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Ring fragmentation processes resulting from acid catalysed diazo ketone cyclisations

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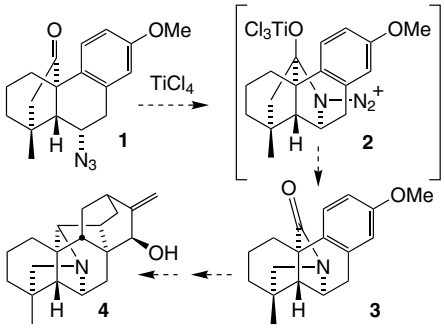
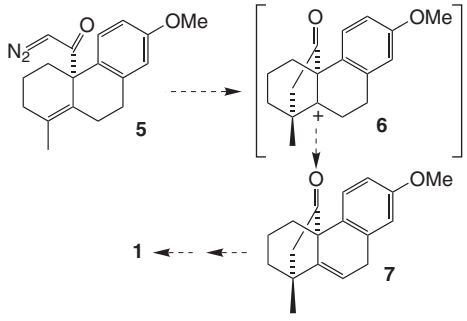
Abstract—The initial products from the cyclisation of hexahydrophenanthryl diazo ketones with participation by either the alkene bonds or the aromatic ring ($Ar_{1,4}$) undergo rearrangement by 1,2 bond shifts or unexpected bond fission. Benzocyclo-octanyl ketones were formed from the latter process.

The complex structures of the diterpene alkaloids have attracted the attention of numerous synthesis groups for the last four decades, resulting in a considerable output of elegant chemistry and useful methodology.[1–3] The construction of the hetisine group of alkaloids, of which the extensively bridged kobusine (**4**) is the simplest member, poses the ultimate challenge for the C_{20} derivatives and has very recently been met successfully by Murutake and Natsume.[4,5] In contemplating other ways of preparing these alkaloids, we were attracted to the idea of assembling the C–N bonds by means of the intramolecular azido-Schmidt[6,7] strategy summarised in Scheme 1.



Scheme 1.



Scheme 2.

To prepare the necessary precursor(s), we envisaged carrying out the cyclisation of diazoketone **5** to form **6** and thence **7** (Scheme 2).[8–13] Our efforts to access **7** and its analogues are the subject of this letter.

Ketone **9** was readily assembled by Robinson annelation of the β-tetralone **8** as reported by Fuchs and co-workers.[14] To remove the unwanted carbonyl function, the enone was reduced under Luche conditions[15] followed by treatment with base to form lactone **10**, which was then reduced with lithium in liquid ammonia to afford acid **11** as outlined in Scheme 3.

Diazoketone **5** was prepared via the acid chloride by a method that we have found to be effective for sterically hindered substrates[16] and treated with a variety of acids and Lewis acids. Although the desired product **7** was formed by treatment of **5** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −20 °C, it was obtained in only 20% yield. The major

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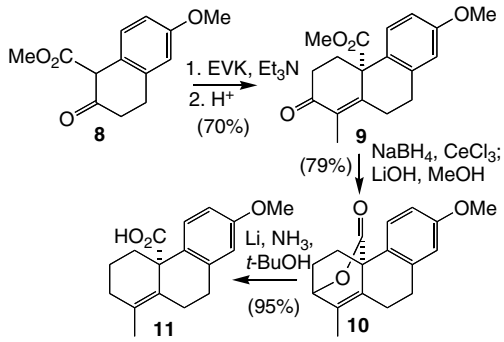
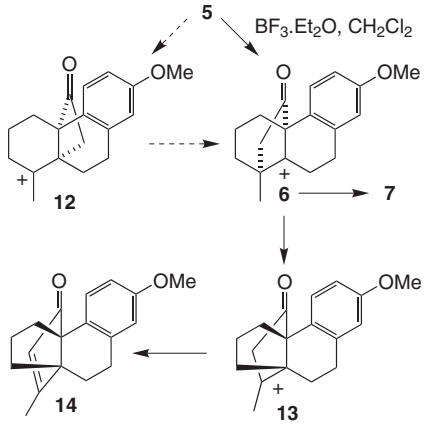


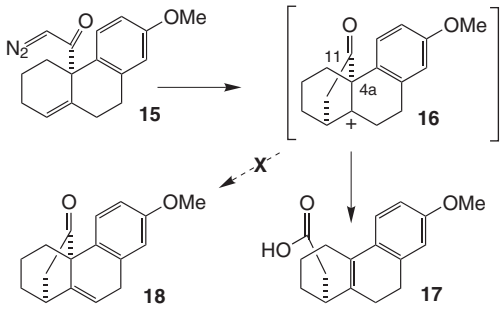
Scheme 3.



