Novel Cationic Rearrangements of the [3.3.3]Propellane System: Application to the Total Synthesis of Decarboxyquadrone

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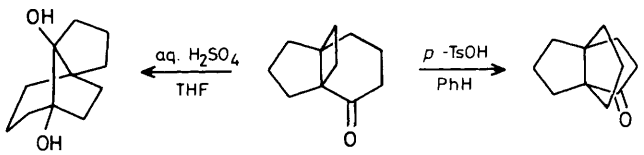
The first carbonium ion rearrangement of the [3.3.3]propellane ring system to the tricyclo[4.3.2.$0^{1,5}$]undecane and tricyclo[6.3.0.$0^{1,5}$]undecane skeletons has been observed and extended to the total synthesis of the biologically active compound decarboxyquadrone.

Propellanes have attracted the attention of organic chemists because their molecular shape and variation in size confers on them the ability to undergo a variety of interesting reactions and rearrangements.[1] In particular, [*m.n.*2]propellanes ($m \geq 3$, $n \geq 3$) exhibit marked propensity towards carbonium ion mediated rearrangements, *e.g.*, Scheme 1, and these have been extensively explored in recent years from mechanistic as well as synthetic considerations.[2] The driving force for these rearrangements, which are generally under stereo-electronic control, is the strain release through cyclobutane ring expansion. Consequently, cationic rearrangements of [*m.n.*3]propellanes are virtually unknown and compounds of this skeleton are usually the end products of rearrangements, Scheme 1. However, we find that the strategic placement of a carbonyl group onto [3.3.3]propellanes can perturb the delicate balance between the stability of closely related tricycloundecanes and we report here the *first* example of a carbonium ion mediated skeletal rearrangement of a [3.3.3]propellane system into tricyclo[4.3.2.$0^{1,5}$]undecane (quadrane) and tricyclo[6.3.0.$0^{1,5}$]undecane (angular triquinane) frameworks present in several natural products of current interest. As an application of this finding, a short synthesis of the biologically active compound decarboxyquadrone (**12**)[3] is also described.

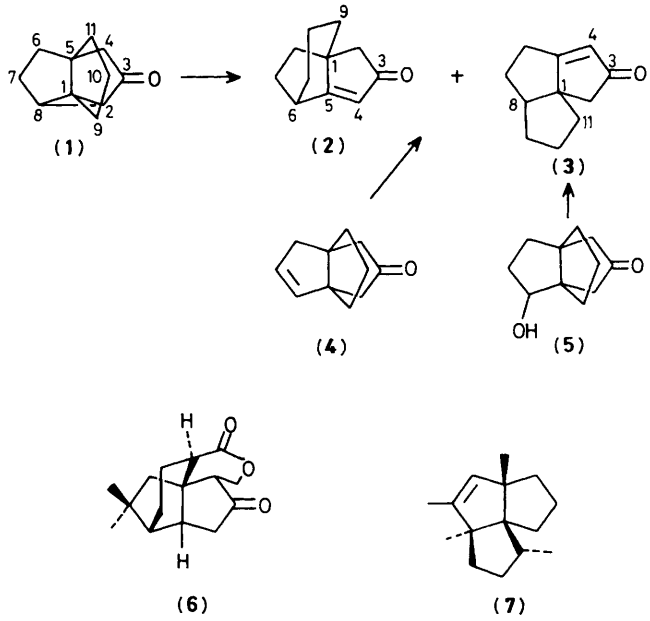
When the tetracyclic ketone (**1**)[4,5] was exposed (2 h, 30 °C) to H_2SO_4 (95—98%) in dichloromethane solution, a ~ 65 : 35 mixture (h.p.l.c.) of two enones (**2**) and (**3**), respectively, was obtained in 80—85% isolated yield. The structure of the major enone (**2**) [$\lambda_{max.}$ (MeOH) 229 nm; $\nu_{max.}$ (film) 1703, 1640 cm^{-1}; δ_H (100 MHz, $CDCl_3$) 5.6 (1H, s), 3.0 (1H, m), 2.2 (2H, s), 1.25—2.0 (10H, m), δ_C (25 MHz, $CDCl_3$) 210.4, 194.3, 117.4, 49.0, 48.3, 40.9, 36.8, 32.9, 31.7, 29.8, 18.4] followed from its spectral data and was further verified through direct spectral comparison with the authentic compound reported recently.[3b] The minor enone (**3**) [$\lambda_{max.}$ (MeOH) 233 nm; $\nu_{max.}$ (film) 1705, 1625 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.76 (1H, dd, J 1, J' 1.8 Hz), 2.58 (2H, m), 2.40 (2H, s), 2.23 (1H, m), 2.07 (2H, m), 1.53—1.82 (6H, m); δ_C (25 MHz, $CDCl_3$) 210.4, 192.5, 123.3, 60.8, 52.5, 47.5, 40.3, 35.2, 33.3, 26.7, 26.6] was formulated on the basis of spectral data and decoupling experiments at 400 MHz. The same two enones (**2**) and (**3**) were also formed from the keto-olefin (**4**) and hydroxy-ketone (**5**) in comparable yield when treated under conditions similar to those employed in the case of (**1**). While the formation of (**2**) and (**3**) from any of the precursors (**1**), (**4**), and (**5**) can be readily explained by 1,2-migrations and proton elimination, the non-interconvertibility of (**2**) and (**3**) under the reaction conditions and the profound influence of alkyl substituents on the product distribution between type (**2**) and (**3**) products[6] indicates that their formation might be more eventful. We are presently subjecting this rearrangement to detailed mechanistic scrutiny.

