Preparation of New [2.1.1]-bicyclohexanes: an opening towards new chemical space

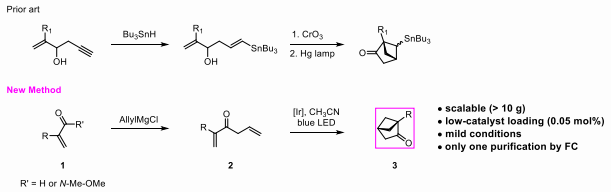
Loïc Herter[a,b], Ilias Koutsopetras[a,b], Lorenzo Turelli[a,b], Thomas Fessard[a], Christophe Salomé[a]

a) SpiroChem AG, Rosental area, WRO-1047-3, Mattenstrasse 22, 4058 Basel, Switzerland

b) Bio-Functional Chemistry (UMR 7199), LabEx Medalis, University of Strasbourg, 74 Route du Rhin, Illkirch, 67400, France

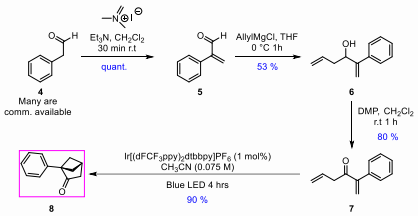
Introduction

Saturated bicycles are becoming more important in the design and development of new pharmaceuticals. In line with these aspirations, SpiroChem continues to expand the collection of isosteres available by exploring new chemical space while following the mantra ***escape from flatland***. To our surprise, the synthesis of 1,2-substituted [2.1.1]-bicyclohexanes is barely described and the incorporation of exit vectors is almost inexistent (only phenyl, ketone and alcohol). The most common method for the synthesis of [2.1.1]-bicyclohexanes is via a crossed [2+2]-cycloaddition of a 1,5-diene using a mercury lamp. Unfortunately, the use of such a lamp is often not easy (special equipment and glassware needed) and the reaction is therefore difficult to scale up. A robust route was then designed to obtain different analogs of **3**. The 1,5-diene **2** was irradiated with LEDs (λ = 385 nm or 450 nm) in the presence of a photocatalyst (Iridium or Thioxanthone)



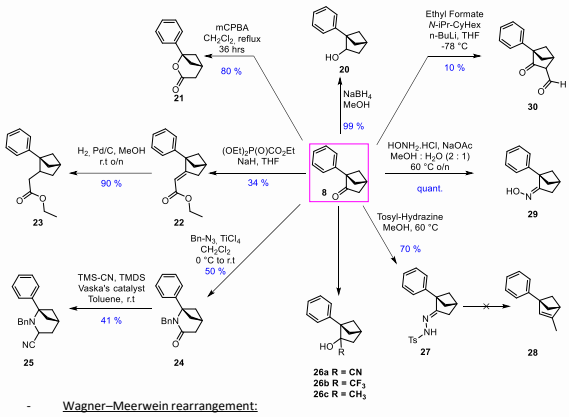
Synthesis of the scaffold

From phenylacetaldehyde **4**, the methylene moiety was incorporated using Tetramethylammonium iodide in quantitative yield. The allyl was added on the aldehyde **5** and the secondary alcohol was oxidized with DMP leading to **7** in moderate yield over 2 steps (40%). The 1,2 substituted [2.1.1]-bicyclohexane (8) was then obtained in nearly quantitative yield using photochemistry. The sequence was upscaled to multigram quantities (> 10 g) with no issues.



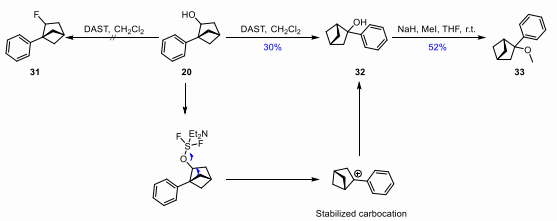
Positions 2 & 3 diversification

- To access new building blocks bearing new exit vectors, different chemical transformations were performed. The ketone of **8** could easily be, reduced to secondary alcohol **20** and transformed via Wittig reaction and reduction to the ethyl acetate derivative **23**. We could also achieve the oxime **29** or the hydrazone **27**. Unfortunately, the different attempts of the Shapiro reaction on **27** to get **28** led only to complex mixtures. Some nucleophiles were also positively added to ketone **8** forming tertiary alcohols **26a-c**. Ring expansions were performed via Baeyer–Villiger and Schmidt rearrangements to obtain lactone **21** and lactam **24**. Noteworthy, the lactam **24** could be activated to form aminonitrile **25**. Finally, an aldol-type reaction was successfully performed to obtain the aldehyde **30**, although in poor yield due to the lack of enol-reactivity of the ketone **8**.



