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Regioselective Thermal Cage-Opening Reactions of 4-Amino Substituted 1,3-bishomocubanones

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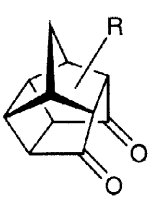
Abstract: Thermolysis of 4-substituted 1,3-bishomocubanones is strongly dependent on the electronic nature of the bridgehead substituent. 4-(N-benzyl)amido-substituted cage compounds **12** unexpectedly furnish bicyclic annelated cyclopentenones **13**, whereas the 4-acetoxy-1,3-bishomocubanone is thermally stable up to 750°C. The free benzylamine **16** undergoes cage opening even at room temperature to give tetracyclic dione **17**.

Strained polycarbocyclic cage compounds constitute an attractive class of substrates for mechanistic and theoretical studies.[1] Many of these cage structures are now readily accessible due to the currently available efficient and high yielding synthetic methodology. They are valuable precursors for the regio- and stereoselective synthesis of new structurally complex cage or non-cage polycyclic molecules.[1,2] An illustrative example is the thermal cage opening of pentacycloundecanes **1** to give triquinanes **2**,[3] which is the basic skeleton of a variety of naturally occurring compounds, such as hirsutene and coriolin. The extensive studies of our group on the nucleophilic eliminative ring fission of bridgehead oxygen substituted cubane type structures revealed that product formation in these cage opening reactions is highly dependent on the cage substitution pattern.[2b] This is typically exemplified by the flash vacuum thermolysis of 4-methoxy-1,3-bishomocubane **3** which affords the all *cis*-tricyclo[5.3.0.$0^{2,5}$]decadienone system **4** in excellent yield,[4] whereas parent 1,3-bishomocubanone **5** lacking the 4-methoxy substituent resulted essentially in cycloreversion to give cyclopentadiene and cyclopentadienone.[5] In the preceding paper we reported the synthesis of 4-amido-substituted 1,3-bishomocubanones **6**.[6] These bridgehead amino cage compounds are of



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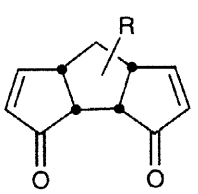

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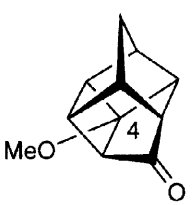

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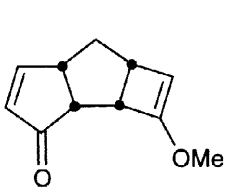

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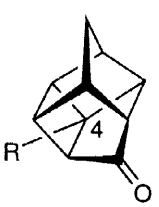

5 R= H
6 R= R_1R_2N
7 R= OAc
8 R= Me

great interest as they allow the study of the electronic impact of the electron-releasing 4-amino substituent on the cage-opening reaction of 4-substituted 1,3-bishomocubanones. For sake of comparison the corresponding 4-methyl- and 4-acetoxy-1,3-bishomocubanones **7**[7] and **8**[8] were also included in this thermolysis study as these structures contain a slightly electron releasing and a slightly electron withdrawing group, respectively.

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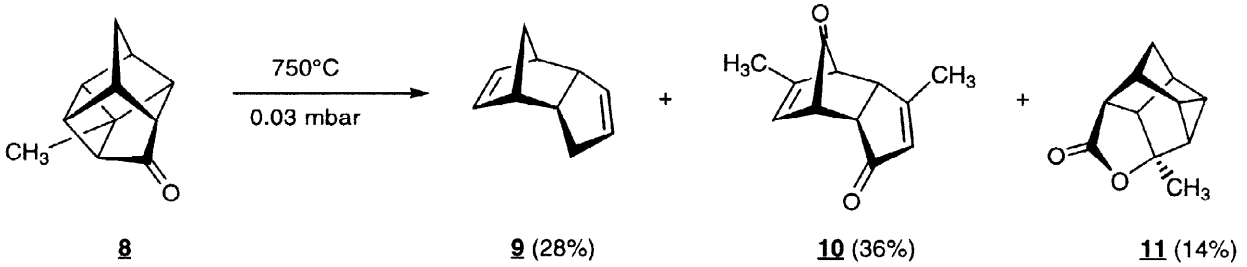
In this report an unprecedented thermal cage opening of **6** to a novel class of bicyclo[3.3.0]octadienone enamines is reported.

