Tetrahedron Letters 61 (2020) 152367

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Attempted synthesis of central furopyran core of Diocollettines A *via* a Gold-Catalyzed cascade 1,6-Diyne cycloisomerization process

Venkannababu Mullapudi [a,b], Chepuri V. Ramana [a,b,*]

[a] Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India
[b] Academy of Scientific and Innovative Research (AcSIR), Anusandhan Bhawan, 2 Rafi Marg, New Delhi 110002, India

ARTICLE INFO

Article history:
Received 2 July 2020
Revised 8 August 2020
Accepted 12 August 2020
Available online 25 August 2020

Keywords:
Diocollettines A
Gold-catalysis
Alkynol cycloisomerization
1,6-Hexadiyne
Total synthesis

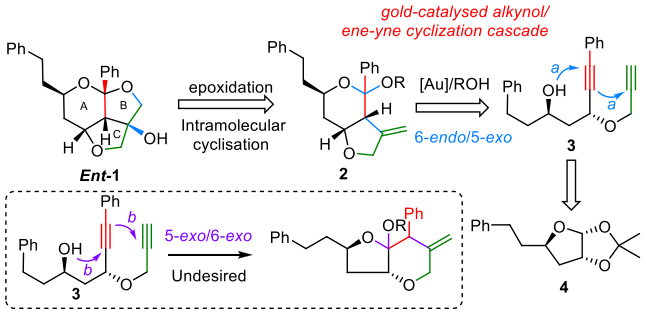
ABSTRACT

Herein, we describe an Au-catalyzed cascade diyne cycloisomerization process that was projected to construct the central furopyran bicyclic core of Diocollettines A. Our intended strategy for the annulation of the third thf ring is based on epoxidation and subsequent intramolecular acetalization. However, the initial alkynol cyclization occurred in an undesired 5-*exo*-dig mode, ultimately leading to an undesired furopyran.

Introduction

The accomplishment of the total synthesis of any natural product has its own significance in terms of the strategy, which has paved the path and choice/compatibility of functional/protecting groups and chemical transformations that contribute to this success [1]. However, in many cases, there are bottlenecks and roadblocks resulting from the incompatibility between the components, which result in the undesired reactivity/selectivity at an advanced stage [2]. As has been described by Nicolaou, each successful total synthesis was a result of learning from many unsuccessful efforts [3]. In this manuscript, we describe an unsuccessful effort towards the synthesis of the recently isolated natural product Diocollettines A (**1**), due to an undesired regioselectivity in the key skeletal construction event.

In 2017, Gao and co-workers reported the isolation of Diocollettines A (**1**) from the rhizomes of the plant *D. collettii* (belonging to the genus *Dioscorea*). Diocollettines A is a novel diaryl heptanoid possessing an unprecedented [6–5–5] fused tricyclic skeleton comprising of one tetrahydropyran ring and two tetrahydrofuran rings with five stereogenic centres [4]. The preliminary biological evaluation of Diocollettines A (**1**) against the lung cancer cell line NCL-H460 revealed promising cytotoxity (IC_{50} = 20.15 μM). Very recently, streptoglycerides A – D, having a similar unique [6–5–5] tricyclic core of Diocollettines A, were isolated from the *Streptomyces* strain and found to have anti-neuroinflammatory activity [5]. After the report on the isolation of Diocollettines A appeared, we started a program of synthesizing the natural product by following a modular strategy that employs an alcohol initiated yne-yne cyclization cascade process. Recently, the Ito and Kuwahara groups reported the enantioselective total syntheses of Diocollettines A, featuring stereoselective aldol reaction as one of the key steps [6].



