NPC Natural Product Communications

2017
Vol. 12
No. 8
1209 - 1214

Synthesis of Natural Products and the Development of Synthetic Methodology: The Case Study of (–)-Atrop-abyssomicin C

Filip Bihelovic, Bojan Vulovic and Radomir N. Saicic*

Faculty of Chemistry, University of Belgrade, Studentski trg 16, POB 51, 11158 Belgrade 118, Serbia

rsaicic@chem.bg.ac.rs

Received: December 6th, 2016; Accepted: January 12th, 2017

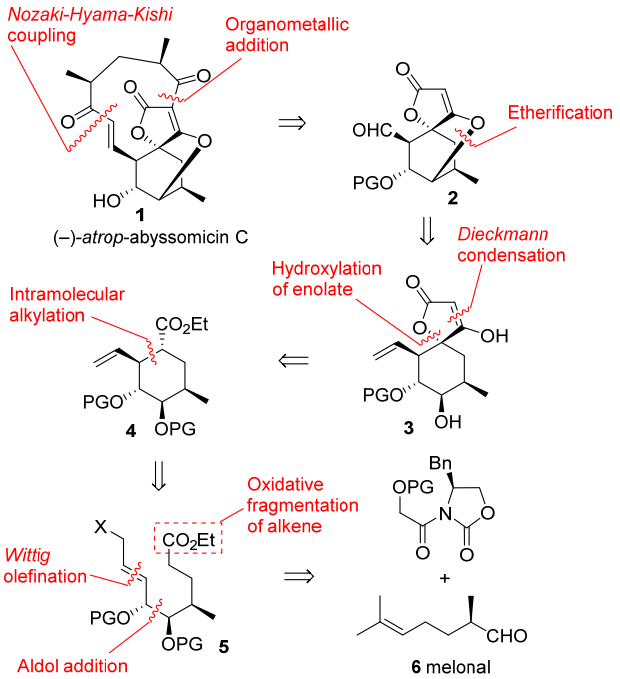
During our attempt to follow the planned synthetic route to the naturally occurring antibiotic (–)-*atrop*-abyssomicin C, we encountered two shortcomings, which forced us to reconsider our tactics and find new methods to overcome the problems. These methods turned out to be of general applicability, as demonstrated later in total syntheses of two other natural products: (+)-allokainic acid and (–)-gabosine H. The paper provides a brief account of these endeavors.

Keywords: Abyssomicin C, Kainic acids, Gabosine, Natural products, Total synthesis, Synthetic methods.

Natural products have traditionally provided a strong impetus for the development of synthetic methodology. Within 3.5 billion years of combinatorial chemistry, nature has filled a vast chemical space by myriads of molecules with highly diverse structural features. Faced with the formidable challenge of synthesizing structures of ever increasing complexity, synthetic chemists continuously improve strategy and tactics of their discipline. New ideas are often born out of necessity: failures and shortcomings in realization of initial synthetic plans are strong motifs for the development of new reactions and alternative tactical approaches, which enrich synthetic methodology. Here we would like to present our experience from the synthetic arena, where the problems encountered in the synthesis of a complex organic molecule served as a stimulus for the development of synthetic methodology and eventually enabled the syntheses of two other natural products. The aim of this paper is not to provide a detailed account on these endeavors (full details are available elsewhere), but rather to focus to the feedback between the total synthesis and synthetic methodology, as illustrated in the concrete example.

Total synthesis of (–)-atrop-abyssomicin C

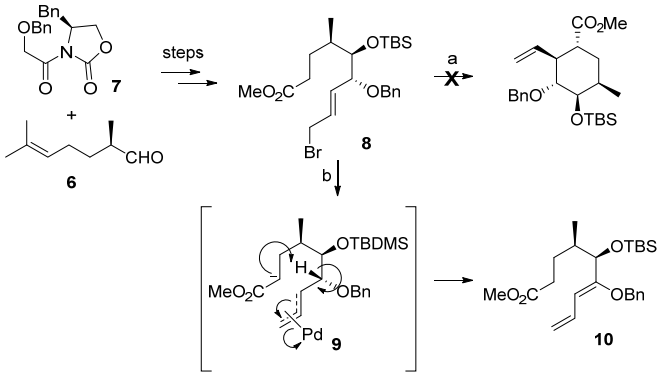
Some time ago, we embarked on a total synthesis of (–)-*atrop*-abyssomicin C (**1**) – a complex, polycyclic antibiotic with a new mechanism of action, isolated from a rare *Verrucosispora* strain collected in Japanese Sea at a depth of –289 m [1]. A combination of interesting and important biological activity and the unusual architecture immediately attracted the attention from synthetic chemists [2]. Not surprisingly, the first two syntheses of this compound used Diels-Alder reaction as a key step in the formation of a polycyclic framework, as this powerful cycloaddition allows for a rapid access to structures where cyclohexane ring is embedded in topologically complex systems [3]. However, we followed a different strategy, aiming to develop the synthesis that would (in addition to the target compound) also make available, for SAR studies, structural analogues complementary to those obtainable by the DA approach. The retrosynthetic disconnection of the 11-membered ring simplifies **1** to the tricyclic intermediate **2** (Scheme 1). This compound would be obtained by intramolecular etherification of spirotetronate **3**, on its turn obtainable from the cyclohexane derivative **4**. The formation of this latter compound by the cyclization of the suitably functionalized proenolate **5** was



