ChemSusChem

Research Article
doi.org/10.1002/cssc.202400013

Chemistry Europe
European Chemical Societies Publishing

www.chemsuschem.org

Cu-Catalyzed Tandem Oxidation-Intramolecular Cannizzaro Reaction of Biorenewables and Bioactive Molecules

Hristo Petkov,[a] Martin A. Ravutsov,[a] Manuel J. Verganista,[b] Yavor N. Mitrev,[a] Nuno R. Candeias,[b, c] and Svilen P. Simeonov*[a, d]

A tandem Cu-catalyzed oxidation-intramolecular Cannizzaro reaction leading to bioactive α-hydroxyesters from α-hydroxyketones is reported. The process uses oxygen as a sole oxidant to achieve the formation of glyoxals, which are efficiently converted *in situ* to important α-hydroxyesters. The mechanistic insights are provided by isotopic labeling and supported by DFT calculations. The transformation proved a robust synthetic tool to achieve the synthesis of human metabolites and hydroxyl esters of various biologically active steroid derivatives.

Introduction

The intramolecular Cannizzaro reaction that converts glyoxals [RC(O)CHO] to the corresponding α-hydroxy carboxylic acid or esters [RCHOH(CO_2R_1)] has been known since the end of the 19th century.[1,2] Through the years this transformation has been intensively explored and the harsh reaction conditions initially employed (e.g. strong bases, high temperatures) have been replaced by Lewis acid catalysis that operate under milder conditions.[3–10] More recently asymmetric versions have been developed.[11–14] However, most of the reported transformations require the use of α-ketoaldehydes or their corresponding hydrates as starting materials. Due to the unstable nature of the α-ketoaldehydes, in several instances they have been used *in situ* for further transformations.[15–17] The reported approaches are often limited to the use of aryl substrates, which furnish more stable glyoxal-type intermediates owing to conjugation with the aromatic ring. The access to this materials usually requires application of expensive and toxic stoichiometric oxidants such as SeO_2,[13] Kornblum oxidation with I_2,[15,16] 2-iodoxybenzoic acid (IBX),[18] or dichloro-pyridine-*N*-oxide.[19] Despite the possibility of using Cu-complexes to catalyze such a transformation, the aerobic oxidation of primary alcohols usually results in overoxidation to carboxylic acids.[20,21] The catalytic approaches remain limited to the use of Fe-$(OAc)_2$/TEMPO/O_2[17] and Cu$(OAc)_2$/O_2,[22,23] and suffer from the need of very high catalyst loading. A recent report on the selective Cu(I)-catalyzed oxidation of primary α-ketoalcohols using O_2 as a sole oxidant overcame these drawbacks.[24]

The intramolecular Cannizzaro reaction has been achieved under Cu catalysis,[4] and it proved particularly useful for the synthesis of asymmetric α-hydroxyesters from α-ketoaldehydes.[11,13] Despite its obvious utility, the tandem Cu-catalyzed oxidation-intramolecular Cannizzaro reaction of α-ketoalcohols has been scarcely explored. Such transformation could be rather challenging owing to the possible C–C cleavage of the formed α-hydroxy carboxylic acid.[25] To the best of our knowledge, the herein showcased tandem Cu-catalyzed oxidation-intramolecular Cannizzaro reaction of α-hydroxyacetones has been reported only in one instance and regarded as a side reaction.[24]

Prompted by the above-mentioned challenges, we report a Cu-catalyzed direct conversion of primary α-ketoalcohols to α-hydroxyesters that proceeds *via* oxidation of the alcohol to the corresponding aldehyde, followed by successive Cannizzaro reaction. Driven by sustainability and applicability considerations, we focused our efforts on the utilization of biorenewable substrates and steroids that give rise to biologically active derivatives (Figure 1).

Recently, we reported a Ru-catalyzed isomerization of Achmatowicz derivatives that results in the formation of 4-keto-δ-valerolactones.[26] In particular, the Achmatowicz product derived from the biorenewable furfuryl alcohol was converted in high yields to dihydro-2H-pyran-2,5(6H)-dione (**KVL**). Therefore, we foresee the hydroxy ketone moiety in its corresponding methyl ester **1** (Scheme 1) as an excellent starting material to achieve the synthesis of esters of α-hydroxyglutaric acid, which is an oncometabolite[27–30] and potential cardioprotective agent.[31] Noteworthy, its esters have been explored in the

[a] H. Petkov, Dr. M. A. Ravutsov, Prof. Y. N. Mitrev, Prof. S. P. Simeonov
Institute of Organic Chemistry with Centre of Phytochemistry
Bulgarian Academy of Sciences
Acad. G. Bonchev str., bl. 9, Sofia 1113, Bulgaria
E-mail: svilen.simeonov@orgchm.bas.bg

[b] M. J. Verganista, Prof. N. R. Candeias
LAQV-REQUIMTE
Department of Chemistry
University of Aveiro, 3810-193 Aveiro, Portugal

[c] Prof. N. R. Candeias
Faculty of Engineering and Natural Sciences
Tampere University
Korkeakoulunkatu 8, 33101 Tampere, Finland

[d] Prof. S. P. Simeonov
Research Institute for Medicines (iMed.ULisboa)
Faculty of Pharmacy
Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cssc.202400013