Scheme 4.

product (34% yield) was enone **14**, formed by rearrangement of the presumed intermediate carbocation **6** (Scheme 4). Although we suspect that **6** may not be formed directly from **5**, but rather that *exo*-4 cyclisation affords carbocation **12** which then rearranges to **6**,[17] the involvement of this alternative pathway would have had no bearing on the eventual outcome. The structure of **7** was apparent from infrared data that showed a band at 1746 cm^{-1} and from ^1H NMR spectra that showed a doublet of doublets ($J = 2.5$, 4.7 Hz) at 5.64 ppm for the alkene proton that was coupled to an AB system at δ 3.47 (dd, $J = 21.3$, 2.5 Hz), and δ 3.32 (dd, $J = 21.3$, 4.7 Hz) for the benzylic protons. A second AB system arising from the methylene adjacent to the carbonyl group was observed at δ 2.36 (d, $J = 17.9$ Hz) and δ 2.06 (d, $J = 17.9$ Hz). The enone system in **14** was evident from IR absorption at 1697 and 1619 cm^{-1} as well as the chemical shift of the alkene proton at 6.03 ppm and of the allylic methyl group at δ 2.12 (d, $J = 1.3$ Hz) in the NMR spectra. When cyclisation was conducted in trifluoroacetic acid (TFA)-nitromethane, enone **14** was the only isolable product. In light of these results, we elected to study the cyclisation of diazoketone **15**, which was accordingly prepared in an analogous fashion to the synthesis of **5**. If the expected intermediate **16** were to undergo a similar 1,2-bond shift to that inferred for **6**→**14**, a secondary cationic centre would be generated and such a rearrangement should therefore be rendered unfavoured. In the event, when **15** was treated with TFA-dichloromethane, formation of the desired **18** did not occur at all. Two discrete products were obtained (Scheme 5), one of which, produced in 21% yield, proved to be the acid **17**. NMR spectra showed a tetra-substituted double bond, and an isolated $–CH_2–CH_2–$ fragment consistent with a dihydronaphthalene structure, indicating that the carbocation **16** had presumably been formed, but that the C(4a)-(11) bond had then undergone fission.

A second product, formed in 27% yield, was also a result of bond fission. The NMR spectra of this product indicated a methine group bonded to an oxygen function (t, δ 5.30, $J = 4.2$ Hz), a tetra-substituted double bond and a deshielded, isolated methylene group (s, δ 3.80). Following hydrolysis, the methine resonance moved to higher field, indicating hydrolysis of a TFA group. These data were consistent with structures **21** and **22**, respectively, which were confirmed by single crystal X-ray analysis of the latter product (as the hydrate) (Fig. 1). The formation of **21** is rationalised in terms of $Ar_{1,4}$ cyclisation followed by fragmentation of the cyclobutanone ring as outlined in Scheme 6 and in the light of the derivation of structure **22**, we were able to return to an examination of two unstable products formed from diazo ketone **5**. NMR spectra of the more



Scheme 5.

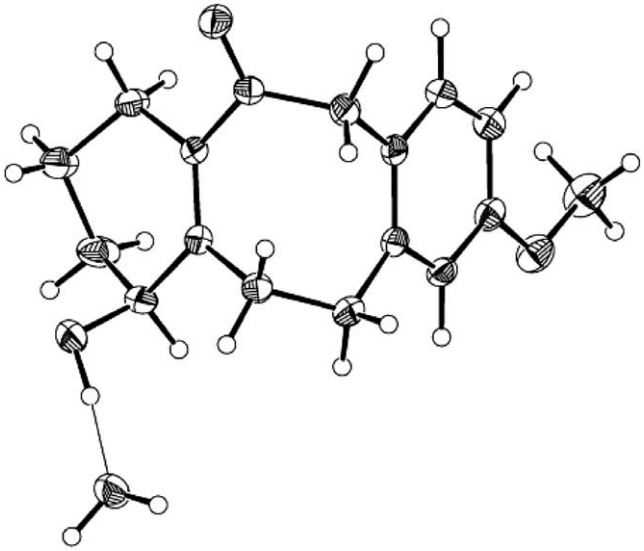
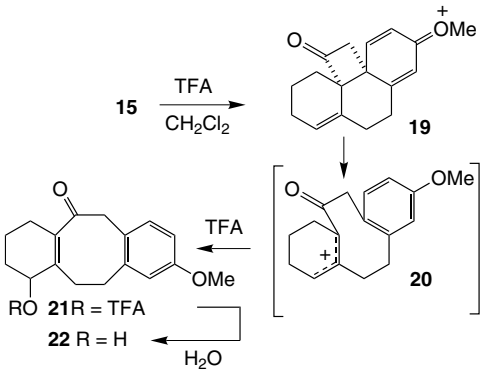