Scheme 1: Retrosynthetic analysis of (–)-*atrop*-abyssomicin C.

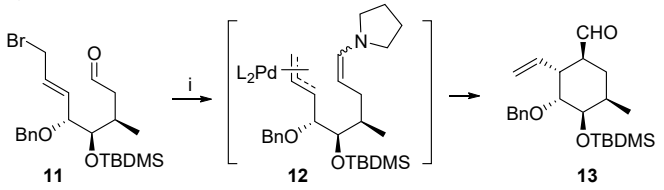
expected to proceed routinely. Two oxygen-bearing stereogenic centers in **5** would be introduced by enantioselective aldol addition, whereas the chiral methyl-bound stereocenter would be "imported" from melonal (**6**).

Starting from the Evans oxazolidinone **7** and melonal, the synthesis proceeded according to the plan until the cyclization step where, unexpectedly, we faced a serious obstacle: all attempts to effect the cyclization of ester **8** under basic conditions failed, resulting either in no reaction, or in decomposition of the starting material. Attempt to additionally activate the allylic halide leaving group via a π-allylpalladium complex, by the addition of a catalytic amount of $Pd(PPh_3)_4$ resulted in the formation of diene **10** (Scheme 2). We realized that the enolate anion **9** is too basic for the reaction



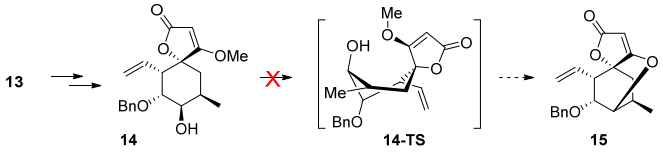
Scheme 2: Unsuccessful attempts of cyclization of the ester enolate. Reagents and conditions: a) LDA, THF, -78°C to rt; b) KHMDS, $Pd(PPh_3)_4$, THF, -78°C to rt, 87%.

with π-allylpalladium complex, and that a softer and less basic nucleophile is required. Enamines are known to react with allylic halides; however, it would be difficult to prepare an enamine that contains an allylic halide unit (due to quaternization). Therefore, we envisaged a reaction sequence that relied on double catalysis, with simultaneous formation of enamine and π-allylpalladium complex within the same molecule (*i. e.* **12**) [4]. Indeed, this approach proved fruitful, as in the presence of pyrrolidine and $Pd(PPh_3)_4$ we obtained the desired product **13** in excellent yield (Scheme 3) [5]. We considered this result not only as a solution of a particular synthetic problem, but as a proof of principle of doubly catalyzed cyclization that may have a wider methodological significance and decided to study its' scope and limitations in more detail (see below, after the part dedicated to the synthesis of *atrop*-abyssomicin C).



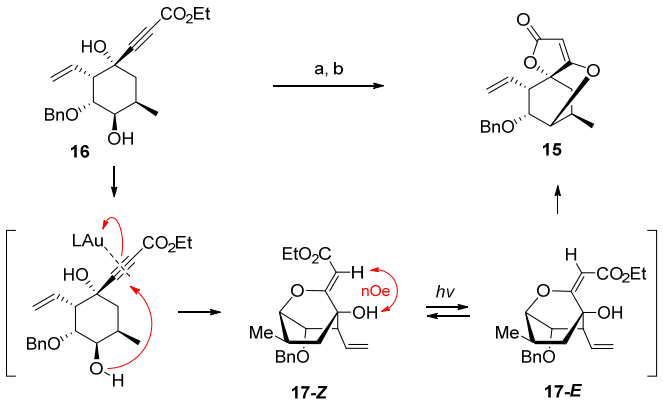
Scheme 3: Cooperatively catalyzed cyclization of aldehyde **11**. Reagents and conditions: $Pd(PPh_3)_4$ (10 mol%), pyrrolidine (1.2 equiv), THF, rt, 2 h, 90%, dr 5:1.