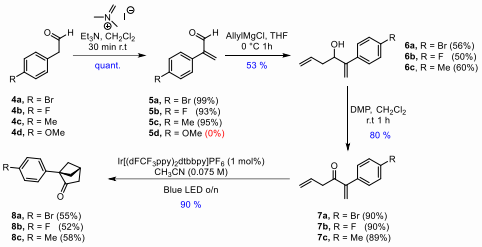
- Wagner–Meerwein rearrangement:

Attempts to replace the secondary alcohol of **16** by fluoride atom were realized. Different conditions were used (Selectfluor, DAST, Deoxo-Fluor,...). Unfortunately, the expected target **27** was never observed, instead the major isolated compound was compound **28**, obtained from a 1,2 rearrangement. The tertiary alcohol was easily methylated using NaH and MeI in THF to obtain **33**.

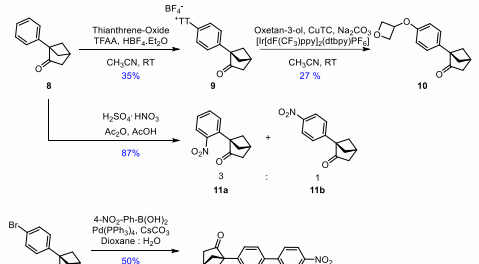


Position 1 diversification

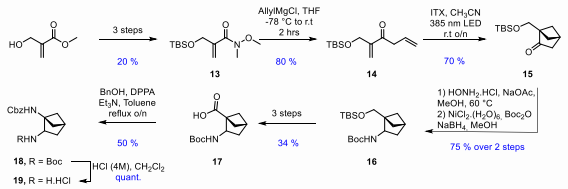
Different *para*-substituted phenylacetaldehydes (**4a-d**) were engaged into the optimized sequence. The corresponding [2.1.1]-bicyclohexanes **8a-8c** were obtained in good yields. Unfortunately, the first step with the para-methoxy phenylacetaldehyde did not lead to the acrolein derivative **5d**.



As some substituents on the aromatic ring were not tolerated, attempts to functionalize the phenyl ring were successfully performed. The phenyl of compound **8** could be easy "thiantrenized" using Ritter's conditions, then, a secondary alcohol was introduced at the 4 position to obtain **10** in moderate yield (27%). Nitration of **8** led successfully to the mono nitrated **11** as a 3:1 mixture of regio-isomers. Finally, a Suzuki cross-coupling was satisfyingly performed on compound **4a** in 50 % yield.

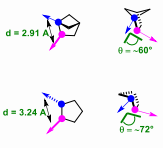


The introduction of alkyl group remained difficult and the 2+2 photocyclization could not afford the expected 1-alkyl-2-oxo-[2.1.1]-bicyclohexanes. We assumed that the replacement of a phenyl group by an alkyl group may change the triplet energy of the system. A screening of conditions was performed and allowed access to compound **15** (Iso-propyl-thioxanthone ITX, 385 nm).With **15** in hand, we were able to obtain the protected amino acid **17** and the diamine **19** in 5 and 7 steps, respectively.



Exit vectors Geometry

The different new buildings blocks were minimized in 3D to have an overview of the geometry of the molecules. We compared the geometric parameters with a classical 1,2-*trans*-cyclopentyl. In this method, substituents at the disubstituted scaffold were simulated by two exit vectors (blue and purple arrows). The relative spatial arrangement of vectors is described by 2 geometric parameters: the distance between the 2 vectors and the dihedral angle Φ. Analysis of this data reveals that the 2 exit vectors are closer in the [2.1.1]-bicyclohexanes than the cyclopentyl derivatives. We also note that the dihedral angles is less important in the [2.1.1]-bicyclohexanes. X-ray crystallography study is ongoing to affine the conclusion.



Conclusion

To conclude a new class of [2.1.1]-bicyclohexanes were successfully obtained. The optimized [2+2] reaction gives access to a new atom arrangement (1,2-substitution). Different substitutions on the aromatic ring could be obtained on the position 1, but we also were able to introduce alky group using another strategy and condition for the [2+2] reaction. We also derivatized the ketone to other functional groups allowing the access to new building blocks. The new synthesized building blocks opens a new chemical space and offers a new dihedral angle interesting for medicinal chemists.