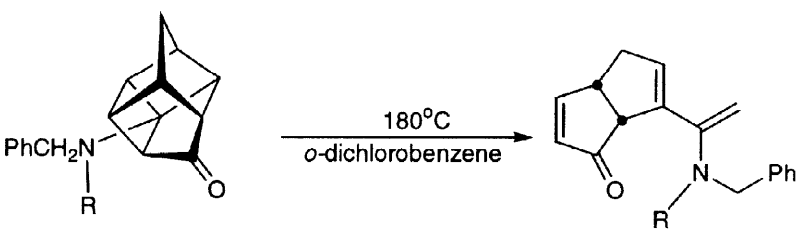
The thermolyses of 4-acetoxy- and 4-methyl-1,3-bishomocubanones **7** and **8**, respectively, were carried out in the gas phase using typical FVT-conditions ($3x10^{-2}$ mbar). In sharp contrast to its methoxy-substituted analogue **3**, which is completely converted into **4** at 325°C, 4-acetoxy-1,3-bishomocubanone **7** is stable even at 700°C. The methyl analogue **8** also showed a considerably higher kinetic stability than **3**. No reaction occurred at temperatures lower than 550°C. At temperatures as high as 750°C almost complete consumption of **8** was observed, giving a mixture of three compounds which were identified as the dimers of cyclopentadiene **9** (28%), methylcyclopentadienone **10** (36%) and a novel tetracyclic lactone **11** (14%) (Scheme 1). The structure of the last mentioned compound was established using 2D-COSY and 2D-NOESY NMR techniques. The formation of **9** and **10** can satisfactorily be explained by a $[\pi^2+\pi^2]$-cycloreversion followed by $[\pi^4+\pi^2]$ - cycloadditions and conforms to the outcome of the gas phase thermolysis of parent **5**.[5] However, the formation of **11** is unique and difficult to explain as it requires an additional oxygen atom; this is suggestive of an oxidative process taking place, but the mechanism has not yet been established.



8 **9** (28%) **10** (36%) **11** (14%)

Scheme 1

The thermal behavior of the N-acylated bridgehead 4-benzylamino-1,3-bishomocubanones **12** was studied first. These amido-1,3-bishomocubanones are insufficiently volatile to allow the study of their thermolysis in the gas phase. Therefore, they were subjected to typical static conditions in *o*-dichlorobenzene. At an optimum temperature of 180°C complete conversion was attained for all compounds **12**, albeit with different reaction rates (Scheme 2). In all cases one major compound was produced in yields up to 54%. Isolation and unequivocal identification was possible for the products derived from the bridgehead amides **12c**, **d** and **e**. Based on a detailed 2D-NMR analysis structures **13c**, **d** and **e** were assigned to these cage-opened products. For the products obtained from **12a** and **12b** complete separation using flash



12 **13**

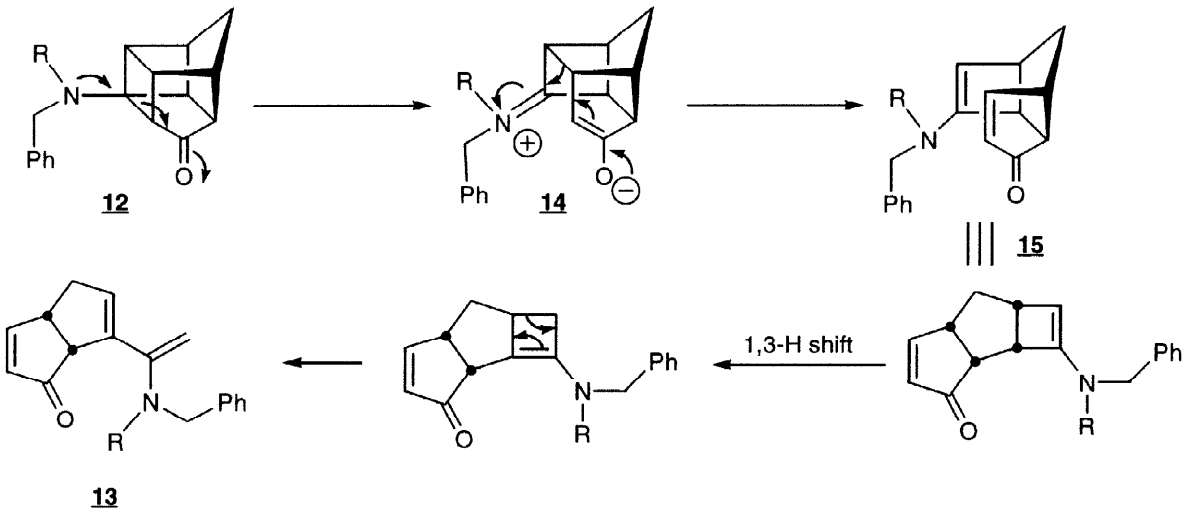
Substrate	time (h)	yield (%)
a R= COMe	3	42[a]
b R= CO_2Me	28	50[a]
c R= $COCH_2Ph$	21	49
d R= CO_2CH_2Ph	28	54
e R= $CO_2(CH_2)_2SO_2Me$	6	50

a) Major component in a two-component mixture

Scheme 2

chromatography appeared impossible, however their ^{1}HNMR-spectra clearly established the presence of **13a** and **13b** as the major component in the thermolysis product mixture.