Figure 1. Anisotropic displacement ellipsoid plot of ketone **22**. Ellipsoids show 30% probability levels and hydrogen atoms are drawn as circles with small radii.

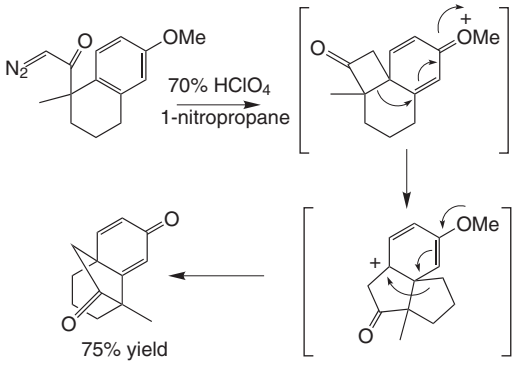


Scheme 6.

abundant compound (24% yield) revealed a methylene group (2 × s, δ 4.93, 5.24) and a two-proton singlet at δ 3.85, consistent with structure **23** (Fig. 2), while the remaining compound (17% yield) could be identified as ketone **24** from the observation of resonances at δ 5.74 for the alkene proton, and at δ 1.86 for a vinyl methyl group, as well as the now characteristic two-proton singlet at δ 3.90 for the benzylic protons adjacent to the carbonyl group.

Thus, it became clear that alkene and $Ar_{1,4}$ cyclisation are proceeding at similar rates in these examples. In previous studies on similar substrates, the latter process is usually followed by one or more alkyl shifts,[18–22] but in the present investigation, the presence of the double bond allows delocalisation of the positive charge that would develop adjacent to the carbonyl group during fragmentation of the cyclobutanone ring. This pathway then becomes favoured over the alkyl shifts that otherwise lead to less strained cyclopentanone moieties as in the example outlined in Scheme 7.[23] Finally, the formation of acid **17** from **15** has precedents in the work of Smith et al., who have likened this type of process to a vinylogous Wolff rearrangement.[24,25]

Selected spectroscopic data—Diazo ketone **5**: IR (NaCl) (cm^{-1}): 2934, 2100, 1723, 1609, 1497, 1337, 1040. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (1H, d, J = 8.6 Hz); 6.78 (1H, dd, J = 2.8 Hz, J = 8.6 Hz); 6.67 (1H, d, J = 2.8 Hz); 5.18 (1H, s, –C*H*N_2); 3.79 (3H, s, OMe); 2.68–2.73 (2H, m); 2.48–2.53 (3H, m); 2.07 (2H, br s); 1.72–1.88, (3H, m); 1.7 (3H, s, Me). ^{13}C NMR



Scheme 7.

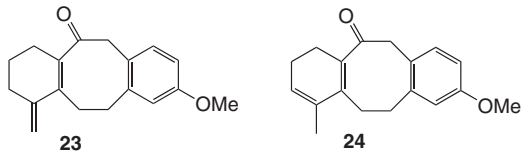


Figure 2.

(75.5 MHz, $CDCl_3$): δ 198.0, 158.2, 140.5, 132.3, 130.7, 127.6, 127.0, 113.1, 111.7, 55.2, 54.6, 53.4, 34.1, 31.9, 29.4, 27.0, 19.8, 19.1. MS (EI): m/z 268 (M^+-N_2, 7%) 227 (100); 211 (7); 167 (7); 115 (6).