Aldehyde **13** was converted into spirotetronate **14** – a planned precursor for the synthesis of the tricyclic key-intermediate **15** via intramolecular etherification. However, spirotetronate **14** was reluctant towards cyclization: it did not react under mild conditions, and decomposed under more energetic ones. This unfavorable result was not quite unexpected, as the relatively rigid bicyclic substrate **14** should assume energetically unfavorable twisted boat conformation (**14-TS**) in the transition state for cyclization. Therefore, the formation of ether linkage should be accomplished at a conformationally more flexible stage of the synthesis, before the tetronate ring closure. We designed compound **16** as an appropriate substrate for the heterocyclization and turned our attention towards gold(I) complexes as suitable promoters of this reaction, in light of the well-known property of gold(I) complexes to activate alkynes toward nucleophilic addition. The use of a catalytic amount of Ph_3PAuCl in dichloromethane indeed induced cyclization, but it was followed by rearrangements. After some experimentation, we found that smooth heterocyclization of **16** could be accomplished in isopropanol as a solvent. However, gold-catalyzed cyclization produced the "wrong" geometrical isomer **17-*Z***, whereas **17-*E*** was required for the second cyclization and the tetronate formation. Isomerization could be accomplished photochemically, but the



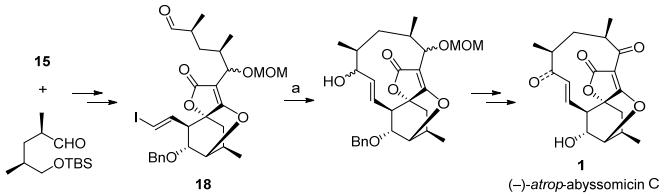
Scheme 4: Unsuccessful attempt to obtain tricyclic key intermediate **15** by cyclization of **14**.

equilibrium was not favorable. After some experimentation, we found that the key intermediate **15** could be obtained from **16** in a one-pot reaction sequence comprising gold(I)-catalyzed cyclization, followed by UV-light irradiation in the presence of sodium isopropoxide in isopropanol. Under these conditions, the initially formed **17-*Z*** underwent photolytical isomerization to **17-*E***, which was funneled into the final product **15** by a base-catalyzed lactonization (Scheme 5). In addition to allowing us to accomplish an important step in the synthesis, the efficiency of the gold(I)-catalyzed cyclization, as well as the possibility to influence the reaction outcome by varying the reaction conditions, gave us some additional ideas about expanding the scope of this reaction to the carbon-carbon bond forming process, as will be presented below.



Scheme 5: Synthesis of tricyclic tetronate **15**. Reagents and conditions: a) $Au(PPh_3)NTf_2$ (10 mol%), *i*-PrOH, 70°C; b) *hv*, quartz, *i*-PrONa, 60% (from **16**).

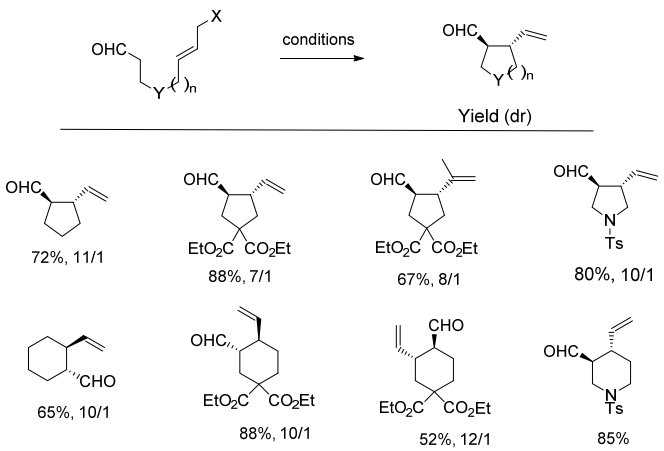
With the key-intermediate **15** in hand, the road was open toward the synthesis of the target compound. The final stage of the synthesis of *atrop*-abyssomicin C is represented in Scheme 6. The last important step of the synthesis – the closure of the 11-membered ring – was accomplished efficiently by the Nozaki-Hiyama-Kishi reaction with iodoaldehyde **18**. Subsequent functional group transformations allowed us to synthesize both the target compound **1** and another structurally related natural product – abyssomicin H (not shown) [6].



Scheme 6: Attachment of the side chain and completion of the synthesis of (–)-*atrop*-abyssomicin C. Reagents and conditions: $CrCl_2$, $NiCl_2$, DMF, rt to 45°C (90%; 96% based on recovered material).

