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Unprecedented photochemical induced cascading rearrangement of the 3-azabicyclo[3.3.1]nonane skeleton †

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Certain 3-azabicyclo[3.3.1]nonane derivatives undergo unprecedented stereospecific skeletal cleavage when subjected to light affording a novel heterotricyclic skeleton.

The 3-azabicyclo[3.3.1]nonane (3-ABN) skeletal system (*e.g.* **1**),[1] easily constructed *via* a double Mannich reaction,[2] has been known for some time, as this moiety exists as part of both the C_{19}- (*e.g.* chasmanine **2**) and C_{20}- (*e.g.* atisine **3**) diterpene alkaloid AE ring motif (Fig. 1).[3,4]

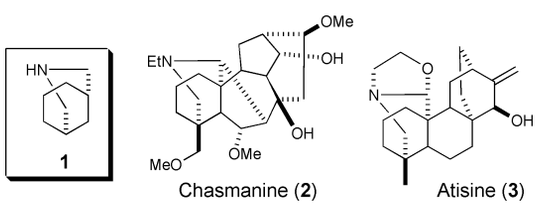
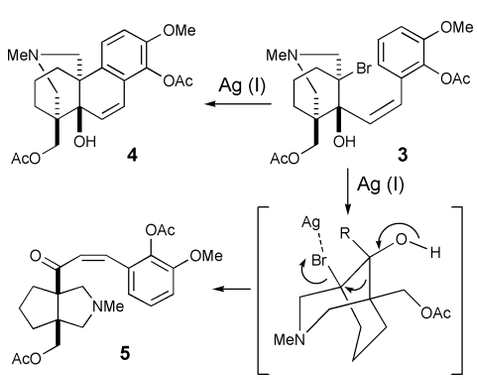


Fig. 1 Chemical structures of 3-ABN **1**, chasmanine **2** and atisine **3**.

Biosynthetic rearrangement of the diterpene alkaloid AE ring system is seldom observed,[5] although norditerpene alkaloids such as yunaconitine give AE ring rearranged products when treated chemically.[6] Synthetic 3-ABN's have been reported to undergo retroaldol,[7] pinacol-type[8] and thermal[9] rearrangements, and although norditerpene alkaloids have been found to display unusual behaviour when exposed to light,[10] photochemical rearrangement of the AE ring system or 3-ABN's in general has not been observed.

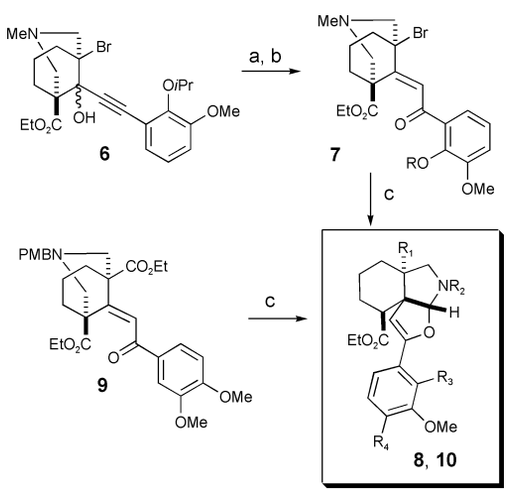
In the course of attempting to optimise our recently reported[11] synthesis of the hetisan type diterpene alkaloid advanced intermediate **4**, that is, hydroxy group removal to avoid the silver(I) mediated competing pinacol type rearrangement of **3** to **5** in the final step (Scheme 1), we discovered a novel, photochemically induced 3-ABN skeletal rearrangement pathway.



Scheme 1 Silver(I) mediated pinacol-type rearrangement.

† Electronic supplementary information (ESI) available: experimental details and characterisation data for compounds **8** and **10**. See http://www.rsc.org/suppdata/ob/b4/b402200a/

Of the various methods available to remove hydroxyl groups only a Meyer–Schuster rearrangement[12] proved successful. Treating propargylic alcohol **6**[11] with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in trifluoroacetic acid (TFA) gave **7** (R = H) (70%), which was reprotected as the isopropyl ether[13] **7** (R = *i*Pr) (93%) (Scheme 2). In an attempt to obtain the *Z*-enone, a requirement for probing silver(I) mediated cyclization (*e.g.* **3** to **4**, Scheme 1), enone **7** (R = *i*Pr) was photolysed. Irradiation (300 nm/Pyrex) in oxygen free *N*,*N*-dimethylformamide gave a mixture of *Z* and *E* products (51%), but unexpectedly produced tricycle **8** (18%), as a pure diastereomer, confirmed by X-ray crystal structure analysis ‡ (Fig. 2). Unfortunately the conversion of **7** (R = *i*Pr) to **8** could not be driven to completion due to competing decomposition. Endeavouring to obtain synthetically useful amounts of this novel heterocyclic system and to further probe the mechanistic pathway, enone **9** was chosen for investigation. In addition, enone **9** removes both steric hindrance caused by the



8 (R_1 = Br, R_2 = Me, R_3 = O*i*Pr, R_4 = H)
10 (R_1 = CO_2Et, R_2 = PMB, R_3 = H, R_4 = OMe)

Scheme 2 Photochemical induced rearrangement. Reagents: a) TMSOTf/TFA, b) *i*PrBr/K_2CO_3, c) *hv* (300 nm)/DMF.

