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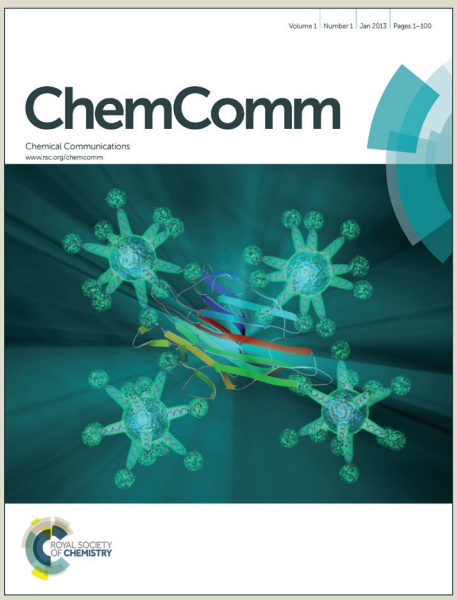

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ARTICLE TYPE

Concise Synthesis of the Tricyclic Skeleton of Crotobarin and Crotogoudin via a Gold-catalyzed Cycloisomerization Reaction

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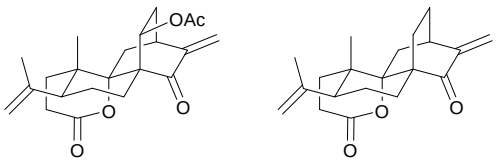
A concise synthesis of the tricyclic skeleton of crotobarin and crotogoudin via gold-catalyzed 1,6-enyne cycloisomerization reaction is reported.

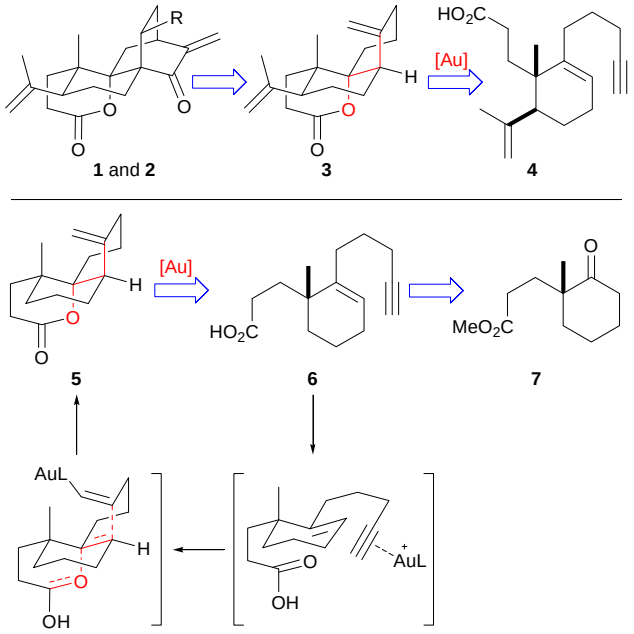
Crotobarin (**1**) and crotogoudin (**2**), two closely related 3,4-*seco*-atisane diterpenes, were isolated by Vincent Dumontet and Philippe Rasoanaivo from two Madagascan plants *C. barorum* Leandri and *C. goudotii* Baill in 2010. They showed strong cytotoxic activities against the P388 murine lymphocytic leukemia cell line, and arrested the cells at the G2/M growth stage in the K562 human leukemia cell line.[1] The structural characteristics of crotobarin and crotogoudin feature a congested tetracyclic ring system containing a bicyclo[2.2.2]octane moiety and four contiguous stereocenters including three contiguous quaternary carbon center on the tetracyclic skeleton (Fig. 1), which is highly challenging for the synthesis. The unique structural features and promising biological profiles of crotobarin and crotogoudin make them attractive targets for total synthesis.[2] Recently, Carreira and co-workers reported the first total synthesis of (+)-crotogoudin (**2**), featuring a novel radical cyclopropane-opening/annulation/elimination cascade, and they also determined the absolute configurations of the natural products.[2a] Herein we report a concise synthesis of the tricyclic skeleton of crotobarin (**1**) and crotogoudin (**2**) via gold-catalyzed cycloisomerization reaction.



(+)-crotobarin **(1)** (+)-crotogoudin **(2)**

Fig. 1 Structure of (+)-crotobarin and (+)-crotogoudin.

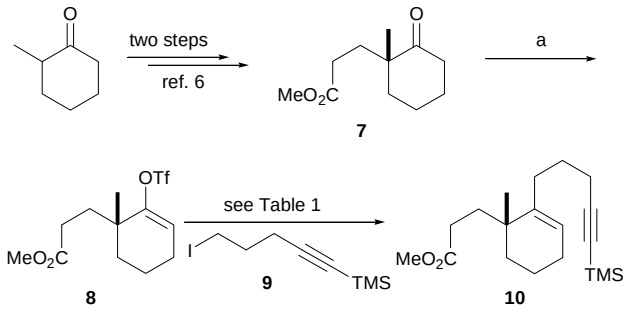
Our retrosynthetic analysis is illustrated in Scheme 1. We envisioned that **1** and **2** could be assembled from tricyclic precursor **3** through functional-group manipulations. The tricyclic compound **3** could be constructed from 1,6-enyne acid **4** by using the recently developed gold-catalyzed cyclization[3,4] of substituted 1,6-enyne with carboxylate trap.[5] In order to examine the feasibility of this key reaction quickly, we designed a model reaction by removing the isopropenyl group on the compound **3**. Thus, the simplified structure **5** could be obtained from 1,6-enyne acid **6** based on the mechanism proposed by Fürstner and co-workers, in which an anti addition of the alkyne and the carboxylate to the two sides of the alkene was generated most likely through a highly ordered, chair-like transition state.[5a] In turn, the corresponding 1,6-enyne acid **6** could be prepared from the known keto-ester **7** by a sequence of enol triflate formation, Negishi cross-coupling reaction, and hydrolysis.