Cooperatively catalyzed Tsuji-Trost cyclization and total synthesis of (–)-allokainic acid

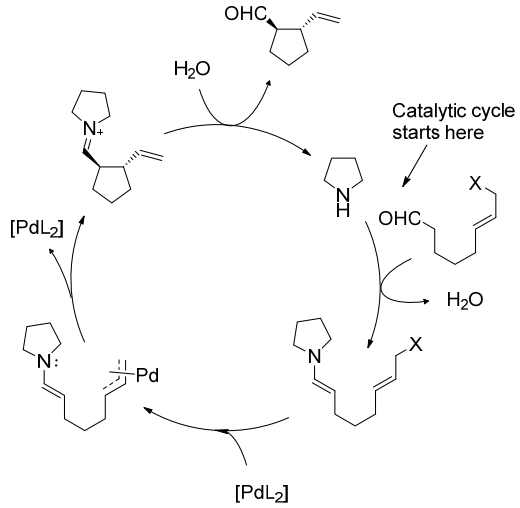
Successful closure of cyclohexane ring in **13** by a synergistic action of organocatalyst and a transition metal catalyst prompted us to extend this approach to the synthesis of other carbo- and



Scheme 7: Reagents and conditions: For X = Cl or Br: $Pd(PPh_3)_4$ (5-10 mol%), pyrrolidine (40 mol%), Et_3N (1 equiv), THF, rt, 30 min; for X = OAc: $Pd(PPh_3)_4$ (5-10 mol%), DMSO, rt, 30 min.

heterocyclic rings (in the meantime, the principle has become popular in the synthetic community and was named cooperative catalysis) [7]. Some selected examples are shown in Scheme 7 [8].

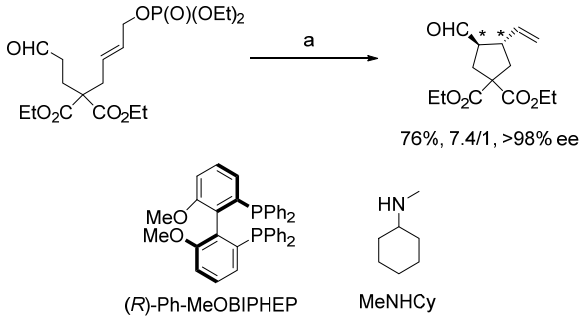
From the mechanism of the transformation, which is represented in Scheme 8, it may be concluded that both catalysts could influence the stereochemical outcome of the cyclization. This offers the possibility of enantioselective cyclization, by using chiral organocatalyst, or chiral metal catalyst, or both simultaneously.



Scheme 8: The proposed mechanism of the cooperatively catalyzed cyclization.

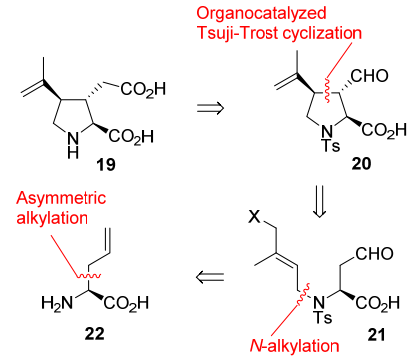
Indeed, by substituting BINAP for PPh_3, we were able to perform the cyclization as a catalytic asymmetric reaction. The highest level of asymmetric induction was obtained with BIPHEP-type catalyst, as shown in Scheme 9.

We decided to demonstrate the synthetic applicability of the cooperatively catalyzed cyclization by applying it in total synthesis of natural products. We surmised that some members of the kainic acids family could be suitable targets for the application of the new methodology. Kainates are naturally occurring amino acids of marine origin, discovered in 1953 by Takemoto and collaborators [9]. Some of them show strong biological activities, such as neuroexcitatory, insecticidal, or anthelmintic properties [10]. Our retrosynthetic analysis of allokainic acid (**19**) is represented in Scheme 10 [11]. The key step – pyrrolidine ring closure – was

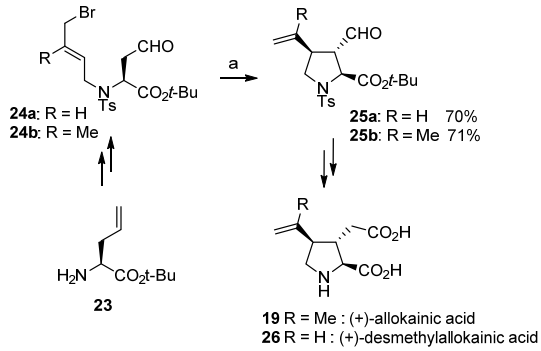


Scheme 9: Reagents and conditions: a) $Pd(OAc)_2$ (7 mol%), (*R*)-Ph-MeOBIPHEP (14 mol%), methylcyclohexylamine (5 equiv), THF, 0-7°C, 2 h.

planned to be effected by cooperatively-catalyzed cyclization. However, there is an important difference, with respect to the aforementioned, reagent-controlled reactions: here, the absolute stereochemistry of the product should be determined by a single stereogenic center in the substrate **21**; this stereochemical information would be transferred to the newly formed stereocenters in the product **20** via a well-organized, cyclic transition state (substrate-controlled reaction).