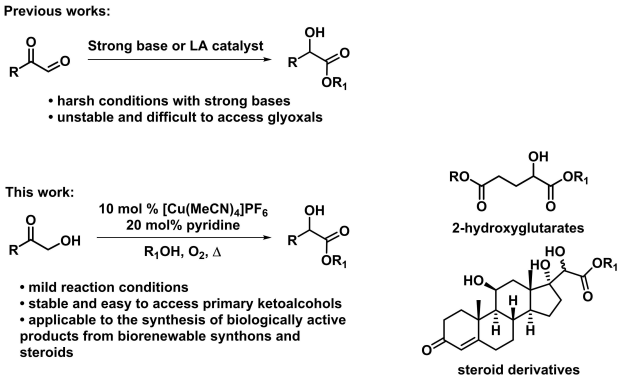
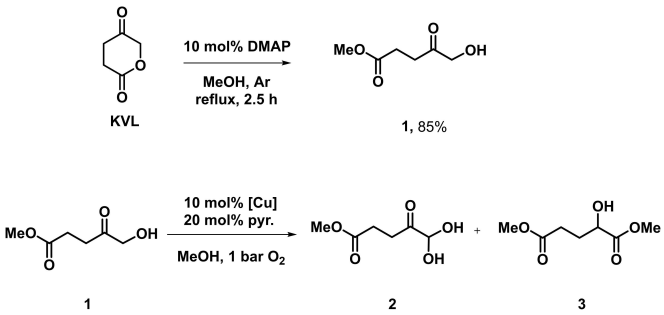


Figure 1. Tandem oxidation-intramolecular Cannizzaro reaction of biorenewables.



Scheme 1. Tandem oxidation-intramolecular Cannizzaro reaction of methyl 5-hydroxylevulinate.

synthesis of several bioactive scaffolds[32–36] and natural products.[37] Moreover, α-hydroxyacids or esters have become important building blocks for the production of polyester monomers from cellulosic biomass[38] and biobased polymers with tunable functionality.[39]

Results and Discussion

We began our studies by screening a range of Cu(I) and Cu(II) complexes (see Table S1, SI) for their ability to catalyze the oxidation of **1** to hydrate **2** and further promote its intramolecular Cannizzaro-type rearrangement to the corresponding dimethyl α-hydroxyglutarate **3** (Scheme 1).

We observed the formation of both oxidation product **2** and Cannizzaro derivative **3** in all cases. The preliminary screened catalysts provided low to moderate yields of **3** (Table 1, entries 1–6). The previously reported copper(I) complex for oxidation of α-hydroxyketones to glyoxalates,[24] $[Cu(MeCN)_4]PF_6$ in 10 mol%, exhibited the best performance under our conditions, resulting in 82% yield (Table 1, entry 7). Noteworthy, the reaction also proceeded with 5 mol% catalyst loading and in the presence of aerobic oxygen as oxidant. Nevertheless, in both cases, significantly longer reaction times of above 17 h were required. In addition, we achieved the synthesis of **2** in 87% isolated yield (Table 1, entry 8). The selective formation of **2** was observed upon cooling to 0 °C and on using a shorter reaction time (1 h),

Table 1. Selected catalytic experiments.[a]

Entry	Catalyst	Pyridine mol%	NMR yield (%)	
			2	**3**
1	$Cu(OAc)_2.H_2O$	20	33	13
2	CuCl	20	48	24
3	$CuSO_4$	20	57	8
4	CuBr	20	30	33
5	$Cu(OTf)_2$	20	18	51
6	$Cu(OTf)(C_6H_6)_{0.5}$	20	5	64
7	$[Cu(MeCN)_4]PF_6$	20	9	82 (80[b,c])
8	$[Cu(MeCN)_4]PF_6$	10	87%[b,d]	–
9	$[Cu(MeCN)_4]PF_6$	–	34	16
10	$[Cu(MeCN)_4]PF_6$	–	33	33[e]
11	–	20	No reaction[e]	
12	$Ag(MeCN)_4BF_4$	20	No reaction[f]	

[a] 0.25 mmol scale, MeOH (0.1 M), oxygen atmosphere (1 bar), 60 °C, 2 h, trimethoxybenzene as internal standard. [b] isolated yield. [c] 2 mmol scale. [d] 4 mmol scale, 5 mol% catalyst, 0 °C, 1 h. [e] **2** used as a starting material. [f] up to 17 h.

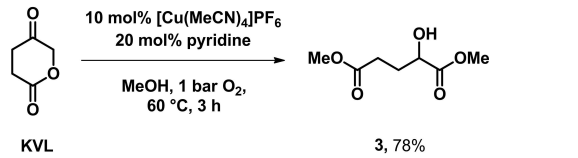
as the appearance of product **3** was promoted by higher temperatures and longer reaction times. Unsurprisingly, the absence of pyridine rendered lower yield (Table 1, entry 9), as pyridine has been previously reported to accelerate the oxidation step.[24] With the idea to test its influence on the Cannizzaro rearrangement we performed the reaction starting from the intermediate hydrate **2**. The lower reaction yield and the presence of 33% starting material after 2 h of reaction time suggested that the presence of pyridine accelerates both alcohol oxidation and Cannizzaro rearrangement (Table 1, entry 10). However, the pyridine as base alone did not catalyze the Cannizzaro reaction from **2** (Table 1, entry 11). Finally, we performed an attempt to achieve the synthesis of **3** using the similar $Ag(MeCN)_4BF_4$ catalyst. Nevertheless, this attempt was unsuccessful (Table 1, entry 12).

We further observed that the use of a protic solvent is of pivotal importance for the reaction outcome (see Table S2, SI). We found no reactivity when using MTBE, MeCN and CPME as solvents, while the use of chlorinated solvent such as DCE rendered **3** in only 11% yield. The use of water as a sole solvent was also not tolerated.

