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Radical cyclizations of bromo ketals from decalin homoallylic and bis-homoallylic alcohols

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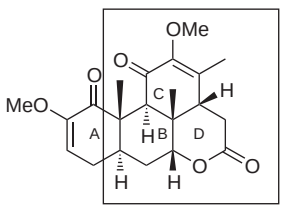
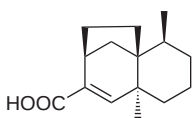
Abstract—The radical cyclizations of bromo ketals derived from the Birch-alkylation products of α-tetralones are described. The carbon–carbon bond formation proceeds in a regio- and stereoselective way. The intra- and intermolecular trapping behavior was also explored.

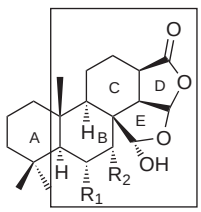
A large number of natural terpenoids, which contain highly complex ring systems in their structures, such as those shown in the Quassin[1] **A**, Bruceantin,[2] Nudenoic Acid[3] **B** and Espongians[4] **C** have been the subject of many synthetic studies due to their important biological activities. In the course of our research toward the synthesis of complex decalin systems related to interesting natural products and the study of synthetic useful reactions,[5] we have found an interesting radical cyclization reaction that was employed in the synthesis of a model caged ketal backbone of Saudin.[6] This reaction produces a six-membered ring from a homoallylic alcohol, building a bridge between two adjacent rings, being completely regio- and stereoselective via 6-*exo*-trig cyclization.[7]



A



B



R_1=R_2=H, OH, OAc, OCOPr

C

Many years ago Stork introduced carbon–carbon bond formation using bromo ketals, mainly used for the five-member lactone ring generation from allylic alcohols. In fact, this reaction is established in organic synthesis as an important tool to introduce five-membered lactones.[8] The first application of this reaction to homoallylic alcohols was also reported by Stork, using a 1-hydroxymethyl-2-cyclohexene.[9] Recently, Lallemand[10] used a 6-*endo*-trig transannular silyl methyl cyclization reaction over a decalinic allylic alcohol, however, the utilization of homoallylic alcohols has remained unexplored. Therefore, we decided to extend our initial studies to find out the applicability of the reaction over different decalin systems. We also wanted to explore the possibility of performing intra- and intermolecular trapping of the intermediate radicals.

We began our study by optimizing the reaction conditions. For the preparation of the halo-ketal, the use of *N* - iodo - succinimide/ethyl - vinyl ether/CH_2Cl_2 at –20°C,[11] on the homoallylic alcohol, always led to incomplete reactions or even to the complete decomposition of some of the substrates, due to the re-aromatization reactions.[12] On the other hand, when we used 1,2 - dibromo - ethyl - ethyl - ether/*N*,*N* - dimethyl - aniline/CH_2Cl_2, at room temperature, the conversion was

Keywords: radical cyclization; transannular reaction; trapping reactions.

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quantitative. For the regular radical reaction we selected the 'in situ' methodology for the generation of the trapping tin hydride.

The use of catalytic (10%) amounts of tributyltin chloride and sodium cyanoborohydride[13] prevented over-reduction of the starting halide and greatly improved the messy work-up of the organotin compounds. Finally, as solvent we preferred the use of *t*-BuOH instead of benzene following the safety regulation recommendations.

Tables 1 and 2 show the radical reactions carried out in the study. First, we tested the reaction with different epoxides. The reaction over the α-epoxide **1b** (entry 2) produced the 6-*exo*-trig product, in a similar way as epoxide **1a**, and confirms that the presence of a larger axial substituent does not affect the selectivity nor the yield of the reaction (72%). However, when the reaction was conducted with the β-epoxide **1c** (entry 3), it was necessary to extend the reflux over 4 hours to complete the reaction, and it produced a mixture of compounds. After purification two main products could be isolated, the tricyclic allylic alcohol **3c** and the ketal derivative **4**. The cyclization of this substrate was more difficult, probably due to the conformation of the decalin, and a significant amount of debrominated product took place. Based on the structure of the cyclic product **3c**, it is reasonable to think that, in order to react, the oxirane must first rearrange to the allylic alcohol and then, when the decalin adopted a planar conformation, the cyclization took place.