Scheme 1. The proposed retrosynthetic strategy and possible modes of gold-catalyzed cyclization of 1,6-diyne **3.**

* Corresponding author at: Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India.
E-mail address: vr.chepuri@ncl.res.in (C.V. Ramana).

https://doi.org/10.1016/j.tetlet.2020.152367
0040-4039/

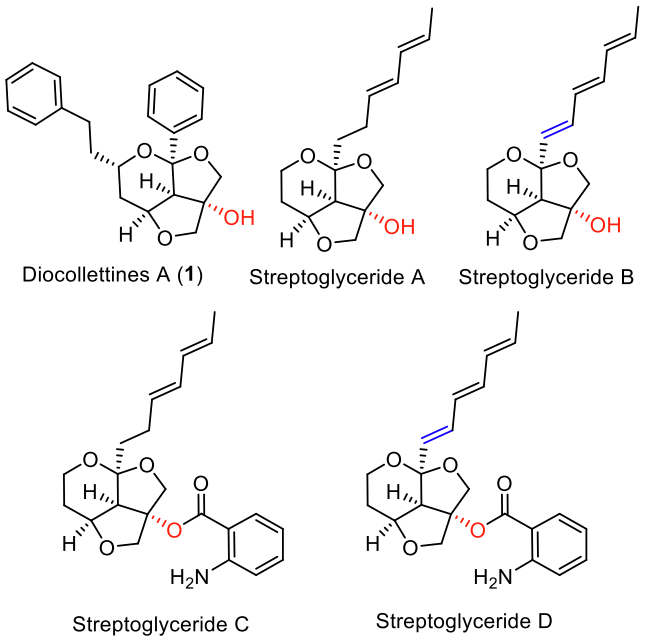


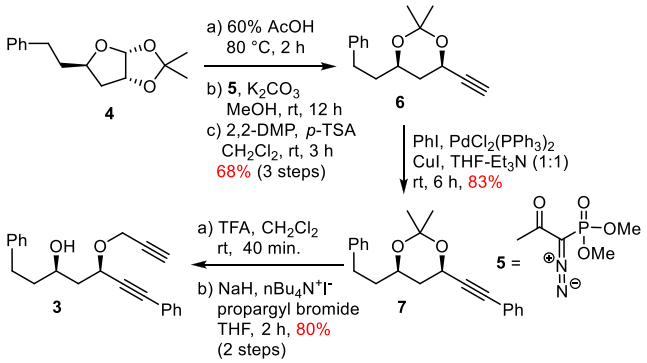
Fig. 1. Structures of [6–5–5] fused tricyclic molecules Diocollettines A (**1**) and Streptoglycerides A-D.

Results and discussion

As shown in Scheme 1, our applied key skeletal construct was inspired from the work of Yang's group on gold catalyzed tandem cyclisation of 1,6-/1,7-diynes for the synthesis of natural products like oxygenated C-15 sesquiterpeniods and Cladiellins [7,8]. We intended to employ a gold-catalyzed cascade cyclisation of the 1,6-diyne system (a dipropargyl ether) with an ether linkage, which had not been explored earlier [9]. A regioselective 6-*endo*/5-*exo* dig mode of cascade cyclisation of 1,6-diyne **3** should result in the construction of the AC ring of tricyclic diocollettines A (Fig. 1), which upon epoxidation and intramolecular ketalization is expected to deliver the natural product. However, there is a competing alternative possibility comprising of an unwanted 5-*exo*/6-*exo* dig mode cyclisation of 1,6-diyne **3** in the initial gold-catalyzed cycloisomerization [10]. Previous reports from our laboratory and others in the gold catalysed cyclisation of alkynols indicated more chances for a desired 6-*endo* selective initial alkynol cyclization (Scheme 1) [10e].

In this context, the diyne **3** has been selected as a suitable substrate to examine our hypothesis. However, as one could notice, it has the opposite configuration at the hydroxyl centers and if our approach is successful, it provides the Diocollettines A enantiomer. One of the reasons why the diyne **3** has been selected is because its synthesis from known furanoside **4** is a straightforward exercise and compound **4** can be easily prepared in 5 steps from glucose diacetonide [11] (Scheme 2).

