Rac-(1S,3bR,7aR)-2',3a,6,6',6'-hexamethyl-3a,3b,6,7-
tetrahydrospiro[benzo[2,3]cyclopropa[1,2-c]pyrazole-
1,1'-cyclohepta[2,4]diene]  
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Abstract: This note describes a novel reaction cascade in which a tosyl hydrazone derivative of 
eucarvone is undergoing a non-classical dimerization process under basic conditions. The key step 
in this sequence is a dipolar cycloaddition between a diazo species and a transient cyclopropene. A 
proposed mechanism for this sequence is presented that is supported by a single crystal X-ray 
analysis of the resulting dimer. We believe this unique transformation is of note as it highlights a 
neat and efficient entry to complex polycyclic architectures containing an embedded pyrazoline 
moiety.  

Keywords: eucarvone; dimerization; cycloaddition; tosyl hydrazone; 1,3-dipole; molecular 
rearrangement; Bamford-Stevens reaction  

1. Introduction  
Molecular rearrangements are of considerable importance to synthetic chemistry as they allow 
to create unprecedented molecular scaffolds that oftentimes warrant further investigation into their 
properties [1]. Additionally, such rearrangements can be part of entire reaction cascades resulting in 
the rapid construction of complex architectures that arise from a well-orchestrated and typically very 
step-efficient process. The discovery of such reaction cascades therefore allows chemists not only to 
access new chemical space, but moreover enables us to subsequently design and create such 
structures in target-oriented synthesis programs.  

2. Results  
A recent synthesis program in our laboratory concerned the conversion of eucarvone 1, that was 
prepared by literature methods [2,3], into its deoxygenated cycloheptatriene counterpart 2 (Scheme 
1). To perform this transformation, we opted to convert eucarvone into its tosyl hydrazone derivative 
(3), which upon treatment with base was expected to undergo a Bamford-Stevens reaction [4,5].  

Upon deprotonation of 3 with a freshly prepared solution of sodium methoxide in methanol (2.0 
equiv.) no reaction occurred at ambient temperature after 1h. However, upon heating of this reaction
mixture at 70 °C the formation of a new species was observed by tlc that reached completion after about 12 h. After quenching the reaction mixture with aqueous ammonium chloride solution and aqueous extraction (DCM/water) the crude product was isolated and purified by silica column chromatography (EtOAc/hexanes 5:95) to yield a colorless solid as main product. Analysis of this material by 1H-NMR revealed that it was not consistent with the reported data for the desired product 2 [6]. Furthermore, HRMS analysis suggested a molecular formula of C32H34N2 implying that a pseudo-dimeric species had been obtained instead. To this end the purified material was crystallized from DCM allowing to perform single crystal X-ray diffraction analysis. The results of the X-ray analysis confirmed that a dimeric species (4) had indeed been formed as part of the intended deoxygenation process (Figure 1).

Figure 1: Single crystal X-ray structure of dimeric product 4 [7].

Furthermore, the presence of an unprecedented tetracyclic (6-3-5-7) ring system containing an embedded pyrazoline ring was revealed. Importantly, it was possible to generate this intriguing product in a reproducible manner as the major product (60-70% isolated yield) of this reaction cascade.

3. Discussion

To account for this unexpected reaction outcome, we propose the following mechanistic rational which is inspired by the classical Bamford-Stevens reaction. As such deprotonation of the tosyl hydrazone 3 is expected to generate the corresponding anion 5 that allows for expelling of the tosyl unit to subsequently yield to a diazo intermediate 6a. This species can be represented through a second resonance form 6b, which then undergoes a ring contraction to a fused (3-6) bicycle 7 accompanied by release of nitrogen gas. Finally, a dipolar cycloaddition between diazo species 6a and bicycle 7 furnishes the observed dimer 4 (Scheme 2). The regioselectivity of this cycloaddition process is likely to be governed by steric elements and the presence of a minor isomer in the NMR spectrum of crude 4 likely accounts for this (original d.r./r.r. ~4:1).

Scheme 2: Proposed mechanism for the formation of dimer 4.
4. Materials and Methods

Eucarvone 1 was prepared from carvone by literature known methods [2,3] and isolated as a colorless oil. The synthesis of tosyl hydrazone 2 from eucarvone 1 was accomplished as follows: To a solution of eucarvone (1, 1 mmol, 150 mg) in MeCN (0.5 M) was added tosyl hydrazine (1.1 mmol, 205 mg) and 1 drop of acetic acid. The resulting mixture was heated at 65 °C for 5 h at which point tlc indicated full conversion of 1. After removal of the solvent the crude mixture was purified by silica column chromatography (10-20% EtOAc in hexanes) to yield 2 as a colorless solid (85% yield, 0.85 mmol, 270 mg). NMR and HRMS data are consistent with this structure:

\[ ^1H-NMR(600\text{MHz},\text{CDCl}_3)\delta/ppm\text{ }7.83\text{ (d, }J=8.4\text{ Hz, 2H)},\text{ }7.75\text{ (s, 1H)},\text{ }7.31-7.27\text{ (m, 2H)},\text{ }5.92\text{ (dt, }J=7.4,\text{ }1.3\text{ Hz, 1H)},\text{ }5.56\text{ (dd, }J=11.6,\text{ }7.3\text{ Hz, 1H)},\text{ }5.53\text{ (d, }J=11.5\text{ Hz, 1H)},\text{ }2.41\text{ (s, 3H)},\text{ }2.40\text{ (s, 2H)},\text{ }1.92\text{ (d, }J=1.4\text{ Hz, 3H)},\text{ }1.00\text{ (s, 6H)}.\]

\[ ^13C-NMR(150\text{MHz,CDCl}_3)\delta/ppm\text{ }155.2\text{ (C)},\text{ }144.1\text{ (C)},\text{ }143.4\text{ (CH)},\text{ }137.9\text{ (C)},\text{ }135.1\text{ (C)},\text{ }129.4\text{ (2CH)},\text{ }128.1\text{ (2CH)},\text{ }127.2\text{ (CH)},\text{ }121.8\text{ (CH)},\text{ }38.2\text{ (CH}_2\text{)},\text{ }35.2\text{ (C)},\text{ }27.5\text{ (2CH}_3\text{)},\text{ }21.8\text{ (CH}_3\text{)},\text{ }21.6\text{ (CH}_3\text{)}.\]

The synthesis of dimer 4 was accomplished by the following procedure: Sodium metal (22 mg, 0.96 mmol, 2.0 equiv.) was dissolved in dry methanol (2 mL) at ambient temperature. To the resulting solution of sodium methoxide (0.48 M) was added tosyl hydrazone 2 (150 mg, 0.47 mmol, 1.0 equiv.). After stirring at room temperature for 1 h the mixture was heated up to 60 °C and maintained for 12 h at which point tlc indicated full consumption of 2 and formation of a new compound. The reaction mixture was cooled to room temperature and evaporated to dryness. Purification by silica column chromatography (5% EtOAc/hexanes) yielded 4 as a colorless crystalline solid (65%, 0.30 mmol, 90 mg). Slow evaporation of a solution of 4 in DCM yielded crystals suitable for X-ray diffraction analysis.

\[ ^1H-NMR(400\text{MHz,CDCl}_3)\delta/ppm\text{ }5.93\text{ (ddt, }J=7.5,\text{ }1.7,\text{ }0.9\text{ Hz, 1H)},\text{ }5.80\text{ (d, }J=11.3\text{ Hz, 1H}),\text{ }5.70\text{ (dt, }J=9.9,\text{ }1.1\text{ Hz, 1H)},\text{ }5.64\text{ (dd, }J=11.3,\text{ }7.5\text{ Hz, 1H}),\text{ }5.55\text{ (dd, }J=9.9,\text{ }3.3\text{ Hz, 1H}),\text{ }2.52\text{ (d, }J=14.8\text{ Hz, 1H)},\text{ }1.75\text{ (dd, }J=15.0,\text{ }1.1\text{ Hz, 1H)},\text{ }1.62\text{ (dd, }J=14.8,\text{ }1.4\text{ Hz, 1H}),\text{ }1.55\text{ (s, 3H)},\text{ }1.41\text{ (s, 3H)},\text{ }1.31\text{ (d, }J=15.0\text{ Hz, 1H)},\text{ }1.27\text{ (dd, }J=1.3,\text{ }0.7\text{ Hz, 3H)},\text{ }1.10\text{ (s, 3H)},\text{ }1.01\text{ (s, 3H)},\text{ }0.96\text{ (s, 3H)},\text{ }0.77\text{ (dd, }J=3.3,\text{ }1.0\text{ Hz, 1H}).\]

\[ ^13C-NMR(100\text{MHz,CDCl}_3)\delta/ppm\text{ }155.2\text{ (C)},\text{ }144.1\text{ (C)},\text{ }143.4\text{ (CH)},\text{ }137.9\text{ (C)},\text{ }135.1\text{ (C)},\text{ }129.4\text{ (2CH)},\text{ }128.1\text{ (2CH)},\text{ }127.2\text{ (CH)},\text{ }121.8\text{ (CH)},\text{ }38.2\text{ (CH}_2\text{)},\text{ }35.2\text{ (C)},\text{ }27.5\text{ (2CH}_3\text{)},\text{ }21.8\text{ (CH}_3\text{)},\text{ }21.6\text{ (CH}_3\text{)}.\]

Melting range: decomposition >105 °C.

5. Conclusions

In conclusion, we have accomplished the efficient synthesis of a complex tetracyclic pyrazoline system (4) by an unprecedented dimerization reaction. This is based on a Bamford-Stevens reaction of a tosyl hydrazone precursor (2) and a mechanistic rational accounting for this transformation is proposed. Due to the novelty of both this scaffold and this process we believe such intriguing entities hold interest as they represent new chemical space.

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Author Contributions: SL and MB performed the experiments. MB and IRB wrote the paper.

Supplementary Materials: The following are available online at www.mdpi.com/xxxx, copies of NMR spectra of 4 and X-ray crystallography data.
Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

References

7. The X-ray structure has been deposited with the Cambridge Crystallographic Data Centre as CCDC XXXXXX.

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