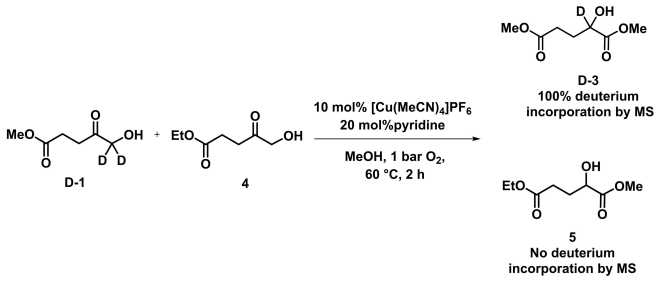
Further, we examined the role of complex counter anion and pyridine equivalents on reaction rate. To this end, $[Cu(MeCN)_4]BF_4$, $[Cu(MeCN)_4]OTf$ and $[Cu(py)_4]PF_6$ were tested. In order to adjust a reasonable time scale for the measurements the reactions were carried out in the presence of 2.5 mol% catalysts and followed by NMR spectroscopy employing trimethoxybenzene as an internal standard (see Table S3, SI). We observed similar kinetics of the different complexes as compared to the standard conditions, thus suggesting that the counter anion is innocent in both alcohol oxidation and Cannizzaro rearrangement. The use of 4 equivalents of pyridine was also found to be of no benefit. With these reaction

parameters in hand, we explored the gram-scale direct synthesis of **3** from **KVL** in a tandem 3-step process. To our delight, the reaction proceeded with an isolated yield of 78% (Scheme 2), which is comparable to the reaction involving **1** as a starting material. This approach provided a sustainable route to "symmetrical" hydroxyglutarates from the biorenewable **KVL**. Compared to the previously reported methods, our work avoids the troublesome diazotization of glutamic acid[32] or multistep esterification and reduction synthesis from ketoglutaric acid.[40,41]

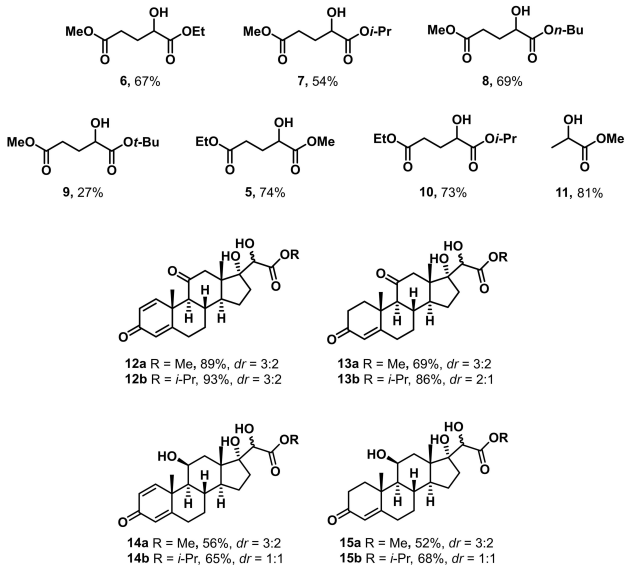
The presence of pyridine, which may act as a base in the Cannizzaro reaction provoked us to study the molecularity of the process. To this end, a deuterium labeling study was undertaken to determine the mechanism. We prepared the isotopically labeled substrate **D-1** and subjected it to a cross-experiment with ethyl ester **4**. The GC/MS analysis of the reaction mixture revealed an intramolecular deuterium transfer leading to formation of product **D-3**, while deuterated product **D-5** was not observed (Scheme 3). This observation was in accordance with the fact that pyridine alone did not catalyze the Cannizzaro reaction (Table 1, entry 11), thus suggesting an entirely intramolecular process.



Scheme 2. Direct application of **KVL** for gram-scale synthesis of dimethyl α-hydroxyglutarate.



Scheme 3. Deuterium labeling studies.



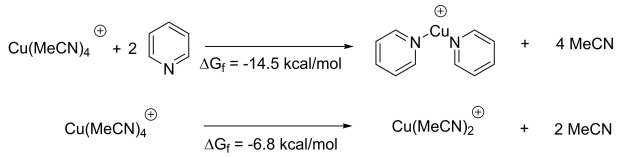
Scheme 4. Scope of the Cu-catalyzed tandem oxidation-intramolecular Cannizzaro reaction.

We further explored the scope of the transformation in the synthesis of "unsymmetrical" in respect to the carboxylic functions hydroxyglutarates (Scheme 4), which are more challenging to obtain *via* formal desymmetrization of the dicarboxylic glutamic and ketoglutaric acid. Starting from **1** we achieved the synthesis of the corresponding ethyl **6** and *i*-propyl **7** esters in moderate yields of 67% and 54%, respectively. The longer alkyl chain *n*-butyl ester **8** was obtained in 69% yield, while the more challenging *t*-butyl ester **9** was isolated in 27% yield, possibly due to sterics. The corresponding "unsymmetrical" diesters **5** and **10** were obtained from ethyl ester **4** in good yields of 74% and 73%, respectively. It is also worth mentioning that except for compound **9**, all other hydroxyglutarates were isolated without the need of chromatographic purification. In addition, using hydroxyacetone as a starting material, we successfully achieved the synthesis of methyl lactate **11** in 81% yield, which is used as a green solvent for various forms of cellulose[42] and finds application in the cosmetics and food industries.[43] Furthermore, we extended the reaction scope to the synthesis of various hydroxy esters derived from steroids bearing α-hydroxyketone moiety (Scheme 3). Prednisone was successfully converted to its methyl **12a** and *i*-propyl α-hydroxyester **12b** in high yields of 89% and 93%, respectively. The products were obtained as an inseparable 3:2 mixture of diastereoisomers. The cortisone-derived esters **13a** and **13b** were achieved in 69% and 86%, respectively. In this case, the use of bulkier *i*-Pr group rendered an improved diastereoselectivity of 2:1. The C11-hydroxy steroids prednisolone and hydrocortisone rendered the corresponding α-hydroxyl esters **14a,b** and **15a,b**, in moderate yields. Methyl esters **14a** and **15a** were achieved with the same degree of diastereoselectivity of 3:2 as their C11-keto analogues **12a** and **13a**. Unexpectedly, we did not observe any diastereoselectivity for the bulkier *i*-Pr esters **14b** and **15b**. However, in this case, the diastereoisomers were readily separable by column chromatography and were isolated as individual products.