The synthesis begins with the preparation of the known intermediate **4** following the literature procedure from glucose diacetonide (GDA). Next, compound **4** was subjected to a three-step sequence comprising of acetonide deprotection in refluxing 60% AcOH followed by the Ohira-Bestmann alkynylation of the resulting lactol and the treatment of the intermediate 1,3-*syn*-diol in the same pot with 2,2-DMP and cat. *p*-TSA in CH_2Cl_2, which afforded the target acetonide **6** in 68% yield over three steps [12]. In the ^{13}C NMR spectrum, the two distinct peaks at 19.4 ppm (Me_{axial}) and 30.2 ppm ($Me_{equatorial}$) clearly indicated the presence of 1,3-*syn*-diol acetonide. The Sonagashira coupling of alkyne **6** with iodobenzene was carried out by employing 5 mol% of bis



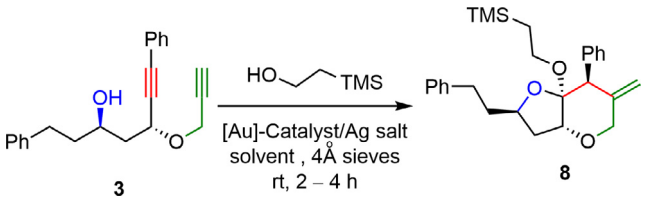
Scheme 2. Synthesis of 1,6-diyne.

(triphenylphosphine)palladium(II) dichloride and 10.0 mol% CuI in a 1:1 mixture of triethylamine and THF to obtain compound **7** in 83% yield [13]. Next, the acetonide group in compound **7** was hydrolyzed employing cat. TFA in CH_2Cl_2 and the resulting crude diol was treated with propargyl bromide in the presence of NaH and tetrabutylammonium iodide in THF at rt to afford the key 1,6-diyne **3** in 80% yield over 2 steps.

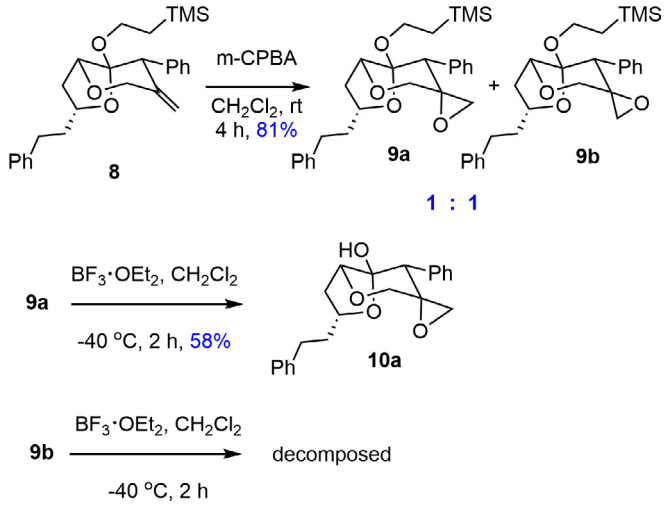
After having 1,6-diyne **3** in hand, next, the proposed gold-catalyzed cascade cyclisation was examined initially by simple gold salts AuCl and $AuCl_3$ and 2-(trimethylsilyl)ethanol as an external nucleophile. In both the cases (entries 1 and 2, Table 1) the decomposition of compound **3** was noticed. Next, we examined the cationic gold complexes in this pursuit. Initially, we examined the Au(PPh_3)Cl in the presence of $AgSbF_6$ as an additive and 2-(trimethylsilyl)ethanol as an external nucleophile in CH_2Cl_2 at room temperature. This resulted in the isolation of a new product **8** in 23% yield (entry 3, Table 1) [7d]. With this promising results, we have optimized this reaction by screening different gold catalysts and silver additives. To our delight, when the Au(PPh_3)Cl/AgOTf combination was employed as an active catalytic system in CH_2Cl_2 at room temperature, the reaction was completed in 4 h and the yield was improved to 58% yield. Further screening of solvents like CH_3CN, THF and toluene has not influenced the yield of the reaction. Since we had obtained the undesired selectivity during the initial alkynol cycloisomerization of diyne **3**, we examined several other possibilities such as placing bulkier ligand on gold, hoping that this may alter the course of cyclisation of the screened (^{i}Pr)AuCl, ^{t}BuXPhos and Au(MeCN)SbF_6. Unfortunately, in all the cases, compound **8** was obtained exclusively (see Table 1).

As mentioned above, without knowing that the undesired product was obtained, we moved to execute our proposed strategy of

Table 1
Optimization of cascade cyclisation **8**.