Scheme 10: Retrosynthetic analysis of (–)-allokainic acid



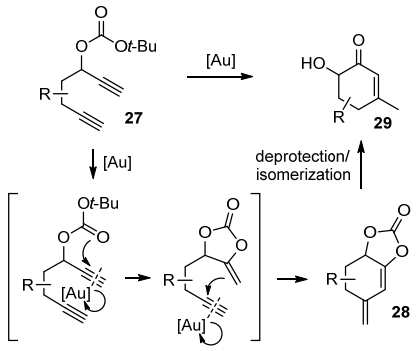
Scheme 11: Synthesis of (+)-allokainic (**19**) and (+)-desmethylallokainic (**26**) acids. Reagents and conditions: a) $[Pd(PPh_3)_4]$ (7 mol %), pyrrolidine (50 mol %), Et_3N (1.25 mol equiv), THF, rt, 2 h.

The pivotal point of the synthesis is represented in Scheme 11. Optically enriched allylglycine **23**, prepared by enantioselective alkylation of glycine derivative under chiral phase transfer catalysis [12], was converted into the cyclization precursor **24** in 5 steps (37%). In addition to **24b**, desmethyl derivative **24a** was also prepared, for the synthesis of non-natural desmethylallokainic acid **26**. Under the conditions of cooperative catalysis, both precursors (**24a** and **b**) cyclized and gave the corresponding pyrrolidine derivatives (**25a** and **25b**, respectively) in good yields and

acceptable diastereoselectivity (10/1/1; minor diastereoisomers not shown). These were subsequently converted into (+)-allokainic acid (**19**) and (+)-desmethylallokainic acid (**26**) in 7 conventional steps (42-46%). The optical purity of **19** was identical to the starting compound **22**, showing that no isomerization/epimerization occurred during the synthetic sequence. In this way we demonstrated that cooperative catalysis under substrate control can be efficiently applied in stereoselective syntheses of natural products.

Domino reactions catalyzed by gold(I) complexes and total synthesis of (–)-gabosine H

The second key reaction in the synthesis of (–)-*atrop*-abyssomicin C was the gold(I)-catalyzed cyclization of ynol **16** [13]. In the course of synthesis, the initial cyclic vinylgold intermediate was protolytically converted into vinyl ether **17**, and subsequently transformed toward the target molecule. However, we surmised that vinyl ether intermediate (and structurally related species) could undergo further useful reactions, other than protolysis: with suitably positioned second alkyne bond, the initially formed vinyl ether could undergo carbocyclization. The transient enol carbonate structural unit could also be formed from propargylic carbonates [14], so we decided to prepare 1,6-diynes of type **27**, assuming that these should be good substrates for a gold(I)-catalyzed domino reaction, as represented in Scheme 12. The product of the domino-cyclization would be enol carbonate **28** – a latent form of synthetically useful hydroxycyclohexenone structure **29**.

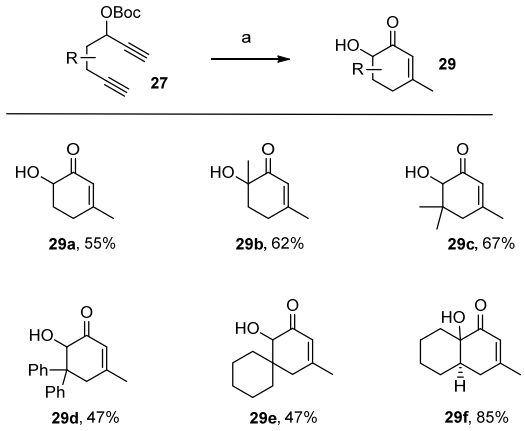


Scheme 12: The blueprint of gold(I)-catalyzed domino reaction of 1,6-diynes.

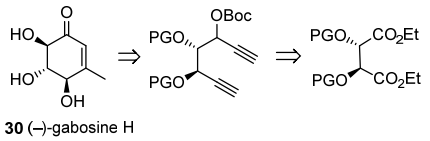
Several 1,6-diynes of type **27** are synthesized and submitted to the cyclization conditions. Gratifyingly, a number of hydroxycyclohexenones were obtained in moderate to good yields, including spiro and condensed bicyclic systems. The results of these experiments are shown in Scheme 13. However, the reaction proved unsuitable for the synthesis of five- and seven-membered rings and, apparently, limited to terminal alkynes.

