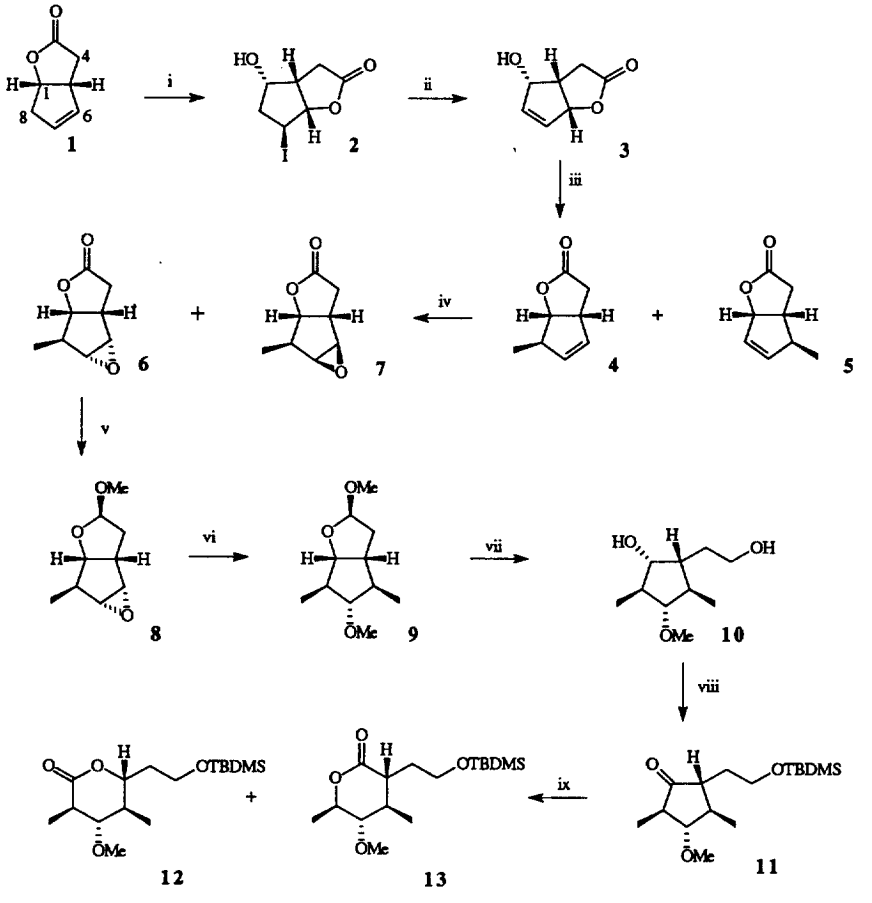
Scheme 1

Results and Discussion

The synthesis of the target compounds requires the introduction of methyl groups from the less hindered *exo*-face at both C-6 and C-8 of the bicyclic framework. We envisaged that an organocopper promoted *anti*-S_N2' type attack on the isomeric unsaturated lactone **3** (Scheme 2) would give the required

8β-methyl substituent. However, from literature precedents of organocopper based reactions on similar systems it was difficult to predict the outcome with any certainty. Commonly the products of *anti* attack are obtained; however, the regioselectively has varied from almost exclusive S_N2'[4] to S_N2[5] as well as a mixture of both[6] depending upon the substituents on the bicyclic framework and upon the reagent used.[7]

Allylic alcohol **3** was prepared in 88% yield from lactone **1** by a modification of the procedure of Corey and Mann.[5] A one-pot hydrolysis and iodolactonisation of **1** gave iodo-alcohol **2** (Scheme 2). Protection of the alcohol as the TBDMS ether and elimination of HI using DBU gave, after removal of the protecting group with TBAF, the required allylic alcohol **3**. (It is necessary to protect the alcohol during the elimination reaction to prevent epoxide formation.) Treatment of **3** with lithium dimethylcuprate gave a disappointing 3:2 mixture of **4** and **5** in 72% yield arising from competing S_N2' and S_N2 attack on the allylic lactone moiety. Similar results were obtained on treatment of the analogous TBDMS ether with



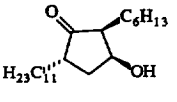
Reagents: i) NaOH then I_2; ii) a. TBDMSCl, imidazole; b. DBU, heat; c. TBAF; iii) MeMgBr, $Me_2S.CuBr$; iv) H_2O_2, AcOH; v) DIBALH then MeOH, H^+; vi) a. Me_2CuLi; b. KH, MeI;vii) a. H^+, MeCN; b. $NaBH_4$; viii) a. TBDMSCl, imidazole; b. PDC, DMF; ix) MCPBA, $NaHCO_3$.