We also explored the regioselectivity of the radical cyclization using 1,4-diene systems with different degrees of substitution (entries 4–7). As expected, according to the literature precedents,[14] the cyclization always took place through the less substituted double bond. In turn, when the axial α-alcohols (entries 4–6) were used as substrates, the stereochemical course of the reaction was established and proceeded with complete control, occurring from the same side of the alcohol. However, when we used the β-alcohol **1dβ** (entry 7) none of the cyclic product was obtained even after all the starting bromo ketal was consumed. For the α-alcohols, the reaction provided only the product expected as a mixture of epimeric ketals in 61–68% yield. Besides, the use of alcohol **1f** (entry 6) produced the tricycle **3e** and allowed us to demonstrate that the entrance of the hydrogen takes place from the opposite direction to the initial radical attack, thus rendering the methyl substituent *cis* to the newly formed C–C bond. Also, it is interesting to note that the only product obtained was the one coming from the radical attack on the C7–C8 double bond. This may be explained keeping in mind the stated preference of 6-*exo*-trig over 7-*endo*-trig cyclization.[15] Besides, the reaction over the C4a–C5 double bond must be produced over the C4a (the more substituted carbon) and it is unfavorable because of a less stable intermediate radical.

It is interesting to remark that tricyclic **3d** shows an interesting arrangement of rings and functional groups that are related to BCD rings of Quassin **A**, Klaineanone and Castelanolide belonging to the

Table 1. Cyclization reactions of different alcohols

Entry	Starting material[a]	Product	yield(%)
1	**1a** R=H	**3a** R=H	78
2	**1b** R=OMe	**3b** R=OMe	72
3	**1c**	**3c** + **4**	(**3c** : **4**) 48 : 32
4	**1dα** R_1=R_2=H	**3d** R_1=R_2=R_3=H	68
5	**1eα** R_1=H R_2=OMe	**3e** R_1=R_3=H R_2=OMe	63
6	**1fα** R_1=Me R_2=H	**3f** R_1=Me R_2=R_3=H	61
7	**1dβ** R_1=R_2=H	Debrominated product	

[a] The alcohols **1a-1f** were prepared following our previous publication.[2a-c]

Table 2. Cyclization reactions of different alcohols in trapping conditions

Entry	Starting material[a]	Product	yield(%)
8	**1dα** R_1=R_2=H	**3g** R_1=R_2=H R_3=CN [b,16]	(**3g** : **3d**) 17 : 42
9	**1h**	**3h**	62

[a] The alcohol **1h** was prepared following our previous publication.[2b]
[b] The reaction was conducted in a 10:1 ratio of *t*-BuNC:substrate.

Quassinoids terpene family, while **3c** and **3f** appear as precursors of BCDE ring systems present in Bruceantin B.[2]

At this point, we decided to test the ability of our system to accept intermolecular radical trapping (Table 2). Therefore, using the bromo ketal of the alcohol **1dα**, we performed the reaction in the presence of acrylonitrile but unfortunately it provided only the tricycle **3d** in low yield. However, when we used *t*-Bu-isocynide, as trapping agent, a mixture of the nitrile **3g** (17%)[16] and the tricycle **3d** (42%) in a 1:2.5 ratio was obtained (entry 8). This result showed us that, in spite of the large excess of the trapping agent (*t*-Bu-isocyanide/tributyltinchloride >100/1), the speed of the reaction of the intermediate radical with $HSnBu_3$ is greater than *t*-Bu-isocyanide. The use of the larger triphenyl- or even trineophyltin hydrides did not improve this ratio.

Finally, we explored the intramolecular radical trapping using the bromo ketal of the alcohol **1h**. The radical cyclization produced (entry 9) exclusively the tetracyclic compound **3h** in 62% yield. The reaction occurs through a 6-*exo*-trig radical cyclization continued to a 5-*exo*-trig reaction according to the Baldwin's rules.[7] This compound has a structure related to the Nudenoic acid **C** and could be a useful intermediate in the synthesis of related compounds. The structure of the tetracycle was confirmed by NMR through 1D, 2D and NOE experiments.[17] The stereochemistry shows that after the first C–C bond was formed the radical attacks the allyl group oriented toward the ketal to produce the new ring.[18]

In conclusion we presented a useful tool to introduce a two-carbon unit from an homoallylic alcohol, that course in a complete regio- and stereoselective way through a radical cyclization reaction using catalytic tin hydride.[19] This reaction shows a great potential to prepare complex frameworks applicable in the synthesis of natural products.