We were interested to verify whether the described cyclization protocol could be applied in synthesis of highly functionalized, oxygenated molecules [15], which would strongly support its synthetic applicability. To this aim, we targeted (–)-gabosine H (**30**) [16] – a member of the growing family of carbasugar-type bacterial metabolites which has attracted considerable attention from the chemical community [17]. According to the newly developed cyclization method, the retrosynthetic analysis of the compound could follow the blueprint represented in Scheme 14, using tartric ester as a suitable optically pure starting material.

Thus, stating from D-(–)-diethyl tartrate, the cyclization precursor **32** was prepared *via* the known aldehyde **31** [18], as an unseparable

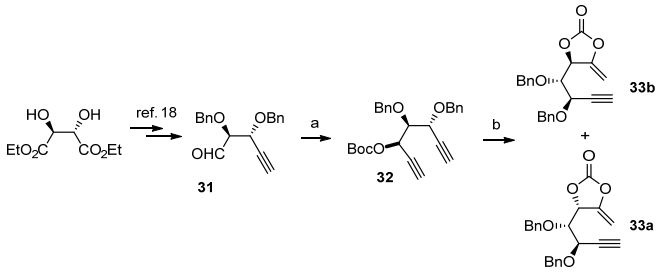


Scheme 13: Gold(I)-catalyzed domino reaction of 1,6-diynes: Reagents and conditions: a) JohnPhosAuCl (5 mol%), $AgSbF_6$ (20 mol%), DCE, rt.

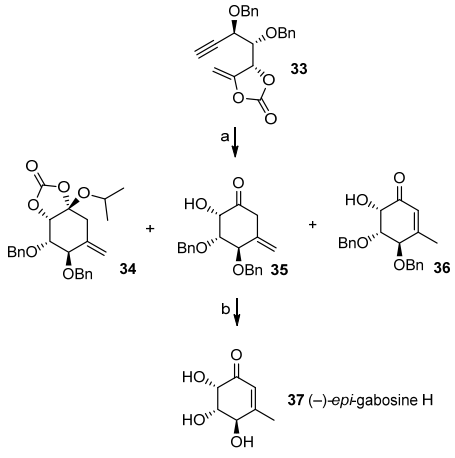


Scheme 14: Retrosynthetic analysis of (–)-gabosine H (**30**).

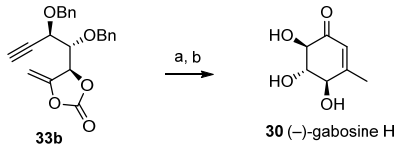
mixture of diastereoisomers (Scheme 15). These were submitted to the conditions of gold(I)-catalyzed monocyclization, to give enolcarbonates **33a** and **33b**, which were separated by chromatography and separately treated with the gold(I) catalyst.



Scheme 15: Synthesis of the cyclization precursors **33a** and **33b**. Reagents and conditions: a) *i*) HCCMgBr, Et_2O, 0°C; *ii*) Boc_2O, DMAP, CH_2Cl_2, 91% (over 2 steps); b) $Ph_3PAuNTf_2$ (5 mol %), CH_2Cl_2, rt, 80 min; then chromatographic separation, 76%.



Scheme 16: Synthesis of (–)-*epi*-gabosine H (**37**). Reagents and conditions: a) JohnPhosAuCl (2.5 mol %), $AgSbF_6$ (10 mol %), *i*-PrOH (1.9 equiv), DCE, rt, 9 h; b) BCl_3, CH_2Cl_2, 0°C, 15 min, 61% (over 2 steps).



Scheme 17: Synthesis of (–)-gabosine H (**30**). Reagents and conditions: a) JohnPhosAuCl (8 mol %), $AgSbF_6$ (32 mol %), *i*-PrOH (1.9 equiv), DCE, rt, 24 h; b) BCl_3, CH_2Cl_2, 0°C, 15 min (25% over two steps).

Upon exposure to gold(I) catalyst, **33a** gave a mixture of 3 products (**34**, **35** and **36**). This was not a complication (from the synthetic point of view), as the mixture was not separated, but directly treated with BCl_3, where all three intermediates converged into (–)-*epi*-gabosine H (**37**) in a very good yield (Scheme 16).

However, the cyclization of another diastereoisomer (**33b**) turned out to be slower, giving place to some side reactions (Au(I)-catalyzed hydration of the triple bond). By applying the same reaction sequence as for **33a**, enol-carbonate **33b** was converted into (–)-gabosine H (**30**) in 25% overall yield (Scheme 17).