Scheme 2

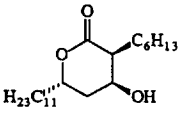
lithium dimethylcuprate. In contrast, reaction of allylic lactone **3** with 3 equivalents of the reagent derived from methylmagnesium bromide and one equivalent of copper (I) bromide: dimethyl sulfide[8] gave the required 8β-methyl derivative **4** in 90% yield (only 2% of the 6β-methyl lactone **5** was obtained).

A variety of conditions were then examined to prepare the required *endo*-epoxide **6**.[9] Treatment of **4** with dimethyl dioxirane (DMDO)[10] gave a 3:1 mixture of *endo:exo* epoxides **6** and **7** in 78% yield whereas with hydrogen peroxide and acetic acid a pleasing 11:1 mixture of *endo:exo* epoxides was obtained, which were readily separated by flash chromatography. The second methyl group was introduced via an organocuprate reaction, but first it proved necessary to protect the lactone as the acetal **8**. Opening the epoxide with lithium dimethylcuprate then proceeded with complete regio- and stereocontrol giving, after protection, methyl ether **9** in 86% yield.

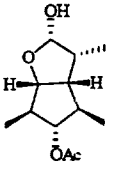
To complete the synthesis of cyclopentanone **11**, the acetal was hydrolysed to the lactol and subsequently reduced with sodium borohydride to give diol **10**. Selective protection of the primary alcohol as the TBDMS ether and oxidation of the secondary alcohol with PDC gave **11**. The final stage of the synthesis of the target δ-lactone was a Baeyer-Villiger oxidation. It is well established that the regiochemical outcome of the Baeyer-Villiger reaction can be predicted by the migratory aptitude of the neighbouring groups to the ketone.[11] However, in this case both α-centres are trisubstituted and so it was of interest to investigate the effects of more remote substituents on the outcome of this reaction. Previous studies have shown that oxidation of cyclopentanone **14** with MCPBA gave a single regioisomer **15** with insertion of oxygen occurring away from the hydroxyl group.[12] We found that treatment of cyclopentanone **11** under similar conditions gave a 3:1 mixture of lactones **12** and **13**.



14

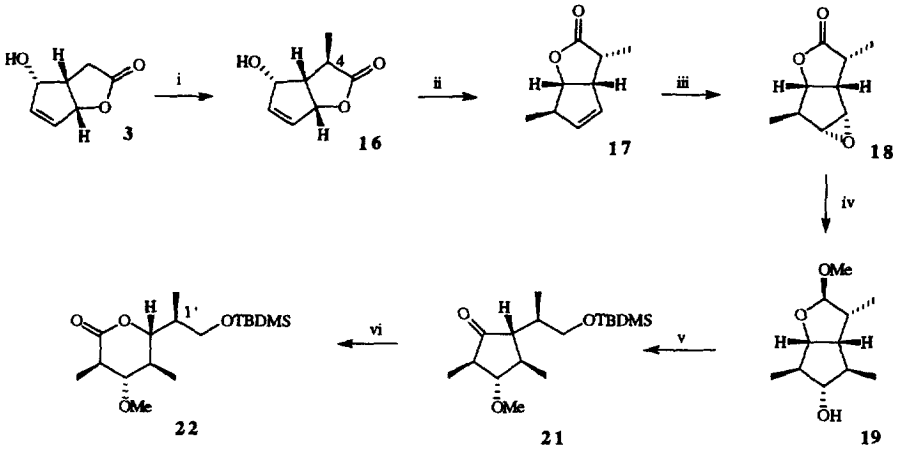


15



20

Many of the naturally occurring δ-lactones e.g invictolide[1a] have an additional methyl substituent at C-1'. Our approach may be simply adapted for the preparation of such compounds as shown in Scheme 3. Treatment of lactone **3** with LDA and methyl iodide introduced the methyl group to the less hindered *exo*-face at C-4. Reaction of the allylic lactone **16** with lithium dimethylcuprate proceeded smoothly, with concommitant rotation at C-4, leading to methyl substituents at the 4α- and 8β- positions in **17**. Surprisingly epoxidation of the alkene **17** proceeded with greater stereocontrol than in the case of **4** (without the 4α-methyl group) giving **18** as the sole product. Acetal formation and epoxide opening with lithium dimethylcuprate gave alcohol **19**. In view of all the molecular acrobatics which had occurred during this synthetic sequence it was essential to establish unequivocally the structure of **19**. This was achieved by NMR studies on **19** and from X-ray crystallography of the crystalline acetate **20** prepared from **19**. Following an analogous pathway to that delineated above, alcohol **19** was converted to cyclopentanone **21** in 61% yield. Interestingly in contrast to oxidation of cyclopentanone **11**, Baeyer-Villiger oxidation of **21** occurred with complete regioselectivity giving lactone **22** as the sole product.[13]



Reagents: i) LDA, MeI; ii) MeMgBr, $Me_2S.CuBr$; iii) H_2O_2, AcOH; iv) a. DIBALH then MeOH, H^+; b. Me_2CuLi; v) a. MeI, KH; b. H^+, MeCN; c. $NaBH_4$; d.TBDMSCl, imidazole; e. PDC, DMF; vi) MCPBA, $NaHCO_3$.

