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Regiocontrolled Synthesis of Spiro Furopyrone-Cyclohexane Ring Systems : Approach to the Pyranoditerpene Lygodinolide

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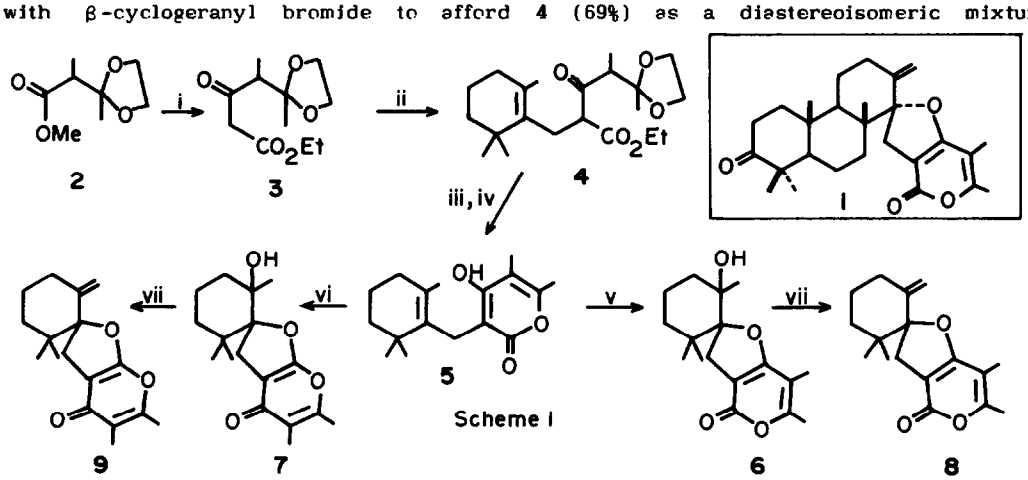
Abstract : The isomeric α- and γ-pyrones **8** and **9** have been synthesised through oxidative cyclisation of the intermediate **5**, prepared via Claisen condensation of a protected β-ketoester with lithio ethyl acetate.

Lygodinolide (**1**), a novel pyranoditerpene, was recently isolated [1] by us as a minor constituent of the fern Lygodium flexuosum, reported[2] to exhibit antifertility activity. The unique structural features and the potential bioactivity of the molecule prompted us to undertake a total synthesis of **1**. It was perceived that the construction of the crucial spiro furopyrone ring system with an adjacent methylene substituent would form an ideal initial target. Herein we report the highly regioselective synthesis of the model compound **8** and the isomer **9**, containing the spiro furo-α-pyrone and -γ-pyrone moieties respectively, through a common intermediate **5**.

As outlined in Scheme 1, the synthesis involved Claisen condensation of the ketal ester **2** with the lithio salt of ethyl acetate followed by alkylation of the product **3**[3] with β-cyclogeranyl bromide to afford **4** (69%) as a diastereoisomeric mixture



Scheme I

Reagents and conditions : (i) LiHMDS (2 eqv), ethyl acetate (2 eqv), -78° to 0°C, 2h; (ii) NaH (1.25 eqv), β-cyclogeranyl bromide (1.2 eqv), THF, 0° to 25°C, 16h, then reflux, 3h; (iii) Pd(II) chloride-acetonitrile (2 mole %), acetone, rt, 24h; (iv) DBU (1 eqv), benzene, reflux, 14h; (v) m-CPBA (50%, 2.5 eqv), CaO (6.5 eqv), anh. sodium sulfate (24.3 eqv), dichloromethane, 15° to 25°C, 14h; (vi) m-CPBA (50%, 1.3 eqv), CSA (Cat), dichloromethane, 0° to 25°C, 17h; (vii) sulfuryl chloride (2 eqv), DBU (5 eqv), dichloromethane, -20°C, 4h.

(although separated chromatographically for characterisation, the mixture as such was used for the subsequent steps). Diketalisation of **4** with $PdCl_2$ $(CH_3CN)_2$ in acetone[4] to the desired diketoester and subsequent cyclisation with DBU in benzene[5] then produced the pyrone **5** in 85% yield. This approach for pyrone synthesis permits a wide flexibility in introducing the substituents.

Oxidative cyclisation of **5** with m-chloroperbenzoic acid gave a 3:7 mixture of the isomeric spiro furo-α-pyrone **6** and -γ-pyrone **7** separated by column chromatography. The desired selectivity in product formation could however be realised through a remarkable control of reaction conditions. Thus, using a catalytic amount of camphor sulphonic acid, the γ-pyrone was formed almost exclusively (85%). On the other hand, the product ratio could be dramatically altered in favour of the desired isomer **6** (74%) by carrying out the reaction in presence of an acid scavenger (CaO).

Finally, dehydration of **6** led to the olefin **8** (82%) representing the crucial spiro furo-α-pyrone-cyclohexane ring structure of **1**, while **7** yielded **9** (85%).

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3. Selected data for **3-9**. UV spectra recorded in MeOH, NMR (100 MHz) in $CDCl_3$.
   3, bp. 160-165°C/10 mm; IR (neat) : 1740, 1711 cm^{-1}.
   4, oil; NMR : δ_H 0.95,0.98,1.31(3x3Hs), 1.12(3Hd,J 7Hz), 1.24(3Ht,J 7Hz), 1.92 (2Hm), 2.65(2Hd,J 7Hz), 3.08(1Hg,J 7Hz), 2.92(5Hm), 4.15(2Hg,J 7Hz).
   5, m.p. 118-119°C; UV : λ_{max} 292 nm; IR (KBr) : 3254, 1671 cm^{-1}; NMR : δ_H 1.02,1.71,1.84,2.20(5x3Hs), 2.04(2Hbrd), 3.28(2Hs), 8.36(1Hs).
   6, m.p. 198-200°C; UV : λ_{max} 297 nm; IR (KBr) : 3398, 1700, 1647 cm^{-1}; NMR : δ_H 0.78,1.06,1.14,1.90,2.21(5x3Hs), 1.38-1.84(6Hm), 2.92,3.13(2x1Hd,J 16Hz).
   7, m.p. 184-185°C; UV : λ_{max} 265,274 nm: IR (KBr) : 3390,1666,1612 cm^{-1}; NMR : δ_H 0.84,1.12,1.16,1.91,2.24(5x3Hs), 2.94,3.20,(2x1Hd,J 15Hz).
   8, oil; IR (neat) : 1736,1715,1653,869 cm^{-1}; NMR : δ_H 0.88,1.00,1.98,2.22(4x3Hs); 2.87,3.19(2x1Hd,J 15Hz), 4.84(2Hbrs); δ_C 170.5,161.9,160.1,146.9,102.8,99.5,98.5,39.0 (8xs), 107.4,36.8,32.4,32.1,21.9(5xt), 22.9,21.7,16.9,9.1(4xg).
   9, m.p. 105°C; IR (KBr) : 1676,1630,1602,925 cm^{-1}; NMR : δ_H 0.91,1.00,1.92, 2.26 (4x3Hs), 2.90,3.20(2x1Hd,J 15Hz), 4.86,4.96(2x1Hbrs); δ_C 177.0,166.5,154.7,146.1, 119.1,97.7,95.3,38.9(8xs), 107.8,36.4,32.2,30.7,21.7(5xt), 22.5,21.7,16.8,9.7(4xg).
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