Diastereoselective Synthesis of the Lactone Portion of Compactin and Mevinolin

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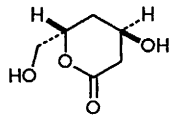
The highly diastereoselective [4 + 2] cycloaddition of 1-methoxybuta-1,3-diene (**3**) to (2*R*)-*N*-glyoxyloylbornane-10,2-sultam (**2**) afforded the adduct (**4**) which was effectively transformed into (4*R*,6*S*)-4-hydroxy-6-hydroxymethyltetrahydro-2-pyrone (**1**), a key synthon for the lactone moiety of compactin and mevinolin.

Compactin and mevinolin have been shown to reduce serum cholesterol levels and thus provide potential tools for the mitigation of arteriosclerosis.[1] In recent years these compounds have elicited much synthetic interest.[2] The (4*R*,6*R*)-lactone moiety of compactin and mevinolin is crucial for their biological activity.[3] Despite its simple structure, the synthesis of the (4*R*,6*R*)-tetrahydro-2-pyrone ring has proved to be challenging.[4–6] Most earlier syntheses suffered from low overall yields, a large number of steps, and low stereoselectivity.[2] In this connection, we report an efficient and highly stereoselective synthesis of (4*R*,6*S*)-4-hydroxy-6-hydroxymethyltetrahydro-2-pyrone (**1**),[6] potentially useful as a key intermediate in the synthesis of compactin and mevinolin, starting from non-carbohydrate precursors.

Recently, we have published[7] the highly diastereoselective [4 + 2] cycloaddition of 1-methoxybuta-1,3-diene (**3**) to optically pure (2*R*)-*N*-glyoxyloylbornane-10,2-sultam (**2**). The reaction is catalysed by 2 mol% of $Eu(fod)_3$,† followed by treatment with pyridinium *p*toluenesulphonate (PPTS),[8] which led to the diastereoisomerically pure cycloadduct (**4**).‡

Reduction of compound (**4**) with lithium aluminium hydride, followed by benzylation of the resulting alcohol, afforded benzyl ether (**5**) which was subjected to anomeric oxidation.[9,10] Treatment of the resulting hydroperoxide with a mixture of acetic anhydride and pyridine yielded the known α,β-unsaturated δ-lactone (**6**).[6] The latter compound has, after chromatographic purification, $[\alpha]_D^{18}$ −115.8° (*c* 1.2, chloroform), lit.[6] $[\alpha]_D^{24}$ −115.1° (*c* 1.0, chloroform). Spectral data are identical in all respects with those of an authentic material. Compound (**6**) was finally transformed into the pyrone (**1**) according to the known procedure given by Takano *et al.*[6] (Scheme 1).

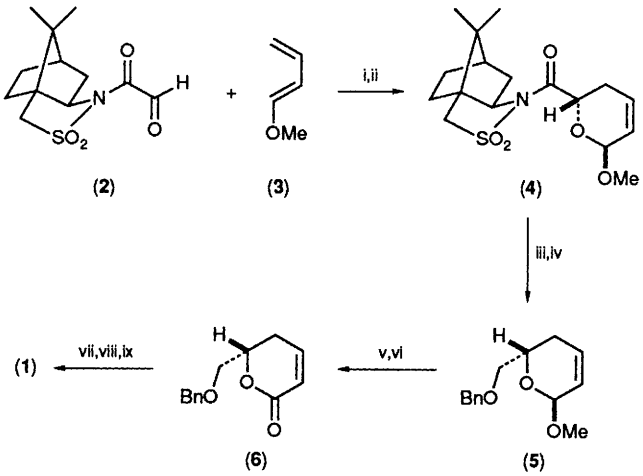
The present synthesis of (**1**) is an interesting practical alternative to the known approaches.[4–6] Moreover, it exemplifies the usefulness of the sultam (**2**) as an effective dienophile in asymmetric hetero-Diels–Alder reactions.



(**1**)

† $Eu(fod)_3$ is [tris(6,6,7,7,8,8,8-heptafluoro-2,2,dimethyloctane-3,5,dionato)europium(III)].

‡ Satisfactory analyses and spectral data were obtained for all new compounds.



Scheme 1. *Reagents and conditions* (all reactions at room temperature): i, 2 mol% $Eu(fod)_3$, CH_2Cl_2; ii, PPTS, MeOH; iii, $LiAlH_4$, tetrahydrofuran (THF); iv, NaH, BnBr, THF; v, 30% H_2O_2, MoO_3(cat); vi, Ac_2O, pyridine; vii, 30% H_2O_2, 6 M NaOH, MeOH; viii, $(PhSe)_2$, $NaBH_4$, AcOH, Pr^iOH; ix, H_2, $Pd(OH)_2$, AcOEt. Bn = $PhCH_2$.

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References

1 A. Endo, *J. Med. Chem.*, 1985, **28**, 401.
2 T. Rosen and C. H. Heathcock, *Tetrahedron*, 1986, **42**, 4909.
3 G. E. Stokker, W. F. Hoffmann, A. W. Alberts, E. J. Cragoe, A. A. Deana, J. L. Gilfilan, J. W. Huff, F. C. Novello, J. D. Prugh, R. L. Smith, and A. K. Willard, *J. Med. Chem.*, 1985, **28**, 347.
4 B. D. Roth and W. H. Roark, *Tetrahedron Lett.*, 1988, **29**, 1255.
5 W. S. Johnson, A. B. Kelson, and J. D. Elliott, *Tetrahedron Lett.*, 1988, **29**, 3757.
6 S. Takano, Y. Shimazaki, Y. Sekiguchi, and K. Ogasawara, *Synthesis*, 1989, 539.
7 T. Bauer, C. Chapuis, J. Kozak, and J. Jurczak, *Helv. Chim. Acta*, 1989, **72**, 482.
8 J. Jurczak, T. Bauer, and A. Gołebiowski, *Bull. Pol. Acad.: Chem.*, 1985, **33**, 397.
9 J. Mieczkowski, J. Jurczak, M. Chmielewski, and A. Zamojski, *Carbohydr. Res.*, 1977, **56**, 180.
10 M. Chmielewski, J. Jurczak, and S. Maciejewski, *Carbohydr. Res.*, 1987, **165**, 111.