Chiral Bicycles from Ribonolactone

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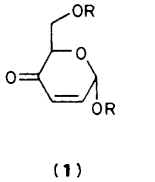
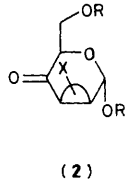
The preparation of the chiral butenolide (**4b**) is described, together with its use in annulation reactions yielding stereochemically defined bicyclo[4.3.0], [3.3.0], and [3.1.0] ring systems; the synthetic utility of these species is indicated.

Fraser-Reid and co-workers have recently[1] described their work with 'annulated pyranosides,' which has allowed access to a wide range of stereochemically defined cycloalkyl compounds. They employed an enone like (**1**) to produce either cycloadduct (**2**) or (**3**) (or both), and these were then converted into a variety of natural products.

It occurred to us that similar annulations could be carried out with chiral butenolides like (**4**), and that the resultant cycloadducts would be equally useful for elaboration into natural products and analogues. The first requirement was an efficient route to (**4**), which would provide multigram quantities of this key intermediate. A synthesis from L-glutamic acid (*e.g.* ref. 2a) which involved the use of phenylselenenyl chloride for introduction of the double bond was unattractive, as were routes (*e.g.* ref. 2b) which used a pyrolytic step. The route devised by Ireland[3] seemed appropriate, and this proceeds from D-(+)-ribonolactone *via* the 5-*O*-trityl derivative (**5a**), the *O,O*-thiocarbonate (**6a**), and thence to butenolide (**4a**) after Raney nickel treatment. We have repeated this synthesis using the 5-*O*-t-butyldiphenylsilyl derivatives (R = $SiPh_2Bu^t$ throughout) and on a larger scale than that used by Ireland. The yields for the first two steps were good (70—90%) on a 20—100 g scale, and the Raney nickel[4] step has been carried out routinely on a 10—15 g scale [refluxing tetrahydrofuran (THF), 1—2 h] to produce the butenolide



(**1**)



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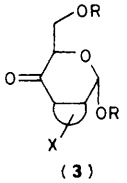

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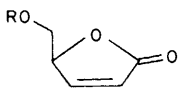
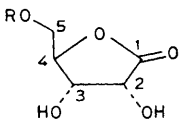
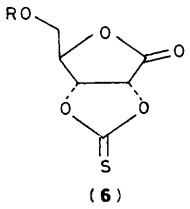


(**4**)

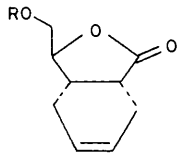


(**5**)

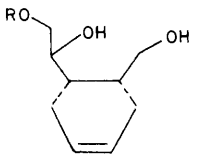


(**6**)

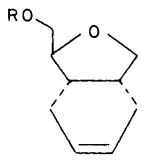
a; R = Ph_3C
b; R = $SiPh_2Bu^t$



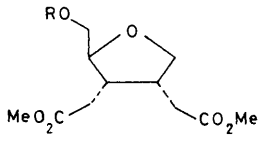
(**7**)



(**8**)



(**9**)



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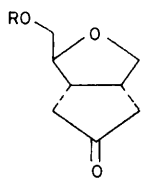
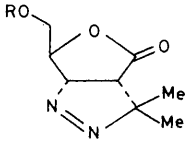
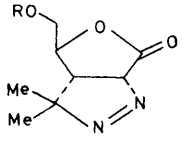


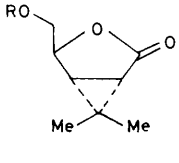
(**11**)



(**12**)

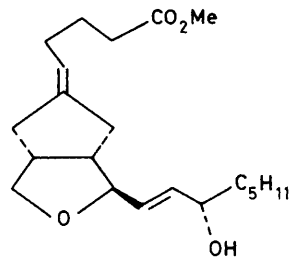


(**13**)

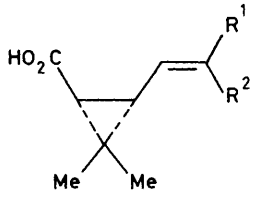


(**14**)

R = $SiPh_2Bu^t$



(15)



(16)

(**4b**) (70—80%), m.p., 79—80 °C; $[\alpha]_D^{24}$ −76.6° (*c* 10.5, $CHCl_3$); $\nu_{max.}$ 1770 and 1750 cm^{-1}.