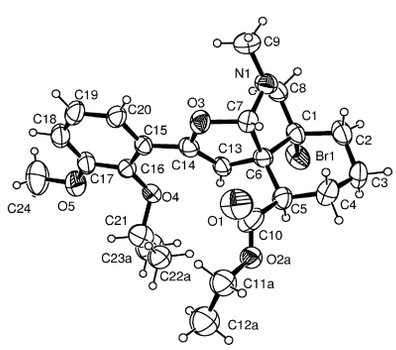


Fig. 2 ORTEP plot of **8** (30% probability ellipsoids).

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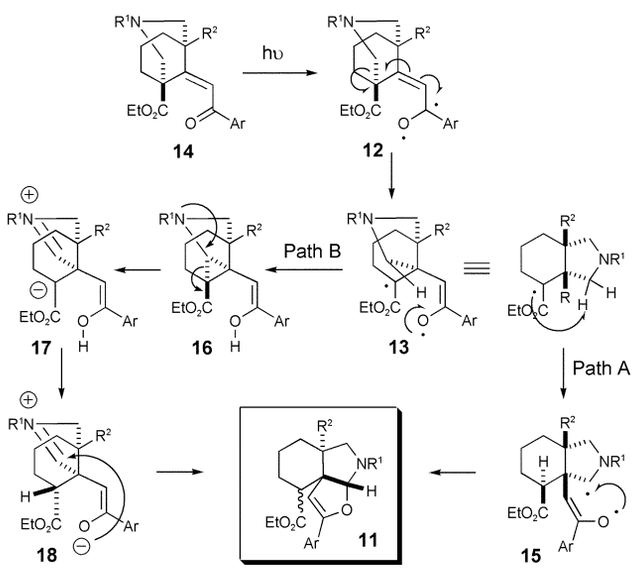
isopropyl ether and the single electron susceptible bridgehead bromide function from the equation. Synthesis of **9** was achieved in 3 steps in 56% overall yield: double Mannich reaction with diethyl 1,6-cyclohexanonedicarboxylate and *p*-methoxybenzylamine[14] followed by reaction with magnesium 3,4-dimethoxyphenylacetylide and subsequent Meyer–Schuster rearrangement with borotrifluoride etherate in trifluoroacetic acid. Photolysis of **9** this time afforded the corresponding tricycle **10** (Scheme 2), in 86% yield, as a pure diastereomer, with the same stereochemical arrangement seen with tricycle **8** (as determined by X-ray crystal structure analysis).§

Two mechanistic pathways to **8** and **10** (*e.g.* **11**) are proposed (Scheme 3). Both involve a 1,2-sigmatropic shift (**12** to **13**) initiated by ketone **14** excitation (triple state). The subsequent formation of radical **15** (Path A) appears justified on the basis of recent data provided by Croft *et al.*[15] Ring closure of **15** leads to the final tricycle **11**. Alternatively, rearrangement of radical **13** (Path B) leads to the unstable cyclopropane intermediate **16**. Anionic ring opening of **16** would afford **17**, which undergoes immediate proton exchange on the less hindered face with concomitant ring closure, *via* the oxyanion **18**, affording **11**. An intermolecular pathway has been ruled out in this instance; deuterium atom abstraction from d_7-DMF was not observed.



Scheme 3 Suggested mechanistic pathway for the formation of **8** and **10**.

It should be noted that only mechanistic pathway B (Scheme 3) arrives at the observed stereochemistry for the non-bridgehead ester group [**11** (β)] whereas pathway A would afford stereochemistry opposite [**11** (α)] to that seen in both X-ray crystal structures (structures **8** and **10**).

In conclusion, we have discovered for the first time a photochemical rearrangement of the 3-ABN skeleton, which affords a unique heterotricyclic system. We are currently investigating the synthetic utility of this process by substituting the ketone functionality of **8** and **10** for carbon.[16,17]

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Notes and references

‡ Compound **8**: $C_{24}H_{32}BrNO_5$, M = 494.42, monoclinic, space group $C2/c$, a = 25.75(1), b = 11.464(2), c = 20.370(7) Å, β = 125.61(2)°, V = 4889(3) Å^3, Z = 8, T = 296(2) K. 4395 reflections collected, 4295 unique (R_{int} = 0.0461). R_1 = 0.0529 (for 1781 obs. refs), wR_2 = 0.1662 (all data). The isopropyl and ethoxy groups were rotationally disordered and refined with the aid of geometrical restraints on the C–C bond lengths. For clarity, only a single contributor to this disorder is shown in Fig. 2.

§ Compound **10**: $C_{32}H_{39}NO_8$, M = 565.64, triclinic, space group $P\bar{1}$, a = 7.2889(8), b = 12.260(1), c = 16.917(4) Å, α = 99.24(1), β = 97.78(2), γ = 90.40(1)°, V = 1477.7(4) Å^3, Z = 2, T = 150(2) K. 5646 reflections collected, 5198 unique (R_{int} = 0.0783). R_1 = 0.0776 (for 1814 obs. refs), wR_2 = 0.2736 (all data).

All calculations were performed using the WINGX crystallographic software package. CCDC reference numbers 224382 and 224383. See http://www.rsc.org/suppdata/ob/b4/b402200a/ for crystallographic data in .cif or other electronic format.

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