Compared to previously reported methods, the sequential establishment of the ester group provided straightforward access to "unsymmetrical" esters without troublesome "desymmetrization" reactions. Concerning the synthesis of hydroxyester derivatives of important steroids, our approach overcomes the previously used large amount of catalysts[22] and substoichiometric amounts of strong bases,[23] thus providing a sustainable route to achieve the synthesis of new biologically active compounds.

Considering the intramolecularity of the process, several pathways were taken into account and studied by means of density functional theory calculations at the PBE1PBE (PCM–MeOH)/6-31G**/6-31 + G* level of theory. The Cannizzaro hydride transfer in 1-hydroxy-1-methoxypropanone was used as

model reaction. Given the low affinity of acetonitrile and pyridine as neutral ligands for copper species, we first considered the energetics for the formation of cations $[CuPy_2]^+$ and $[Cu(MeCN)_2]^+$ from $[Cu(MeCN)_4]^+$ (Scheme 5). Both processes were deemed spontaneous, although the formation of the copper–pyridine complex was somewhat more favorable ($\Delta G_f = -14.5$ vs -6.8 kcal/mol). Nevertheless, the close energies for the formation of both species and when considering the reaction conditions (60 °C), the formation of both is likely to result in competing mechanisms. With that in mind, the transition states for Cannizzaro reaction of 1-hydroxy-1-methoxypropanone (Figure 2a) were computed considering four pathways: a) in the presence of $[CuPy_2]^+$ and pyridine as a base (**IM1**–**TS1**–**P1**); b) in the absence of any copper species, with pyridine acting as a base to assist the proton migration between the oxygen atoms (**IM2**–**TS2**–**P2**); c) in the presence of $[Cu(MeCN)_2]^+$ and pyridine as a base (**IM3**–**TS3**–**P3**), and d) in the presence of $[Cu(MeCN)_2]^+$ and absence of base (**IM4**–**TS4**–**P4**) (Figure 2b). In general, the four pathways show somewhat similar activation barriers to be overcome, lying in the 27.0–32.6 kcal/mol range. The computed transition states in which pyridine was considered as a base to assist the hydrogen migration between the oxygen atoms (**TS1**–**TS3**) show a simultaneous hydride shift between carbons. Among the four mechanisms presented, the one considering the formation of $[CuPy_2]^+$ requires a lower energy barrier (**TS1**) to be overcome, in line with the more favorable formation of such copper complex. Whilst the role of $[CuPy_2]^+$ in **TS1** not being obvious, due to the rather long distance between the oxygen atoms and copper ($d_{O-Cu} = 3.10$ and 3.40 Å), the Wiberg index analysis shows weak interactions between O•••Cu pairs. The interaction between the metal center and the hemiacetal oxygen decreases along the process ($WI_{IM1} = 0.06$ vs $WI_{P1} = 0.02$) whilst the change in the oxygen hybridization keeps the same level of interaction ($WI_{IM1} = WI_{P1} = 0.05$), being stronger during the transition state ($WI_{TS1} = 0.07$). Moreover, the energy barrier for the similar transition state **TS2** in the absence of any copper increases considerably by 15.4 kcal/mol. Considering the hypothetical intervention of $[Cu(MeCN)_2]^+$ (pathways c and d), the activation energies are comparable although the presence of pyridine (**TS3**) demands an activation barrier of 5.5 kcal/mol lower than for **TS4**. Notably, whilst $[CuPy_2]^+$ seems to have a weak interaction with any of the oxygen atoms either from carbonyl ketone or the hydroxyl group of the hemiketal in TS1, the same interaction of the deprotonated oxygen atoms with $[Cu(MeCN)_2]^+$ is stronger, according to the $d_{O-Cu} = 2.11$ Å in **TS3** and **TS4**.



Scheme 5. Calculated Gibbs free energy for the formation of copper cations.