We hope to have provided an illustrative example of the feedback between the natural product synthesis and the development of synthetic methodology. We also hope that our future endeavors in the former field will bring about new methodological advances.

References

[1] Bister B, Bischoff D, Ströbele M, Riedlinger J, Reicke A, Wolter F, Bull AT, Fiedler HP, Süssmuth RD. (**2004**) Abyssomicin C—A polycyclic antibiotic from a marine Verrucosispora strain as an inhibitor of the *p*-aminobenzoic acid/tetrahydrofolate biosynthesis pathway. *Angewandte Chemie International Edition*, ***43***, 2574-2576.

[2] For a chapter on abyssomicins in the book, see: Nicolaou KC, Chen JS: *Classics in Total Synthesis III*, Wiley VCH, Veinheim, 2011.

[3] (a) Zapf CW, Harrison BA, Drahl C, Sorensen EJ. (**2005**) A Diels–Alder macrocyclization enables an efficient asymmetric synthesis of the antibacterial natural product abyssomicin C. *Angewandte Chemie International Edition*, ***44***, 6533-6536; (b) Nicolaou KC, Harrison ST (**2006**) Total synthesis of abyssomicin C and atrop-abyssomicin C. *Angewandte Chemie International Edition*, ***45***, 3256-3260; (c) Nicolaou KC, Harrison ST. (**2007**) Total synthesis of abyssomicin C, atrop-abyssomicin C, and abyssomicin D: Implications for natural origins of atrop-abyssomicin C. *Journal of the American Chemical Society*, ***129***, 429-440; (d) Nicolaou KC, Harrison ST, Chen JS. (**2009**) Discoveries from the abyss: The abyssomicins and their total synthesis. *Synthesis*, 33-42.

[4] For the first example of combination of enamine catalysis with π-allylpalladium complexes for the intermolecular alkylation of aldehydes, see: Ibrahem I, Cordova A. (**2006**) Direct Catalytic Intermolecular α-Allylic Alkylation of Aldehydes by Combination of Transition-Metal and Organocatalysis. *Angewandte Chemie International Edition*, ***45***, 1952-1956.

[5] Bihelovic F, Matovic R, Vulovic B, Saicic RN. (**2007**) Organocatalyzed cyclizations of π-allylpalladium complexes: A new method for the construction of five and six-membered rings. *Organic Letters*, ***9***, 5063-5066.

[6] (a) Bihelovic F, Saicic RN. (**2012**) Total synthesis of (-)-*atrop*-abyssomicin C, *Angewandte Chemie International Edition*, ***51***, 5687-5691; (b) Bihelovic F, Karadzic I, Matovic R and Saicic RN. (**2013**) Total synthesis and biological evaluation of (-)-*atrop*-abyssomicin C, *Organic & Biomolecular Chemistry*, ***11***, 5413-5424.

[7] For review articles on cooperative catalysis, see: (a) Shao Z, Zhang H. (**2009**) Combining transition metal catalysis and organocatalysis: a broad new concept for catalysis. *Chemical Society Reviews*, ***38***, 2745-2755; (b) Zhong C, Shi X. (**2010**) When Organocatalysis Meets Transition-Metal Catalysis. *European Journal of Organic Chemistry*, 2999-3025; (c) Patil NT, Shinde VS, Gajula B. (**2012**) A one-pot catalysis: the strategic classification with some recent examples. *Organic & Biomolecular Chemistry*, ***10***, 211-224; (d) Du Z, Shao Z. (**2013**) Combining transition metal catalysis and organocatalysis – an update. *Chemical Society Reviews*, ***42***, 1337-1378; (e) Inamdar SM, Shinde VS, Patil NT (**2015**) Enantioselective cooperative catalysis. *Organic & Biomolecular Chemistry*, ***13***, 8116-8162; (f) Afewerki S, Cordova A. (**2016**) Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chemical Reviews*, ***116***, 13512-13570.

[8] Vulovic B, Bihelovic F, Matovic R, Saicic RN. (**2009**) Organocatalyzed Tsuji–Trost reaction: a new method for the closure of five- and six-membered rings. *Tetrahedron*, ***65***, 10485-10494.

[9] Murakami S, Takemoto T, Shimizu Z. (**1953**) Studies on the effective principles of *Digenea simplex Aq*. *Journal of the Pharmaceutical Society of Japan*, ***73***, 1026-1028.

[10] For a review article on kainoids, see: Parsons AF. (**1996**) Recent developments in kainoid amino acid chemistry. *Tetrahedron*, ***52***, 4149-4174.

[11] For a review article on syntheses of allokainic acid, see: Bhat C, Kumar A. (**2015**) Synthesis of Allokainic acid: A review. *Asian Journal of Organic Chemistry*, ***4***, 102-115.

