Enantioselective Synthesis of the Gibbane Framework Using L-Glutamic Acid as Chiral Template

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Summary A chiral route to the gibbane framework has been developed using L-glutamic acid as a chiral template.

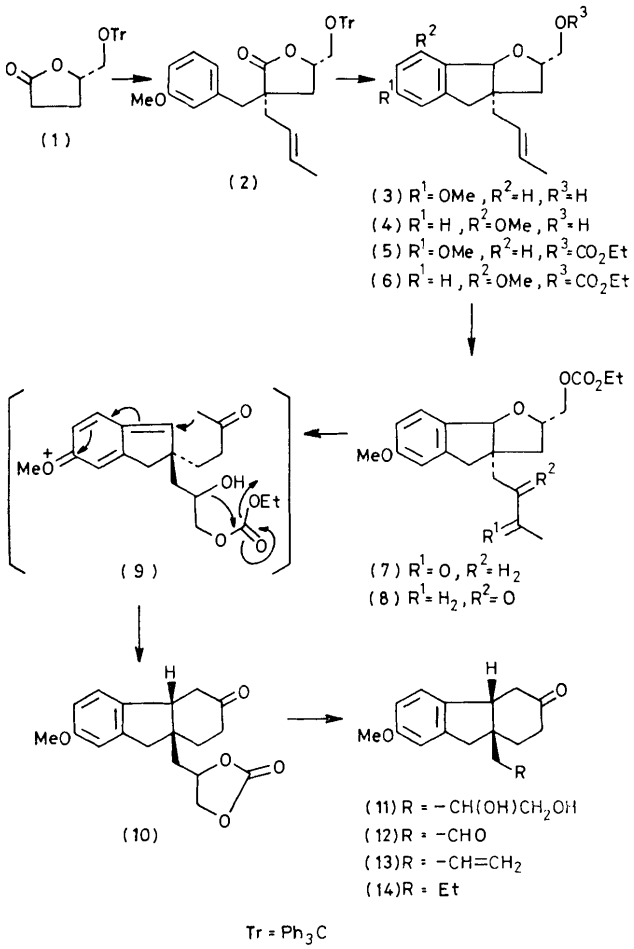
IN parallel with our new chiral synthesis of the gibbane framework by asymmetric intramolecular aldolization,[1] we also explored an alternative chiral route by a fundamentally different method. We now describe an efficient synthesis of the gibbane derivatives (**16**) and (**17**), using L-glutamic acid as a chiral template.[2,3]

The trityl-lactone[2,3] (**1**) {$[\alpha]_D$ + 21·5° (CH_2Cl_2)} obtained from L-glutamic acid[4] was consecutively alkylated in the same flask with but-2-enyl bromide and then 3-methoxybenzyl bromide in the presence of lithium di-isopropylamide to afford 3α-but-2-enyl-3β-(3-methoxybenzyl)-5α-trityloxymethyl-γ-butyrolactone† (**2**) {oil, $[\alpha]_D$ + 48·0° ($CHCl_3$)},‡ stereoselectively in 76% yield. The observed stereochemical outcome apparently resulted from the stereochemistry at the C-5 substituent which allowed selective alkylation to occur successively from the less hindered side.[2] Reduction of (**2**) with di-isobutylaluminium hydride (toluene; −78 °C) afforded the corresponding lactol which on acid-catalysed cyclization [toluene-*p*-sulphonic acid monohydrate (0·1 equiv.; benzene; reflux; 3—5 h)] followed by detritylation (dil. HCl) yielded the regioisomeric tricyclic ethers (**3**) and (**4**) as an inseparable mixture [64% overall from (**2**)]. Treatment of the mixture with ethyl chloroformate (pyridine; room temp.)[5] gave the carbonate (**5**) {oil, $[\alpha]_D$ + 29·0° (MeOH)} in 61% yield accompanied by a minor amount of the isomer (**6**) (7%) after chromatographic purification (silica gel). Palladium-catalysed oxygenation[6,7] [$PdCl_2$ (0·2 equiv.), Cu_2Cl_2 (1 equiv.), aqueous dimethylformamide; 3 days] which has so far been employed mostly for the oxidation of terminal olefins led to the regioselective formation of the methyl ketone (**7**) {oil; $[\alpha]_D$ + 26·6° (MeOH)} in 77% yield accompanied by the ethyl ketone (**8**) (7%). Treatment of (**7**) with toluene-*p*-sulphonic acid§ (1·1 equiv.) in refluxing nitromethane (5 h) led to a smooth stereoselective transformation into the tricyclic ketone (**10**) {70%; oil; $[\alpha]_D$ − 17·8° ($CHCl_3$)} presumably *via* the quinonoid intermediate (**9**). Methanolysis under basic conditions [K_2CO_3, MeOH–tetrahydrofuran (1·5 : 1)] of (**10**) gave the glycol (**11**) {oil; $[\alpha]_D$ − 3·4° ($CHCl_3$)} in 89% yield. Periodate cleavage ($NaIO_4$; MeOH–aq.$NaHCO_3$) of (**10**) gave the crude aldehyde (**12**) which on treatment with hydrochloric acid