Entry	[Au]/Ag salt	solvent	time	Yield
1	AuCl	CH_2Cl_2	4 h	decomposed
2	$AuCl_3$	CH_2Cl_2	4 h	decomposed
3	Au (PPh_3)Cl $AgSbF_6$	CH_2Cl_2	4 h	23%
4	Au(PPh_3)Cl AgOTf	CH_2Cl_2	2 h	58%
5	Au(PPh_3)Cl AgOTf	CH_3CN	2 h	20%
6	Au(PPh_3)Cl AgOTf	THF	4 h	14%
7	^{i}PrAuCl $AgSbF_6$	CH_2Cl_2	2 h	41%
8	^{t}BuXPhos Au(MeCN)SbF_6	CH_2Cl_2	2 h	46%



Scheme 3. The epoxidation of compound **8** and the hydrolysis of the resulting epoxides.

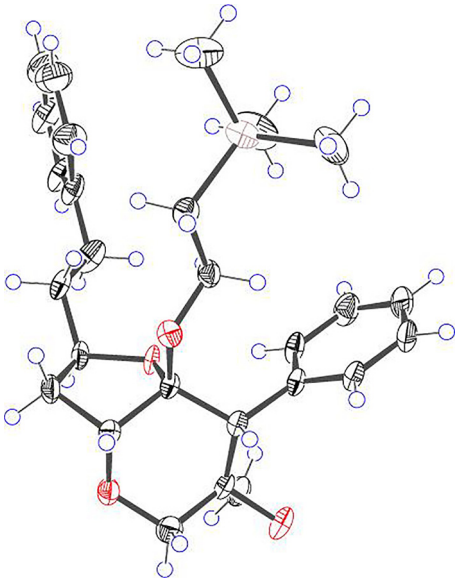


Fig. 2. Molecular Structure of Compound **9b.**

epoxidation followed by the Lewis acid catalyzed intramolecular lactol cyclisation to make the tricyclic core of diocollettines A. Towards this, compound **8** when subjected for epoxidation employing *m*-CPBA in CH_2Cl_2, resulted in a 1:1 separable mixture of diasterisomeric epoxides **9a** and **9b** in 81% yield (Scheme 3) [14].

Our initial attempts to deprotect the trimethylsilylethyl group and the cyclisation of the resultant hemiketal with epoxide to give the desired tricyclic core were not successful when using TBAF in THF at room temperature or even after prolonged heating. Next, we examined acid catalyzed epoxide opening and cyclization of **9a** and **9b** employing $BF_3.OEt_2$ (Scheme 3). Only, in case of compound **9a**, the reaction with $BF_3.OEt_2$ resulted in the isolation of a new compound **10a** and under similar conditions the decompoisition of epoxide **9b** was noticed The spectral data of the compound **10a** revealed the presence a free ketal and showed that the epoxide ring was intact (Scheme 3). Indeed, after realizing that the intramolecular ketalization through opening of the epoxide was not happening, we recorded the single crystal *X*-ray diffraction data for the other epoxide **9b** (Fig. 2), which revealed the undesired selectivity during the initial cyclization.

Conclusion

An approach comprising of gold-catalyzed cascade cyclization of a 1,6-diyne followed by epoxidation and intramolecular ketalization has been proposed for the construction of the central tricyclic core/total synthesis of Diocollettines A (**1**) and attempted. The key gold-catalyzed cascade cyclization resulted in undesired selectivity that has been realized after the failure during the cyclization step of the penultimate epoxides. Currently, work in the direction of tuning the regioselectivity and also further exploration of this novel 1,6-diyne *5-exo/6-exo* cyclization is in progress.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank CSIR, New Delhi for funding and UGC, New Delhi for the award of a Research Fellowship to V.M.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152367.