Ketone **7**: IR (NaCl) (cm^{-1}): 2947, 1746, 1619, 1498, 1248, 733. ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (1H, d, J = 8.5 Hz); 6.83 (1H, dd, J = 2.9 Hz, J = 8.8 Hz); 6.78 (1H, d, J = 2.9 Hz); 5.64 (1H, dd, J = 2.5 Hz, J = 4.7 Hz); 3.78 (3H, s, OMe); 3.47 (1H, dd, J = 2.5 Hz, J = 21.3 Hz. H9); 3.32 (1H, dd, J = 4.7 Hz, J = 21.7 Hz. H′9); 2.36 (1H, d, J = 17.9 Hz H12); 2.06 (2H, d&m, J = 17.9 Hz, H′12); 1.6–1.8 (5H, m) 1.30 (3H, s, 1-Me). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 216.1 (q, C11); 158.0 (q, C7); 147.5, 134.8 (q, C4b, C8a); 128.8, 127.1 (C5, C10a); 112.6, 112.3 (t, C6, C8); 110.4 (t, C10); 55.2 (OMe); 53.5, 51.3 (C12, C4a); 43.0 (C1); 40.1, 39.6 (C2, C9); 30.0, 22.6, 20.7 (C3, C4, C13). MS (EI): m/z 268 ($M^{+\cdot}$, 85%); 240 (50); 225 (100); 184 (72); 165 (30).

Enone **14**: IR (NaCl) (cm^{-1}): 2947, 1697, 1619, 1498, 1248, 733. ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (1H, d, J = 8.5 Hz); 6.79 (1H, dd, J = 2.8 Hz, J = 8.6 Hz); 6.58 (1H, d, J = 2.6 Hz); 6.03 (1H, d, J = 1.2 Hz); 3.76 (3H, s, OMe); 2.50–2.62 (2H, m); 2.12–2.41 (2H, m); 2.12 (3H, d, J = 1.3 Hz); 1.94–2.00 (1H, m); 1.50–1.73 (4H, m); 1.22–1.46 (1H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.5, 180.6, 157.8, 132.7, 138.7, 130.3, 129.7, 113.0, 112.8, 61.7, 58.8, 55.5, 38.6, 37.0, 32.1, 27.9, 23.8, 15.6. MS (EI): m/z 268 (M+, 100%); 253 (29); 240 (20), 225 (32), 200 (30), 165 (20), 115 (19).

Acid **17**: IR (NaCl) (cm^{-1}): 2929 (m); 1704 (s); 1607 (m); 1499 (m); 1254 (m). ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (1H, d, J = 8.2 Hz); 6.69 (2H, s); 3.80 (3H, s); 2.60 (3H, m); 2.0–2.4 (6H, m); 1.8 (3H, m); 1.6 (1H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.9 (q, CO_2H); 158.0 (q, C7); 137.1, 132.4, 129.4, 128.4, 123.0 (C4a, C4b, C5, C8a, C10a); 113.2, 110.9 (t, C6, C8); 55.2 (OMe); 37.9 (C2′), 36.1 (C4), 28.9, 27.8, 27.2, 25.6 (C1, C2, C9, C10), 19.4 (C2). MS (EI): m/z 272 ($M^{+\cdot}$, 23%); 213 ($M^{+\cdot}-CH_2CO_2H$, 100).

Ketone **22**: IR (NaCl) (cm^{-1}): 3420 (bs); 1670 (s); 1606 (m); 1502 (s); 1256 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (1H, d, J = 8.7 Hz); 6.65 (2H, m); 3.90 (1H, bt); 3.80 (2H, s); 3.77 (3H, s); 2.90 (2H, m); 2.69 (2H, m); 1.99 (1H, m); 1.85 (1H, m); 1.4–1.6 (4H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.5 (q, C5); 158.7 (q, C9); 140.9, 138.9, 136.4, 131.1, 126.2 (C4a, C6a, C7, C10a, C12a); 115.7, 111.0 (t, C8, C10); 68.3 (t, C1); 55.0 (OMe); 50.1 (s, C6); 32.4, 31.3, 31.0, 26.0, (s, C2, C4, C11, C12), 17.3 (C3). MS (EI): m/z 272 (M^+, 50%); 226 (100); 134 (70).

Crystal data for ketone **22**: $C_{17}H_{20}O_3 \cdot H_2O$, $M_r = 290.36$, monoclinic space group $P2_1/a$, unit cell parameters $a = 8.5529$ (2) Å, $b = 20.3609$ (5) Å, $c = 8.9489$ (2) Å, $\beta = 96.8096$ (14)°, $V = 1547.41$ (6) Å^3, $Z = 4$, $T = 200$ K, μ (Mo Kα) = 0.099 mm^{-1}, total number of reflections 21,764, number of unique reflections 2732, number of reflections used in refinement [$I > 3\sigma(I)$] 1755, $R = 0.0324$, $wR = 0.0376$. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 263210. Copies of data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0)1223-336033 or email: deposit@ccdc.cam.ac.uk].

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