[12] Lygo B, Wainwright PG. (**1997**) A new class of asymmetric phase-transfer catalysts derived from Cinchona alkaloids — Application in the enantioselective synthesis of α-amino acids. *Tetrahedron Letters*, ***38***, 8595-8598.

[13] For the most recent books and selected reviews on gold-catalyzed reactions, see: (a) *Gold Catalysis. An Homogeneous Approach.* Catalytic Science Series, Vol. 13, Toste FD, Michelet V, Eds.; Imperial College Press, Singapore, 2014; (b) Gagosz F.: Golden Opportunities in the Synthesis of Natural Products and Biologically Active Compounds. In *Modern Tools for the Synthesis of Complex Bioactive Molecules*, Cossy J, Arseniyadis S, Eds.; J. Wiley & Sons Inc., 2012, p. 111-154; (c) Pflästerer D, Hashmi SK. (**2016**) Gold catalysis in total synthesis – recent achievements. *Chemical Society Reviews, **45***, 1331-1367; (d) Fürstner A. (**2014**) From Understanding to Prediction: Gold- and Platinum-Based π-Acid Catalysis for Target Oriented Synthesis. *Accounts of Chemical Research*, ***47***, 925-938; (e) Ranieri B, Escofet I, Echavarren AE. (**2015**) Anatomy of gold catalysts: facts and myths. *Organic & Biomolecular Chemistry, **13***, 7103-7118; (f) Wang Y-M, Lackner AD, Toste FD. (**2014**) Development of Catalysts and Ligands for Enantioselective Gold Catalysis. *Accounts of Chemical Research*, ***47***, 889-901.

[14] (a) Buzas K, Istrate FM, Gagosz F. (**2009**) Gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates. *Tetrahedron*, ***65***, 1889-1901; (b) Buzas K, Gagosz F. (**2006**) Gold(I)-Catalyzed Formation of 4-Alkylidene-1,3-dioxolan-2-ones from Propargylic *tert*-Butyl Carbonates. *Organic Lett*ers, ***8***, 515-518.

[15] When this research was underway, Li, Luo, Yang and collaborators reported the sequential cyclization of 1,7-diynes leading to *exo*-methylene cyclohexene derivatives, and applied it in several elegant syntheses: (a) Shi H, Fang L, Tan C, Shi L, Zhang W, Li C-c, Luo T, Yang Z. (**2011**) Total Syntheses of Drimane-Type Sesquiterpenoids Enabled by a Gold-Catalyzed Tandem Reaction. *Journal of the American Chemical Society*, ***133***, 14944-14947. (b) Yue G, Zhang Y, Fang L, Li C-c, Luo T, Yang Z. (**2014**) Collective Synthesis of Cladiellins Based on the Gold-Catalyzed Cascade Reaction of 1,7-Diynes. *Angewandte Chemie International Edition*, ***53***, 1837-1840.

[16] Isolation and structure elucidation: (a) Tatsuta K, Tsuchiya T, Mikami N, Umezawa S, Umezawa H, Naganawa H. (**1974**) KD16-U1, A new metabolite of streptomyces: isolation and structural studies. *The Journal of Antibiotics*, ***27***, 579–586; (b) Takeuchi T, Chimura H, Hamada M, Umezawa H, Yoshioka O, Oguchi N, Takahashi Y, Matsuda AJ. (**1975**) A glycoxalase I inhibitor of a new structural type produced by *streptomyces*. *The Journal of Antibiotics*, ***28***, 737–742; (c) Müller A, Keller-Schierlein W, Bielicki J, Rak G, Stümpfel J, Zähner H. (**1986**) Stoffwechselprodukte von Mikroorganismen. 237. Mitteilung. (2*S*, 3*R*, 4*R*, 6*R*)-2,3,4-Trihydroxy-6-methylcyclohexanon aus zwei Actinomyceten-Stämmen. *Helvetica Chimica Acta*, ***69***, 1829–1832.

[17] (a) For a review article on gabosines, see: Mac DH, Chandrasekhar S, Gree R. (**2012**) Total Synthesis of Gabosines. *European Journal of Organic Chemistry*, 5881-5895; (b) For the first total synthesis of gabosine H, see: Prasad KR, Kumar SM. (**2011**) Total Synthesis of Gabosine H. *Synlett*, 1602-1604.

[18] Fourriere G, Leclerc E, Quirion J-C, Pannecoucke XJ. (**2012**) Synthesis of *exo*-methylenedifluorocyclopentanes as precursors of fluorinated carbasugars by 5-*exo*-*dig* radical cyclization. *Journal of Fluorine Chemistry*, ***134***, 172-179.