References

[1] (a) K.C. Nicolaou, Tetrahedron 59 (2003) 6683–6738;
(b) K.C. Nicolaou, S.A. Snyder, Proc. Nat. Acad. Sci. USA 101 (2004) 11929–11936.
[2] (a) M.A. Sierra, M.C. de la Torre, F.P. Cossio, More Dead Ends and Detours: En Route to Successful Total Synthesis, Wiley VCH, 2013;
(b) E.J. Sorensen, D.A. Siler, J.D. Mighion, In Strategies and Tactics in Organic Synthesis Harmata, M. Ed. Academic Press: Cambridge 9 (2013) 249–273.
[3] K.C. Nicolaou, Organic synthesis: the art and science of replicating the molecules of living nature and creating others like them in the laboratory, Proc. R. Soc. A 470 (2014) 20130690.
[4] S.S. Jing, Y. Wang, Y.M. Yan, X. Li, X.J. Li, C.C. Zhao, J.C. Sun, P.Y. Qiu, S.L. Man, W. Y. Gao, Tetrahedron Lett. 57 (2016) 3215–3217.
[5] B.K. Choi, S.Y. Park, D.K. Choi, Org. Lett. 20 (2018) 6037–6040.
[6] a) Y. Kawamoto, T. Kobayashi, H. Ito, Org. Lett. 21 (2019) 5813–5816;
b) M. Kawamoto, S. Sato, M. Enomoto, Y. Ogura, S. Kuwahara, Org. Lett. 21 (2019) 10099–10101.
[7] For selected papers on cascade [Au]-catalyzed cyclizations of 1,6-diyne cycloisomerizations via C–O and C–C bond formations see: a) Shi H, Fang L, Tan C, Shi L, Zhang W, C. Li C, Luo T, Yang Z. J. Am. Chem. Soc. 2011; 133: 14944-14947. b) Yue G, Zhang Y, Fang L, Li C-C, Luo T, Yang Z. Angew. Chem. Int. Ed. 2014; 53: 1837-1840. c) Shi H, Tan C, Zhang W, Zhang Z, Long R, Luo T, Yang Z. Org. Lett. 2015; 17: 2342-2345. d) Shi H, Tan C, Zhang W, Zhang Z, Long R, Gong J, Luo T, Yang Z J. Org. Chem. 2016; 81: 751-771. e) Vulovic B, Kolarski D, Bihelovic F, Matovic R, Gruden M, Saicic RN. Org. Lett. 2016; 18: 3886-3889.
[8] a) R. Dorel, A.M. Echavarren, Chem. Rev. 115 (2015) 9028–9072;
b) M. Abdullah, A. Asiri, S.K. Hashmi, Chem. Soc. Rev. 45 (2016) 4471–4503.
[9] (a) Hashmi SK, Weyrauch JP, Frey W, Bats, JW. Org. Lett. 2004; 6: 4391-4394. b) Hirano K, Inaba Y, Takahashi N, Shimano M, Oishi S, Fujii N, Ohno H. J. Org. Chem. 2011; 76: 1212-1227.
[10] a) J.E. Baldwin, J. Chem. Soc., Chem. Commun. 734 (1976);
b) J.E. Baldwin, R.C. Thomas, L.I. Kruse, L. Silberman, J. Org. Chem. 42 (1977) 3846–3852;
c) H. Sashida, M. Kaname, A. Nakayama, H. Suzuki, M. Minoura, Tetrahedron 66 (2010) 5149–5157;
d) I.V. Alabugin, K. Gilmore, M. Manoharan, J. Am. Chem. Soc. 133 (2011) 12608–12623;
e) S. Das, B. Induvadana, C.V. Ramana, Tetrahedron 69 (2013) 1881–1896.
[11] C.V. Ramana, N. Raghupathi, M.K. Gurjar, M.S. Chorghade, Tetrahedron Lett. 46 (2005) 4073–4075.
[12] a) S. Ohira, Synth. Commun. 19 (1989) 561–564;
b) J.C. Gilbert, U. Weerasooriya, J. Org. Chem. 48 (1983) 448–453;
c) S. Müller, B. Liepold, G.J. Roth, H.J. Bestmann, Synlett (1996) 521–522;
d) G.J. Roth, B. Liepold, S. Müller, H.J. Bestmann, Synthesis (2004) 59–62;
e) V. Mullapudi, C.V. Ramana, Asian, J. Org. Chem. 5 (2016) 417–422.
[13] M. Eckhardt, G.C. Fu, J. Am. Chem. Soc. 125 (2003) 13642–13643.
[14] M.T. Crimmins, C.S. Stauffer, M.C. Mans, Org. Lett. 13 (2011) 4890–4893.