

Regioselective Synthesis of Bicyclo[4.2.1]nonane-2,8-diones via $\text{BF}_3 \cdot \text{Et}_2\text{O}$ Mediated Intramolecular Diazo Ketone Insertion Reaction

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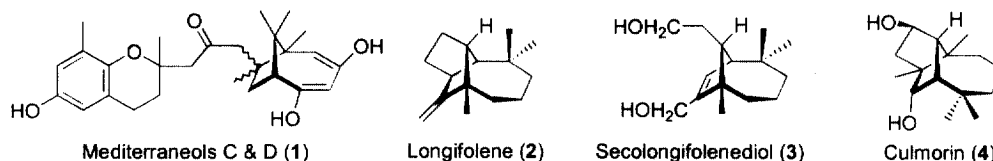
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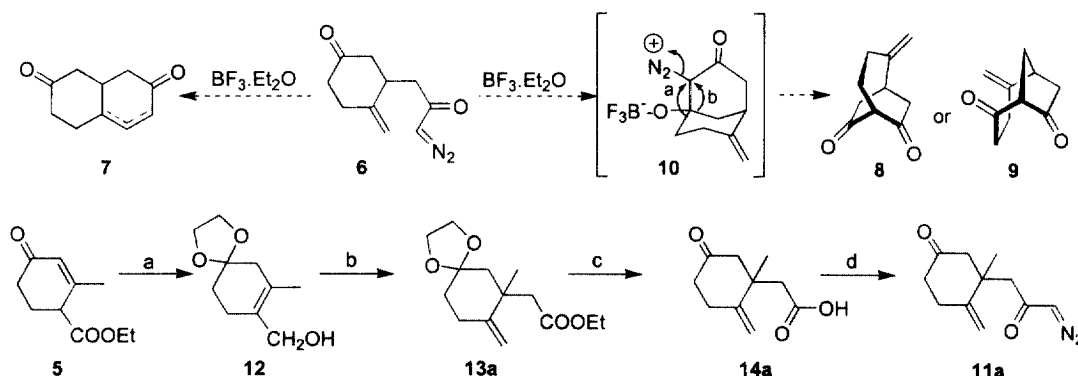
Abstract: Treatment of the diazo diones **11a–d** with boron trifluoride diethyl etherate furnished the bicyclo[4.2.1]nonane-2,8-diones **15a–d** in a highly regioselective manner.

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The bicyclo[4.2.1]nonane ring system is present in several natural products such as the mediterraneols **1**, longifolene **2**, secolongifolenediol **3**, culmorin **4**, etc.¹ The presence of a methyl group at one of the bridgehead positions in addition to the presence of a gem-dimethyl group is very common in these compounds. In our quest for the synthesis of sesquiterpenes containing vicinal quaternary carbon atoms, starting from Hagemann's ester **5**,² we have discovered a new regioselective approach to bicyclo[4.2.1]nonanes³ via a $\text{BF}_3 \cdot \text{Et}_2\text{O}$ mediated intramolecular diazo ketone insertion reaction, which is the subject of this communication.



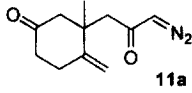
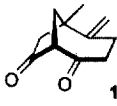
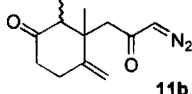
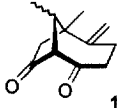
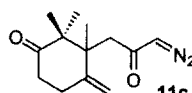
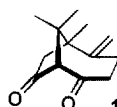
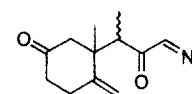
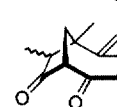
It was envisaged that the reaction of a diazo ketone such as **6** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, in principle, can generate either a bicyclo[4.4.0]decane **7** via participation of the exomethylene group, or the bicyclo[3.2.2]nonane system **8** or the bicyclo[4.2.1]nonane system **9** by the insertion of the diazo ketone into either side of the carbonyl group (migration of a or b) via the intermediate **10**. For investigating this reaction, the starting materials **11** were assembled from Hagemann's ester **5** employing a Claisen rearrangement as the key reaction. Thus, ketalisation of Hagemann's ester **5** followed by reduction with lithium aluminium hydride furnished the allyl alcohol **12**.



Reagents, Conditions and Yields: (a) i. $(\text{CH}_2\text{OH})_2$, *p*-TSA, C_6H_6 , reflux (Dean-Stark), 3.5h, 75%; ii. LiAlH_4 , Et_2O , -70°C , 2h, 90%; (b) $\text{MeC}(\text{OEt})_3$, EtCOOH , 180°C , 5 days, 73%; (c) i. 3N aq. HCl, THF, 3h, 70%; ii. 5% NaOH, $\text{MeOH-H}_2\text{O}$, reflux, 12h; (d) i. $(\text{COCl})_2$, C_6H_6 , rt, 2h; iii. CH_2N_2 , Et_2O , $0-5^\circ\text{C}$, 2h; 75% (3 steps).