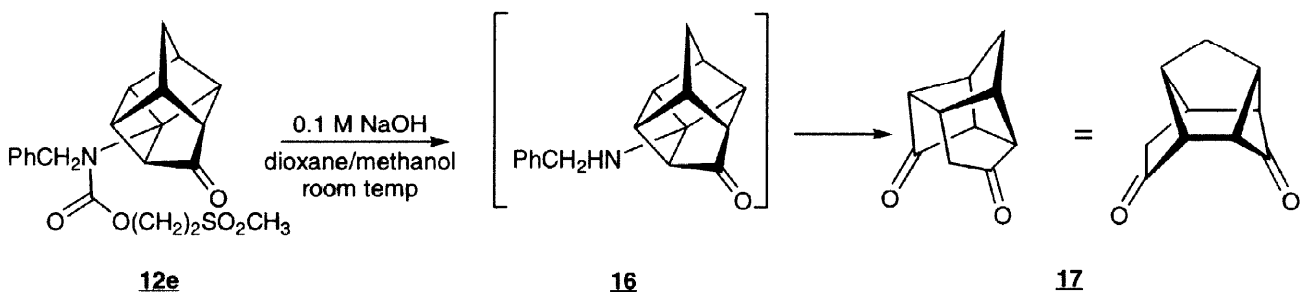
A plausible rationale for the formation of compounds **13** from bridgehead 4-N-benzylamido-1,3-bishomocubanones **12** is depicted in Scheme 3. The initial step involves a nucleophilic eliminative cage fission forming an iminium double bond and the concomitant formation of an enolate anion. This dipolar intermediate **14** undergoes a second ring fission to produce tricyclic enaminone **15**. This structure closely resembles the tricyclic enolether **4** obtained by FVT of 4-methoxy-1,3-bishomocubanone **3**. In contrast to **4**



Scheme 3

this enaminone **15** is not stable but undergoes a subsequent cyclobutene/butadiene ring opening, probably preceded by a 1,3-hydrogen shift, to produce the highly functionalized bicyclo[3.3.0]octadiene enamines **13**. All these ring fissions are thermodynamically favorable processes as there is considerable release of ring strain.

The finding that even an acylated amine function has sufficient electron-releasing capacity to induce ring fission in the 1,3-bishomocubanone system prompted us to evaluate the electronic effect of a free bridgehead 4-amino function on the stability of such 1,3-bishomocubanones. For this purpose N-methylsulfonylethyloxycarbonyl (Msc) protected amine **12e** was deprotected using very mild conditions *viz.* 0.1 M sodium hydroxide in dioxane/methanol/water at room temperature. As reported for similar deprotections in peptide chemistry,[9] the Msc group was smoothly removed within 2 min, however, no bridgehead amine **16** was obtained. Instead, half cage diketone **17** was isolated in quantitative yield, after



Scheme 4

aqueous work up (Scheme 4). This formation of ketone **17** can be readily explained by assuming the intermediacy of 4-benzylamino-1,3-bishomocubanone **16** which is kinetically too unstable to be isolated and immediately undergoes subsequent ring fission to form the corresponding imine **14** (R= H) followed by instantaneous hydrolysis. Further ring fission as observed for the thermolysis of amides **12** is blocked here by the rapid protonation of the intermediate enolate. This cage-opening process has precedent in the spontaneous homoketonization of the corresponding 4-hydroxy-1,3-bishomocubanone which is also too labile to be isolated from the methanolysis of the corresponding acetate.[7]

In conclusion we have shown that 4-N-benzylamido-1,3-bishomocubanones **12** are thermally rather labile and undergo a regioselective and unprecedented triple ring fission to give the interesting bicyclic enamines **13** in acceptable yields. Removal of the N-acyl substituent in **12** leads to such increase in electron density at the amino nitrogen that instantaneous cage opening occurs even at room temperature. The thermal inertness of 4-acetoxybishomocubanone **7** at temperatures up to 750°C further substantiates the influence of the electron releasing capacity of the 4-functionality in 1,3-bishomocubanones on this cage fission process.

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