Scheme 3

Clearly the factors that determine the regioselectivity of the Baeyer-Villiger reaction in these systems are quite subtle and investigations are in hand to delineate these effects.

Acknowledgements. Financial support was gratefully received from the University of Bristol (for CC) and from EPSRC and SB (for CLK).

References and Notes

1. See for example: a) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M. and Lofren, C. S., *Tetrahedron Lett.*, **1983**, *24*, 1983 and 1889; b) Gunasekera, S. P.; Longley, R. E. and Schulte, G. K., *J. Org. Chem.*, **1991**, *56*, 1346; c) Endo, A.; Kuroda, M. and Tsujita, *J. Antibiot.*, **1976**, *29*, 1346.
2. Brown, M. J. B.; Cortes, J.; Cutter, A. L.; Leadlay, P. F. and Staunton, J., *J. Chem. Soc., Chem. Commun.*, **1995**, 1517.
3. See for example: Masamune, S.; Yamamoto, H.; Kamat, S. and Fukuzawa, A., *J. Am. Chem. Soc.*, **1975**, *97*, 3513; Inanaga, J.; Kawanami, Y. and Yamaguchi, M., *Chem. Lett.*, **1981**, 1415; Oppolzer, W.; Walther, E.; Balaso, C. and DeBrabander, J., *Tetrahedron Lett.*, **1997**, *38*, 809.
4. Feng, T. L.; Elliot, R. L. and Curran, D. P., *J. Am. Chem. Soc.*, **1988**, *110*, 5064.
5. Corey, E. J. and Mann, J., *J. Am. Chem. Soc.*, **1973**, *95*, 6832; Grieco, P. A. and Srinivasan, C. V., *J. Org. Chem.*, **1981**, *46*, 2591.
6. Chapelo, C. B.; Finch, M. A. W.; Roberts, S. M.; Woolley, G. T.; Newton, R. F. and Selby, D. W., *J. Chem. Soc., Perkin Trans 1*, **1980**, 1947.
7. For discussions of the mechanisms of these reactions see for example: Goering, H. L. and Underiner, *J. Org. Chem.*, **1991**, *56*, 263; Backwall, J. E., *J. Org. Chem.*, **1994**, *59*, 4126.
8. Curran, D. P.; Chen, M. H.; Leszczweski, D.; Elliott, R. L. and Rakiewicz, D. M., *J. Org. Chem.*, **1986**, *51*, 1612.
9. The formation of *endo*-epoxides and their reactions in similar systems is precedented, see for example: Corey, E. J.; Nicoloau, K. C. and Beams, D. J.; *Tetrahedron Lett.*, **1974**, *28*, 2439.
10. Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O. and Pater, R. H., *J. Org. Chem.*, **1980**, *45*, 4758.
11. Berson, J. A. and Susuki, S., *J. Am. Chem. Soc.*, **1959**, *81*, 4088.
12. Chadha, W. A.; Batcho, A. D.; Tang, L. F.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M. and Uskokovic, M. R., *J. Org Chem.*, **1991**, *56*, 4714.
13. Lactone **22**, clear oil, Found: MH^+, 3331.2309 $C_{17}H_{35}O_4Si$ requires M, 331.2304; δ_H ($CDCl_3$, 400MHz) 0.05 (6H, s, Si $(CH_3)_2$), 0.8 (3H, d, *J* 7, CH_3), 0.9 (9H, s, $C(CH_3)_3$), 1.0 (3H, d, *J* 7, CH_3), 1.4 (3H, d, *J* 7, CH_3), 2.0 (2H, m, 3-H and 5-H), 2.5 (1H, m, 1'-H), 2.9 (1H, dd, *J* 10 and 9, 4-H), 3.4 (3H, s, OCH_3), 3.5 (1H, dd, J 10 and 6, 2'-H), 3.6 (1H, dd, *J* 10 and 1, 2'-H), 4.1 (1H, dd, *J* 11 and 3, 6-H); m/z (CI) 331 (MH^+, 1%), 315 (8), 299 (25), 199 (16), 123 (72), 79 (100) and 57 (42).

(*Received in UK* 12 *August* 1997; *accepted* 12 *September* 1997)