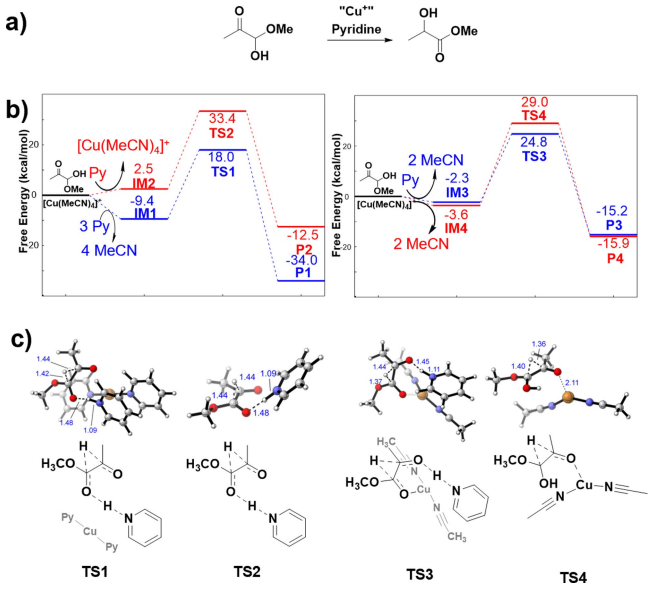
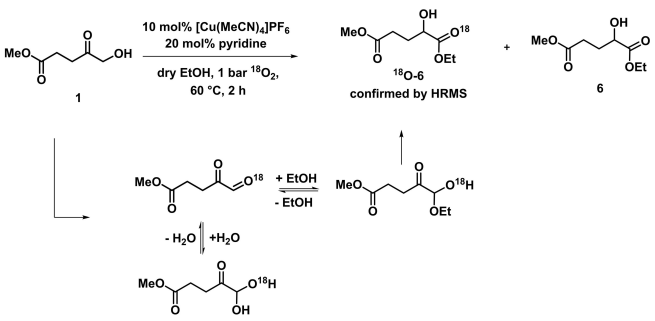


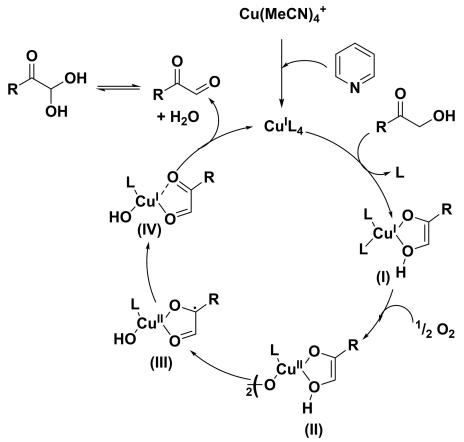
Figure 2. Energy profiles for different pathways of the Cannizzaro reaction computed at the PBE1PBE (PCM–MeOH)/6-31G**/6-31 + G* level of theory. a) Reaction scheme for the model reaction; b) Calculated Gibbs free energies for pathways a)–d) (see text for details); c) transitions states for the hydride transposition in pathways a)–d) (see text for details).

Taking all this together, and considering the reaction conditions, the four pathways herein presented might be competitive with each other and all contribute to the product formation. Nevertheless, whilst disclosure of the role of pyridine as a ligand requires further confirmation, its role as base seems undoubtful when considering the lower energy-demanding profiles for pathways a) and c) versus pathway d). Moreover, whilst the Cannizzaro process could be performed in the absence of pyridine, its presence promotes a faster product formation (Table 1, entries 7 and 9).

Additionally, we performed mechanistic studies concerning the incorporation of oxygen during the oxidation step. To this end, **1** was subjected to a tandem oxidation-intramolecular Cannizzaro reaction in dry EtOH under ^{18}O atmosphere. The resulting "unsymmetrical" diester was analyzed by high-resolution mass spectrometry (HRMS). Despite the possible exchange of the ^{18}O atom in the equilibriums of the intermediate aldehyde, the presence of **^{18}O-6** product was evident by HRMS suggesting the initial oxidation step proceeds with incorporation of oxygen (Scheme 6). A mechanism proposal for the oxidation is described below (Scheme 7), with the first step



Scheme 6. ^{18}O labeling studies.



Scheme 7. Proposed Cu-catalyzed oxidative cycle.

being the formation of a copper–ketol complex (**I**), as previously evidenced by Driscoll and Kosman.[44] Reaction of the complex with molecular oxygen results in oxidation of the metal center and formation of binuclear Cu(II) μ-peroxo species (**II**).[45–47] The homolytic fission of the O–O bond followed by abstraction of the enolic hydrogen should result in formation of a radical (**III**) that ultimately results in copper reduction with concomitant liberation of the dicarbonyl compound and water.[21] ^{18}O-incorporation in the final product might result from hydration of the dicarbonyl product, since the only water present in the mixture is a result of its dissociation from the copper complex, and the heavier C=O^{18} should accumulate over time.[48]

Conclusions

In summary, we have presented a new practical tandem oxidation-intramolecular Cannizzaro reaction specifically focused on sustainable applications. We made use of the biorenewable **KVL** synthon in the synthesis of biologically important hydroxyglutarates. By doing so, we aim at larger visibility of this interesting biorenewable synthon in sustainable organic synthesis and biorefinery. Furthermore, we utilized our findings in the synthesis of biologically active steroid derivatives. The mechanisms involved in the Cu-catalyzed tandem process were studied by both deuterium and ^{18}O labeling, and rationalized by computational means. Currently, asymmetric version of this process is investigated in our Laboratory.

Experimental Section

Materials and methods: The NMR spectra were recorded on Bruker NEO 400 (^1H at 400.1 MHz; ^{13}C at 101.2 MHz) spectrophotometer, experiments were carried out at room temperature. ^1H NMR and ^{13}C NMR chemical shifts were given in ppm and related to residual solvent peaks. ^1H signals were reported as follows: chemical shift (δ) in ppm on the δ scale, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublets, q = quartet, hept = heptet, m = multiplet), coupling constant (Hz), integration and assignment. ^{13}C NMR signals were reported as follows: chemical shift (δ) in ppm on the δ scale. The numbering of the H and C, presented in the formulas, is arbitrary. IR spectra were recorded on a Shimadzu IR Spirit FT-IR spectrometer using QATR-S as a single-reflection ATR measurement attachment. High Resolution Masss-spectra were recorded in a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo ScientificTM Q ExactiveTM Plus). The GC analyses were acquired using Shimadzu Nexis-2030 gas chromatographer with FID and single quadrupole mass detector. For computational details see SI.