The ortho ester Claisen rearrangement of the alcohol **12** furnished the ketal ester **13a**. Hydrolysis of the ketal and ester groups transformed the ketal ester **13a** into the keto acid **14a** which was transformed into the diazo ketone **11a** via the corresponding acid chloride. The same sequence of reactions on the γ -methyl² and γ,γ -dimethyl derivatives of Hagemann's ester furnished the diazo ketones **11b** and **11c**. Alkylation of the ketal ester **13a** with lithium diisopropyl amide and methyl iodide followed by hydrolysis and conversion to the diazo ketone led to the compound **11d**. Treatment of a 0.014 M methylene chloride solution of the diazo ketones **11a-d** with 0.5 equivalents of boron trifluoride diethyl etherate at 0-5 °C for 45 minutes furnished the bicyclo[4.2.1]nonane-2,8-diones **15a-d** in a highly regioselective manner. The results are summarised in the Table. The structures of the products were deduced from their interrelated spectral data.⁴ The presence of a singlet resonance for the H-1 proton in the dione **15c** in the ¹H NMR spectrum and the presence of 11 signals in the ¹³C NMR spectrum of the dione **15a** clearly established the bicyclo[4.2.1]nonane structure (the bicyclo[3.2.2]nonane based dione has a plane of symmetry). In all the reactions only bicyclo[4.2.1]nonane based diones were produced and no detectable amount of the either bicyclo[4.4.0]decane or bicyclo[3.2.2]nonane based diones were observed. Very facile formation of the bicyclo[4.2.1]nonane comprising two vicinal quaternary carbon atoms (entry c) via migration of the tertiary centre is worth noting. Currently, we are investigating the application of this methodology in the synthesis of natural products.

Table: Synthesis of bicyclo[4.2.1]nonanes

entry	diazo ketone	product	% yield ^a (ratio)
(a)	 11a	 15a	83
(b)	 11b	 15b	85 (1:1)
(c)	 11c	 15c	90
(d)	 11d	 15d	85 (1.25:1) ^b

a. Yields (unoptimised) refer to isolated and chromatographically pure compounds. b. Separated on a silica gel column and the minor isomer (*exo*) was found to equilibrate to major isomer (*endo*) on treatment with DBU in methylene chloride.

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References and Notes

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- All the compounds exhibited spectral data consistent with their structures. Spectral data for the dione **15a**: IR (neat): ν_{\max} 1740, 1690, 1090, 900 cm^{-1} . ¹H NMR (300 MHz, CDCl₃): δ 4.85 (1 H, s) and 4.80 (1 H, s) [C=CH₂], 3.34 (1 H, d, $J=8.7$ Hz, H-1), 2.10-2.65 (8 H, m), 1.44 (3 H, s, *tert*-CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 209.9 (C, C-8), 203.0 (C, C-2), 153.5 (C, C-5), 110.8 (C=CH₂), 65.1 (CH, C-1), 52.1 (CH₂, C-7), 43.7 (C, C-6), 42.3 (CH₂, C-3), 39.9 (CH₂, C-4), 30.3 (CH₂, C-9), 26.9 (CH₃). For the dione **15c**: mp. 180 °C. IR: ν_{\max} 1735, 1690, 1630, 900 cm^{-1} . ¹H NMR (400 MHz, CDCl₃): δ 5.10 (1 H, s) and 4.99 (1 H, s) [C=CH₂], 3.16 (1 H, s, H-1), 2.65 (1 H, d, $J=19$ Hz) and 2.57 (1 H, d, $J=19$ Hz) [H-7], 2.55-2.70 (1 H, m), 2.45 (3 H, m), 1.34 (3 H, s), 1.16 (3 H, s) and 1.02 (3 H, s) [3 x *tert*-CH₃]. ¹³C NMR (75 MHz, CDCl₃): δ 210.6 (C, C-8), 203.3 (C, C-2), 151.5 (C, C-5), 114.9 (CH₂, C=CH₂), 78.3 (CH, C-1), 50.9 (CH₂, C-7), 49.2 (C, C-6), 44.1 (C, C-9), 42.3 (CH₂, C-3), 30.4 (CH₂, C-4), 27.8 (CH₃), 20.5 (CH₃), 20.4 (CH₃). Mass: m/z 206 (M⁺, 7%), 123 (33), 83 (100). Anal. Calcd. for C₁₃H₁₈O₂: C 75.69, H 8.8; Found: C 75.40, H 8.9%.