Formation of the tricyclo[4.3.2.$0^{1,5}$]undec-4-en-3-one (**2**) and tricyclo[6.3.0.$0^{1,5}$]undec-4-en-3-one (**3**) bearing the carbocyclic ring system of novel anti-tumour sesquiterpenoids quadrone (**6**)[7] and isocomene (**7**),[8] respectively, from the readily available (**1**) suggested that this [3.3.3]propellane based rearrangement methodology can be adapted to the



THF = tetrahydrofuran, Ts = p – $MeC_6H_4SO_2$

Scheme 1



synthesis of these natural products. Herein, we record the total synthesis of decarboxyquadrone (**12**), the first biologically active analogue[3a] of quadrone (**6**).

Regio- and stereo-selective cleavage of the cyclopropane ring in (**1**) with formic acid and saponification furnished the hydroxy-ketone (**8**) [$\nu_{max.}$ (film) 3430, 1725 cm^{-1}; δ_H (100 MHz, $CDCl_3$) 3.84 (1H, t), 2.32 (2H, s), 2.31 (2H, s), 2.2—1.3 (m, 10H); δ_C (25 MHz, $CDCl_3$) 219.1 (s), 80.6 (d), 58.3 (s), 54.8 (s), 52.7 (t), 51.3 (t), 41.9 (t), 35.9 (t), 34.5 (t), 32.0 (t), 25.3 (t)]. Routine functional group manipulations delivered the keto-acetal (**9**). Geminal dimethylation, $LiAlH_4$ reduction, and deprotection of (**9**) proceeded uneventfully and hydroxyketone (**10**), required for the key carbonium ion rearrangement was acquired, Scheme 2. Subjecting (**10**) to sulphuric acid rearrangement conditions produced an intractable mixture containing only traces of the desired (**11**). Obviously, the presence of the *gem*-dimethyl group α to the carbonium ion was favouring a side reaction. After some trials, we found that the BF_3–ether adduct induced the rearrangement of (**10**) and (**11**) could be isolated in a modest 20—25% yield from the reaction mixture. The identity of (**11**) was established through direct comparison with an authentic sample.[3b,c] Finally (**11**) is convertible into decarboxyquadrone (**12**) through a clean three step sequence.[3a,b]

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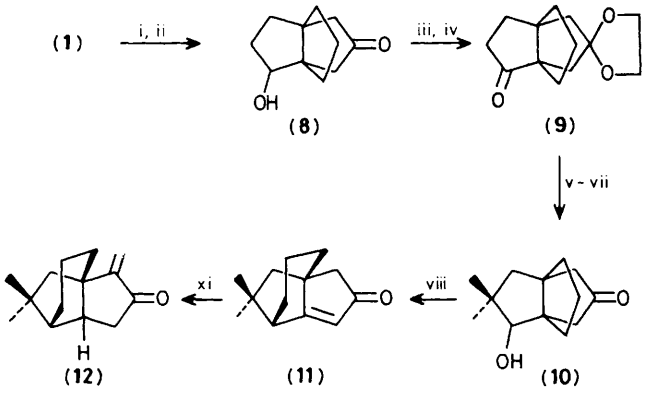

Scheme 2. i, HCO_2H, heat, 2 h; ii, aq. KOH–MeOH, room temp. 30 min, 95%; iii, $HO[CH_2]_2OH$, pyridinium toluene-*p*-sulphonate (PPTS), C_6H_6, 80 °C, 10 h, 95%; iv, pyridinium chlorochromate, CH_2Cl_2, 6 h, 82%; v, $Bu^tO^-K^+$–MeI, tetrahydrofuran, 71%; vi, $LiAlH_4$–Et_2O, 3 h, 95%; vii, acetone–PPTS–H_2O, 60 °C, 4 h, 95%; viii, BF_3–Et_2O, C_6H_6, 80 °C, 10 h, 20—25%; ix, ref. 3a,b.

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