Acknowledgements

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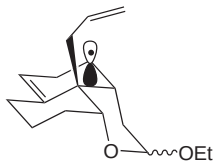
16. Compound **3g** was best characterized as lactone. ^{1}H NMR δ: 5.52 (bs, 1H, C6-H), 4.35 (bs, 1H, C9a-H), 3.01 (dt, $J_1=3.3$ Hz and $J_2=8.32$ Hz, 1H, C4-H), 2.83 (dd, $J_1=10.4$ and $J_2=17.03$ Hz, 1H, C3-H), 2.59 (dd, $J_1=4.2$ and $J_2=17.03$ Hz, 1H, C3-H), 2.4–1.6 (m, 9H, C3a-H, C5-H, C7-H, C8-H and C9-H), 1.28 (s, 3H, C9b-**Me**) ppm; ^{13}C NMR δ 171.04 (C2), 30.35 (C3), 36.57 (C3a), 29.68 (C4), 29.01 (C5), 120.56 (C6), 137.26 (C6a), 19.80 (C7), 25.94 (C8), 24.10 (C9), 81.45 (C9a), 37.48 (C9b), 120.36 (CN) ppm; IR (KBr): ν 2925, 2865, 2250, 1710, 1435, 1305, 1240, 1010, 900 cm^{-1}. HRMS m/z for $C_{14}H_{17}NO_2$ calculated 231.1259, found: 231.1390.
17. Compound **3h** was best characterized as lactone. ^{1}H NMR δ: 5.22 (bd, $J=4.0$ Hz, 1H, C6-H), 4.35 (bd, $J=3.1$ Hz, 1H, C9a-H), 2.59 (d, $J=2.6$ Hz, 1H, C1′-H), 2.55 (s, 1H, C1′-H), 2.32 (dd, $J_1=11.7$ and $J_2=8.2$ Hz, 1H, C3-H), 2.25–1.95 (m, 6H, C9-H, C2′-H, C3a-H, C8-H, C5-H), 1.91 (sa, 1H, C5-H), 1.80 (sa, 1H, C4-H), 1.57 (m, 3H, C7-H and C9-H), 1.01 (d, $J=7.1$ Hz, 3H, C2′-**Me**), 0.99 (dd, $J_1=11.7$ and $J_2=6.4$ Hz, 1H, C3-H); ^{13}C NMR δ 171.91 (C2), 30.01 (C3), 40.09 (C3a), 42.17 (C4), 31.02 (C5), 119.29 (C6), 137.37 (C6a), 18.60 (C7), 29.61 (C8), 29.35 (C9), 84.50 (C9a), 43.83 (C9b), 47.45 (C1′), 38.93 (C2′), 22.27 (C2′-**Me**) ppm; IR (KBr): ν 2905, 2840, 1725, 1330, 1235, 1005, 950 cm^{-1}. HRMS m/z for $C_{15}H_{20}O_2$ calculated 232.1463, found 232.1470.
18. This picture shows the proposed conformation of the intermediate radical in the cyclization of bromo ketal of **1h**.



19. General procedure for bromo ketal generation: 1,2-Dibromo-ethyl ether (1.1 equiv.) was added to solution of the alcohol (1 equiv.) with *N*,*N*-dimethyl-aniline (1.5 equiv.) in dichloromethane (10 mL) at 0°C. The solution was stirred at room temperature over 3 hours and then 1,2-dibromo-ethyl ether (1.1 equiv.) and *N*,*N*-dimethyl-aniline (1.5 equiv.) were added. The mixture was stirred overnight and the solution was flowed down over 20 mL of cold $NaHCO_{3(sat)}$ and was extracted three times with dichloromethane (3×15 mL). The organic phase was washed with cold 1N HCl (3×10 mL), water (1×10 mL) and dried with sodium sulfate. The product was used without purification.
General procedure for radical cyclization: To a degassed solution of the bromo ketal (1 equiv.) in *t*-BuOH (20 mL) over Ar was added $NaBH_3CN$ (2 equiv.), AIBN (0.1 equiv.) and finally Bu_3SnCl (0.1 equiv.). The mixture was refluxed over 1.5 hours over Ar and the *t*-BuOH was evaporated. The residue was dissolved in dichloromethane (30 mL), washed with brine (2×10 mL), dried with sodium sulfate and evaporated. The crude product was purified by column chromatography.