Unless otherwise noted, all chemicals were purchased from commercial sources and were used without further purification. The **KVL** was obtained in 84% according to previously reported procedure.[26] With the exception of $[Cu(py)_4]PF_6$ all the used in this study Cu-catalysts were obtained from Sigma Aldrich and TCI.

Preparation of $[Cu(py)_4]PF_6$: Following a reported procedure,[49] pyridine (15 mL) was added to $[Cu(MeCN)_4]PF_6$ (500 mg, 1.34 mmol) under Argon atmosphere. The solution was stirred for 20 min, then filtered, and the filtrate was concentrated to ca. 5 mL, then kept in a freezer overnight. The precipitate was filtered off, washed with Et_2O and dried to give $[Cu(py)_4]PF_6$ in 88% yield as a greenish microcrystalline solid.

General procedure for tandem oxidation-intramolecular Cannizzaro reaction: A two-neck round-bottom flask was charged with the corresponding substrate, solvent, 10 mol% $[Cu(ACN)_4]PF_6$ and 20 mol% pyridine. The atmosphere was changed to oxygen and then stirred at 60 °C until full consumtion of the starting material by TLC. The reaction mixture was passed through a pad of neutral Al_2O_3 in order to remove the copper catalyst. The filtrate was evaporated and the residue was dissolved in DCM, filtered through a pad of Celite® and where needed further purified by column chromatography (for full experimental details see SI).

Supporting Information

The authors have cited additional references within the Supporting Information.[50–86]

Acknowledgements

The authors acknowledge the National Scientific Program "VIHREN" (grant КП-06-ДВ-1). The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the project UIDB/50006/2020 | UIDP/50006/2020 and PTDC/QUI-QOR/1131/2020. N. R. C. acknowledges FCT for the CEEC-INST/2018.. CSC-IT Center for Science Ltd, Finland is acknowledged for the allocation of computational resources. The authors are grateful to INFRAMAT project (part of the Bulgarian National Roadmap for research infrastructure, supported by the Bulgarian Ministry of Education and Science) for some of the research equipment that was used in this investigation. Dr. Rafael Gomes is acknowledged for the HRMS analysis.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

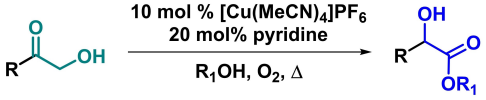
The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Homogeneous catalysis · Copper catalysis · Oxidation · Cannizzaro reaction · Biorefinery