A bicyclo[4.3.0] ring system was prepared *via* a Diels–Alder reaction of (**4b**) with butadiene (excess of diene, 0.33 mol. equiv. $AlCl_3$, CH_2Cl_2, 55 °C, one week; 75% on a 5—10 g scale). The sole product was submitted to extensive n.m.r. analysis and the structure (**7**) was the one most consistent with the data, m.p. 73—74 °C; $[\alpha]_D^{24}$ + 19.6° (*c* 10, $CHCl_3$); $\nu_{max.}$ 1780 cm^{-1}; δ(400 MHz, $CDCl_3$) 2.67—2.73 (m, 1H, $J_{3,4}$ 3.9 Hz, H-3), 3.00 (m, 1H, H-2), and 4.15 (q, 1H, $J_{4,5}$ 3.9 Hz, $J_{3,4}$ 3.9 Hz, H-4). (The numbering system of ribonolactone has been retained.) Only one set of signals was observed even in the presence of the chiral shift reagent $Eu(tfc)_3$, tris-[3-trifluoroacetyl-(+)-camphorato]europium(III).

Reduction of (**4b**) ($LiBH_4$, THF, room temp., overnight) yielded diol (**8**) (80—100%), and this was converted into the substituted tetrahydrofuran (**9**) (1 equiv. tosyl chloride, pyridine, CH_2Cl_2, −15 °C, overnight; then addition of a further 0.3 equiv. tosyl chloride; 75—85%). Cleavage of the double bond ($KMnO_4$–$NaIO_4$, 0.1:11.0; water–acetone, 1:2), was followed by esterification (CH_2N_2) to provide diester (**10**) (70—80% for the two steps). Finally, a bicyclo[3.3.0] ring system was obtained *via* a Dieckmann cyclisation (1.5 equiv. Bu^tOK, benzene, room temp., 4 h) and subsequent demethoxycarbonylation [NaCl, dimethyl sulphoxide, a few drops of water, 100 °C, 5.5 h] to yield (**11**) (80% for the two steps), m.p. 40—42 °C; $[\alpha]_D^{20}$ + 3.3° (*c* 3.6, $CHCl_3$); $\nu_{max.}$ 1745 cm^{-1}; δ(400 MHz, $CDCl_3$) 2.84 (m, 1H, H-3), 2.97 (m, 1H, H-2), 3.61 (dd, 1H, J_{gem} 8.9, $J_{1,2}$ 4.9 Hz, H-1), 3.66—3.78 (m, 3H, H-4 and 2 × H-5), and 4.15 (dd, 1H, J_{gem} 8.9, $J_{1,2}$ 6.7 Hz, H-1). The structure was confirmed by *X*-ray studies, to be published elsewhere.

Finally, reaction of the butenolide (**4b**) with diazopropane[5] produced the two regioisomers (**12**) (Me ^1H resonances at δ 1.35 and 1.62; H-2 at δ 2.74, d, *J* 8.5 Hz) and (**13**) (Me ^1H resonances at δ 1.18 and 1.19; H-2 at δ 5.7, d, *J* 9 Hz) in a ratio of *ca.* 5:2. These were both converted into the same bicyclo[3.1.0] system (**14**) by irradiation[6] (medium-pressure lamp, benzophenone sensitisation, benzene, 52% overall yield for the two steps), m.p. 75.5—77.5 °C; $[\alpha]_D^{22}$ + 33.0° (*c* 5.8, $CHCl_3$); $\nu_{max.}$ 1770 cm^{-1}; δ(220 MHz, $CDCl_3$) 1.14 and 1.16 (2s, 6H, 2 × Me),1.92 (d, 1H, $J_{2,3}$ 6.5 Hz, H-2), and 1.95 (dd, 1H, $J_{3,4}$ 1Hz, H-3).

We are exploring the synthetic utility of these chiral bicycles, but can already report the conversion of cyclopentanone (**11**) into the prostacyclin analogue (**15**),[7] and conversion of cyclopropane (**14**) into chrysanthemic acids of general formula (**16**). The latter are of obvious interest as potential components of synthetic pyrethrins.[8]

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