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 recently¹ 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 Ireland³ 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 =SiPh₂Bu^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 nickel⁴ step has been carried out routinely on a 10-15 g scale [refluxing tetrahydrofuran (THF), 1-2 h] to produce the butenolide



a; $\mathbf{R} = \mathbf{Ph}_3\mathbf{C}$ **b**; $\mathbf{R} = \mathbf{SiPh}_2\mathbf{Bu}^t$





(4b) (70-80%), m.p., 79-80 °C; $[\alpha]_D^{24}$ -76.6° (c 10.5, CHCl₃); v_{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. AlCl₃, CH₂Cl₂, 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, CHCl₃); v_{max} . 1780 cm⁻¹; δ (400 MHz, CDCl₃) 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-[3trifluoroacetyl-(+)-camphorato]europium(III).

Reduction of (4b) (LiBH₄, THF, room temp., overnight) yielded diol (8) (80-100%), and this was converted into the substituted tetrahydrofuran (9) (1 equiv. tosyl chloride, pyridine, CH₂Cl₂, -15 °C, overnight; then addition of a further 0.3 equiv. tosyl chloride; 75-85%). Cleavage of the double bond (KMnO₄-NaIO₄, 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. ButOK, 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, CHCl₃); v_{max} 1745 cm⁻¹; δ (400 MHz, CDCl₃) 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 diazopropane⁵ 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 irradiation⁶ (medium-pressure lamp, benzophenone sensitisation, benzene, 52% overall yield for the two steps), m.p. 75.5–77.5 °C; $[\alpha]_D^{22} + 33.0^{\circ}$ (c 5.8, CHCl₃); v_{max} . 1770 cm⁻¹; δ (220 MHz, CDCl₃) 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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