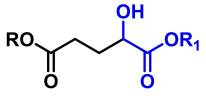
[1] H. von Pechmann, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2904–2906.
[2] R. C. Fuson, H. Gray, J. J. Gouza, *J. Am. Chem. Soc.* **1939**, *61*, 1937–1940.
[3] A. E. Russell, S. P. Miller, J. P. Morken, *J. Org. Chem.* **2000**, *65*, 8381–8383.
[4] S. J. Jin, P. K. Arora, L. M. Sayre, *J. Org. Chem.* **1990**, *55*, 3011–3018.
[5] P. R. Likhar, A. K. Bandyopadhyay, *Synlett* **2000**, *2000*, 538–540.
[6] M. S. Abaee, R. Sharifi, M. M. Mojtahedi, *Org. Lett.* **2005**, *7*, 5893–5895.
[7] M. Curini, F. Epifano, S. Genovese, M. C. Marcotullio, O. Rosati, *Org. Lett.* **2005**, *7*, 1331–1333.
[8] Y. Hayashi, Y. Sasaki, *Chem. Commun.* **2005**, *21*, 2716–2718.
[9] Z. Wang, Y. Jiang, A. Baiker, J. Huang, *ACS Catal.* **2013**, *3*, 1573–1577.
[10] Z. Wang, Y. Jiang, M. Hunger, A. Baiker, J. Huang, *ChemCatChem* **2014**, *6*, 2970–2975.
[11] K. Ishihara, T. Yano, M. Fushimi, *J. Fluorine Chem.* **2008**, *129*, 994–997.
[12] W. Wu, X. Liu, Y. Zhang, J. Ji, T. Huang, L. Lin, X. Feng, *Chem. Commun.* **2015**, *51*, 11646–11649.
[13] P. Wang, W.-J. Tao, X.-L. Sun, S. Liao, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 16849–16852.
[14] E. Schmitt, I. Schiffers, C. Bolm, *Tetrahedron Lett.* **2009**, *50*, 3185–3188.
[15] K. K. D. R. Viswanadham, M. P. Reddy, P. Sathyanarayana, O. Ravi, R. Kant, S. R. Bathula, *Chem. Commun.* **2014**, *50*, 13517–13520.
[16] K. S. Vadagaonkar, H. P. Kalmode, K. Murugan, A. C. Chaskar, *RSC Adv.* **2015**, *5*, 5580–5590.
[17] S. S. Kotha, S. Chandrasekar, S. Sahu, G. Sekar, *Eur. J. Org. Chem.* **2014**, *33*, 7451–7457.
[18] S. S. Kotha, G. Sekar, *Tetrahedron Lett.* **2015**, *56*, 6323–6326.
[19] A. Y. Dubovtsev, N. V. Shcherbakov, D. V. Dar'in, V. Y. Kukushkin, *J. Org. Chem.* **2020**, *85*, 745–757.
[20] A. M. Sakharov, I. P. Skibida, *J. Mol. Catal.* **1988**, *48*, 157–174.
[21] X. Liu, A. Qiu, D. T. Sawyer, *J. Am. Chem. Soc.* **1993**, *115*, 3239–3243.
[22] C. Arbez-Gindre, V. Berl, J.-P. Lepoittevin, *Steroids* **2003**, *68*, 361–365.
[23] H. Hosoda, H. Yokohama, T. Nambara, *Chem. Pharm. Bull.* **1984**, *32*, 1359–1364.
[24] S. Zheng, W. Smit, A. Spannenberg, S. Tin, J. G. de Vries, *Chem. Commun.* **2022**, *58*, 4639–4642.
[25] L. Zhang, X. Bi, X. Guan, X. Li, Q. Liu, B.-D. Barry, P. Liao, *Angew. Chem. Int. Ed.* **2013**, *52*, 11303–11307.
[26] M. Dangalov, A. Fernández-Figueiras, M. A. Ravutsov, E. Vakarelska, M. K. Marinova, N. R. Candeias, S. P. Simeonov, *ACS Catal.* **2023**, *13*, 1916–1925.
[27] J.-A. Losman, R. E. Looper, P. Koivunen, S. Lee, R. K. Schneider, C. McMahon, G. S. Cowley, D. E. Root, B. L. Ebert, W. G. Kaelin, *Science* **2013**, *339*, 1621–1625.
[28] X. Du, H. Hu, *Front. Cell Dev. Biol.* **2021**, *9*, 651317.
[29] R. Janke, A. T. Iavarone, J. Rine, *eLife* **2017**, *6*, e22451.
[30] L. Bunse, S. Pusch, T. Bunse, F. Sahm, K. Sanghvi, M. Friedrich, D. Alansary, J. K. Sonner, E. Green, K. Deumelandt, M. Kilian, C. Neftel, S. Uhlig, T. Kessler, A. von Landenberg, A. S. Berghoff, K. Marsh, M. Steadman, D. Zhu, B. Nicolay, B. Wiestler, M. O. Breckwoldt, R. Al-Ali, S. Karcher-Bausch, M. Bozza, I. Oezen, M. Kramer, J. Meyer, A. Habel, J. Eisel, G. Poschet, M. Weller, M. Preusser, M. Nadji-Ohl, N. Thon, M. C. Burger, P. N. Harter, M. Ratliff, R. Harbottle, A. Benner, D. Schrimpf, J. Okun, C. Herold-Mende, S. Turcan, S. Kaulfuss, H. Hess-Stumpp, K. Bieback, D. P. Cahill, K. H. Plate, D. Hänggi, M. Dorsch, M. L. Suvà, B. A. Niemeyer, A. von Deimling, W. Wick, M. Platten, *Nat. Med.* **2018**, *24*, 1192–1203.
[31] H. He, R. M. Mulhern, W. M. Oldham, W. Xiao, Y.-D. Lin, R. Liao, J. Loscalzo, *Circ. Res.* **2022**, *131*, 562–579.
[32] K. Sun, C. Tao, B. Long, X. Zeng, Z. Wu, R. Zhang, *RSC Adv.* **2019**, *9*, 32017–32020.
[33] C. Jia, K.-W. Yang, C.-C. Liu, L. Feng, J.-M. Xiao, L.-S. Zhou, Y.-L. Zhang, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 482–484.
[34] A. R. Podilapu, S. S. Kulkarni, *Org. Lett.* **2014**, *16*, 4336–4339.
[35] G. D. Glick, P. L. Toogood, X. Hu, T. D. Aicher, L. L. Celeste, X. Liu, C. B. Taylor, C. A. Van Huis (Lycera Corporation), WO2015131035 A1, **2015**.
[36] T. D. Aicher, C. A. Van Huis, A. R. Hurd, D. J. Skalitzky, C. B. Taylor, O. M. Beleh, G. Glick, P. L. Toogood, B. Yang, T. Zheng, C. Huo, J. Gao, C. Qiao, X. Tian, J. Zhang, K. Demock, L.-Y. Hao, C. A. Lesch, R. W. Morgan, J. Moisan, Y. Wang, J. Scatina, C. M. Paulos, W. Zou, L. L. Carter, X. Hu, *J. Med. Chem.* **2021**, *64*, 13410–13428.
[37] R. Nshimiyimana, T. F. Lam, S. Aggarwal, N. G. Bazan, H. E. P. Bazan, N. A. Petasis, *Tetrahedron Lett.* **2022**, *106*, 154091.
[38] R. De Clercq, M. Dusselier, B. F. Sels, *Green Chem.* **2017**, *19*, 5012–5040.
[39] M. Dusselier, P. Van Wouwe, S. De Smet, R. De Clercq, L. Verbelen, P. Van Puyvelde, F. E. Du Prez, B. F. Sels, *ACS Catal.* **2013**, *3*, 1786–1800.
[40] A. R. Battersby, K. S. Cardwell, F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1565–1580.
[41] S. Drioli, P. Nitti, G. Pitacco, L. Tossut, E. Valentin, *Tetrahedron: Asymmetry* **1999**, *10*, 2713–2728.
[42] Y. Medina-Gonzalez, P. Aimar, J.-F. Lahitte, J.-C. Remigy, *Int. J. Sustain. Eng.* **2011**, *4*, 75–83.
[43] X.-Y. Yue, H.-F. Ren, C. Wu, J. Xu, J. Li, C.-L. Liu, W.-S. Dong, *J. Chem. Technol. Biotechnol.* **2021**, *96*, 2238–2248.
[44] J. J. Driscoll, D. J. Kosman, *J. Am. Chem. Soc.* **2002**, *109*, 1765–1772.
[45] S. D. McCann, S. S. Stahl, *Acc. Chem. Res.* **2015**, *48*, 1756–66.
[46] S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234–458.
[47] C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee, W. B. Tolman, *Chem. Rev.* **2017**, *117*, 2059–2107.
[48] S. Wolfe, Z. Shi, K. Yang, S. Ro, N. Weinberg, C.-K. Kim, *Can. J. Chem.* **1998**, *76*, 114–124.
[49] S. C. Davies, M. C. Durrant, D. L. Hughes, K. Leidenberger, C. Stapper, R. L. Richards, *J. Chem. Soc., Dalton Trans.* **1997**, 2409–2418.
[50] G. Tang, H. Tian, D. Ma, *Tetrahedron* **2004**, *60*, 10547–10552.
[51] G. Galley, J. Liebscher, M. Paetzel, *J. Org. Chem.* **1995**, *60*, 5005–5010.
[52] P.-S. Chen, C.-H. Chou, *Tetrahedron* **1997**, *53*, 17115–17126.
[53] M. Xiang, A. Ghosh, M. J. Krische, *J. Am. Chem. Soc.* **2021**, *143*, 2838–2845.
[54] S. P. Simeonov, M. A. Ravutsov, M. D. Mihovilovic, *ChemSusChem* **2019**, *12*, 2748–2754.
[55] V. B. Riatto, M. M. Victor, J. F. Sousa, C. Menegola, *J. Braz. Chem. Soc.* **2019**, *30*, 149–157.
[56] Y. Wang, J. Zhao, T. Qiao, J. Zhang, G. Chen, *Chin. J. Chem.* **2021**, *39*, 3297–3302.
[57] R. Zhao, K. Ploessl, Z. Zha, S. Choi, D. Alexoff, L. Zhu, H. F. Kung, *Mol. Pharm.* **2020**, *17*, 4589–4602.
[58] E. Cheung, C. Alberti, S. Enthaler, *ChemistryOpen* **2020**, *9*, 1224–1228.
[59] H. Ohara, A. Onogi, M. Yamamoto, S. Kobayashi, *Biomacromolecules* **2010**, *11*, 2008–2015.
[60] M. L. Lewbart, V. R. Mattox, *J. Org. Chem.* **1963**, *28*, 1779–1786.
[61] T. Suzuki, H. Tada, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3831–3836.
[62] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian 16, Revision C.02, Gaussian, Inc.: Wallingford CT, **2019**.
[63] W. J. Hehre, L. Radom, P. v. R. Schleyer, J. Pople, *Ab initio molecular orbital theory*, John Wiley & Sons, New York, **1986**.
[64] R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, **1989**.
[65] J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822–8824.
[66] J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1997**, *78*, 1396–1396.
[67] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257–2261.
[68] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213–222.