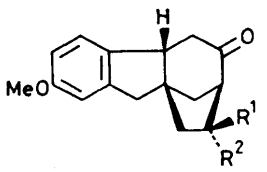
† All new compounds gave satisfactory spectral (i.r., n.m.r., m.s.) and analytical (combustion and high-resolution m.s.) data.

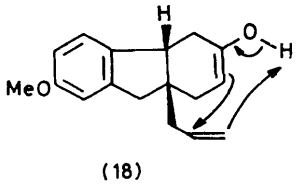
‡ Optical rotations were measured with a JASCO DIP-4B automatic polarimeter.

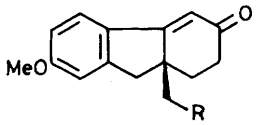
§ Use of toluene-*p*-sulphonic acid monohydrate without dehydration greatly diminished the yield of the tricyclic ketone (**10**).



in acetone (room temp.; 10 h) yielded the tetracyclic ketol (**15**) (m.p. 146—148 °C) in virtually quantitative yield from (**10**) as an inseparable 4:1 mixture of the α-hydroxy- and β-hydroxy-isomers which were easily recognizable in the ^{1}H n.m.r. spectrum. Oxidation of the mixture (**15**) without separation using pyridinium chlorochromate (CH_2Cl_2; room temp.; 4 h) gave the diketone (**16**) {m.p. 124—128 °C, $[\alpha]_D$ + 12·6° ($CHCl_3$)} in 70% yield as a single product.







The gibbane derivative (**17**) was obtained *via* the unsaturated ketone (**13**) by ene reaction. Namely, treatment of the tricyclic glycol (**11**) with dimethylformamide dimethyl acetal [$HC(OMe)_2NMe_2$], followed by acetic anhydride at 140 °C[8] gave the ketone (**13**) {62·5%; oil; $[\alpha]_D$ + 29·0° ($CHCl_3$)} which on thermolysis at 480—500 °C in benzene in a sealed tube led to the stereoselective formation of the gibbane (**17**) {46·7%; oil; $[\alpha]_D$ − 8·0° ($CHCl_3$)} presumably *via* the enol (**18**).

The unsaturated ketone (**13**) was reduced (H_2; 5% Pd–C; EtOH) to the propyl derivative (**14**) {86%; oil; $[\alpha]_D$ + 21·0° ($CHCl_3$)} which was correlated with the corresponding demethoxy tricyclic ketone[1] (**14**; H replaces MeO), obtained by a fundamentally different route, by c.d. measurements.[1] Interestingly the ketone (**14**) on chromic acid oxidation in aqueous acetic acid furnished the propyl-enone (**20**) {m.p. 116—117 °C; $[\alpha]_D$ + 265·0° ($CHCl_3$)} in 97% yield. Similarly the ketone (**13**) was converted into the corresponding enone (**19**) {47·3%; m.p. 128—131 °C; $[\alpha]_D$ + 279·7° ($CHCl_3$)} which was then reduced (H_2; 5% Pd–C; EtOH) to the propyl-enone (**20**) quantitatively.

(*Received*, 24*th February* 1981; *Com.* 208.)

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