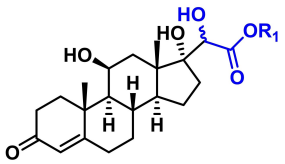
[69] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650–654.
[70] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.
[71] E. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3041.
[72] B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151–5158.
[73] M. Cossi, V. Barone, B. Mennucci, J. Tomasi, *Chem. Phys. Lett.* **1998**, *286*, 253–260.
[74] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
[75] C. Peng, P. Y. Ayala, H. B. Schlegel, M. J. Frisch, *J. Comput. Chem.* **1996**, *17*, 49–56.
[76] C. Peng, H. B. Schlegel, *Isr. J. Chem.* **1993**, *33*, 449–454.
[77] J. E. Carpenter, F. Weinhold, *J. Mol. Struct.: Theochem* **1988**, *169*, 41–62.
[78] J. E. Carpenter, PhD thesis, University of Wisconsin (Madison WI, USA), **1987**.
[79] J. P. Foster, F. Weinhold, *J. Am. Chem. Soc.* **1980**, *102*, 7211–7218.
[80] A. E. Reed, F. Weinhold, *J. Chem. Phys.* **1983**, *78*, 4066–4073.
[81] A. E. Reed, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 1736–1740.
[82] A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735–746.
[83] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926.
[84] F. Weinhold, J. E. Carpenter in *The Structure of Small Molecules and Ions* (Eds.: R. Naaman, Z. Vager), Springer, Boston, MA, **1988**, pp. 227–236.
[85] K. B. Wiberg, *Tetrahedron* **1968**, *24*, 1083–1096.
[86] M.-L. Yao, M. S. Reddy, W. Zeng, K. Hall, I. Walfish, G. W. Kabalka, *J. Org. Chem.* **2009**, *74*, 1385–1387.

Manuscript received: January 3, 2024
Revised manuscript received: February 19, 2024
Accepted manuscript online: February 20, 2024
Version of record online: ■■, ■■



- Tandem two-step process
- Applicable to the synthesis of biologically active products from biorenewable synthons and steroids


2-hydroxyglutarates


steroid derivatives

*H. Petkov, Dr. M. A. Ravutsov, M. J. Verganista, Prof. Y. N. Mitrev, Prof. N. R. Candeias, Prof. S. P. Simeonov**

1 – 8

Cu-Catalyzed Tandem Oxidation-Intramolecular Cannizzaro Reaction of Biorenewables and Bioactive Molecules

A Cu-catalyzed tandem oxidation-intramolecular Cannizzaro reaction that converts α-hydroxyketones into valuable α-hydroxyesters under mild conditions is reported. The substrate scope encompasses biorenewable synthons and complex structures, such as steroids. We provided mechanistic insights using isotope labeling and rationalization by computational means.