Scheme 1 Retrosynthetic analysis of (+)-crotobarin and (+)-crotogoudin.

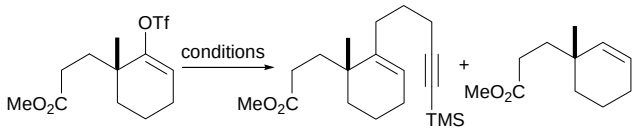
Our synthesis commenced with the known ketoester **7**, which was prepared from commercially available 2-methylcyclohexanone via the asymmetric Michael addition with methyl acrylate developed by d'Angelo and co-workers (Scheme 2).[6] Initial attempts to transform ketoester **7** to the enol triflate **8** chemo-selectively with trifluoromethanesulfonic anhydride in the presence of bases such as 4-methyl-2,6-di-*tert*-butylpyridine (DTBMP)[7] only provided the desired product **8** in low yield, along with many byproducts. Reaction of keto-ester **7** with *N*-phenyl-bis(trifluoromethanesulfonamine) ($PhNTf_2$) in the presence of LDA, LiHMDS or NaHMDS gave the same results. Interestingly, the reaction proceeded smoothly when KHMDS[8] was employed as the base and gave the desired product **8** in 75%

yield.



Scheme 2 Synthesis of the intermediate **10**. *Reagents and conditions*: (a) KHMDS, THF, -78 ºC, 30 min; $PhNTf_2$, THF, then rt, overnight, 75%.

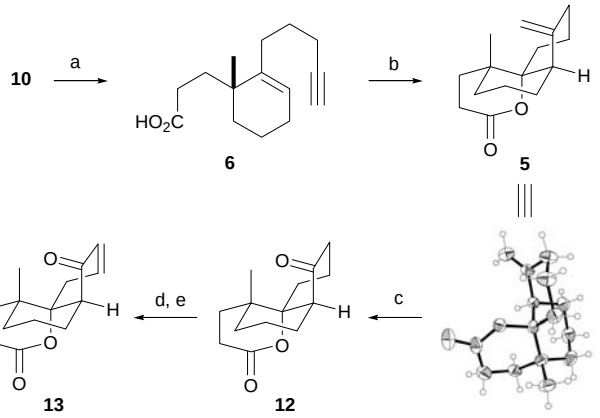
Table 1 Optimizations of the conditions of Negishi coupling reaction



entry	conditions	yield [a] of **10**	ratio[b] **10**:**11**
1	Zn, TMSCl, **9** 1,2-dibromoethane $Pd(PPh_3)_4$ (0.1 equiv.) T = 70 ºC, C = 0.05M	28%	1:1.5
2	Zn, TMSCl, **9** 1,2-dibromoethane $Pd(PPh_3)_4$ (0.5 equiv.) T = 70 ºC, C = 0.05 M	8%	1:5
3[c]	Zn, TMSCl, **9** 1,2-dibromoethane $Pd(PPh_3)_4$ (0.02 equiv.) T = 70 ºC, C = 0.05 M	51%	1.1:1
4	Mg, $ZnCl_2$, **9** $Pd(PPh_3)_4$ (0.1 equiv.) T = 70 ºC, C = 0.05 M	62%	5.2:1
5	Mg, $ZnCl_2$, **9** $Pd(dppf)Cl_2$ (0.1 equiv.) T = 70 ºC, C = 0.05 M	91%	20:1
6	Mg, $ZnCl_2$, **9** $Pd(dppf)Cl_2$ (0.05 equiv.) T = 70 ºC, C = 0.1 M	95%	30:1

T = temperature. C = concentration. [a] isolation yield. [b] measured by NMR. [c] base on the recovery of the starting material.

Subsequent Negishi coupling of the sterically hindered enol triflate **8** with the alkylzinc reagent under various reaction conditions were examined, and some of the representative results are shown in Table 1. Initially, the alkylzinc reagent was prepared from alkyl iodide **9** following the method developed by Knochel (Table 1, entries 1-3).[9] Negishi coupling with **8** using 10 mol% of the commonly employed $Pd(PPh_3)_4$ as catalyst provided the desired product 1,6-enyne ester **10** in 28% yield along with the de-triflated olefin **11** in 42% yield, which could not be separated by column chromatography (entry 1). The byproduct **11** was caused by the well-known hydridopalladium species generated by *β*-hydride elimination from diorganopalladium complex. When the amount of catalyst was increased, the desired product was obtained in only 8% yield (entry 2). However, decreasing the amount of catalyst could enhance the yield of product and reduce the ratio of the byproduct with some starting material recovered (entry 3). It has been reported that the use of magnesium-zinc transmetalation method for the preparation of the alkylzinc compounds has a higher efficiency without producing the dimmer of the alkyl iodide **9**.[10] Thus, the use of this method for the preparation of the alkylzinc compounds was carried out. To our delight, both the ratio and yield of the product **10** were improved dramatically under the same conditions (entry 4). $Pd(dppf)Cl_2$ has been recognized as an excellent catalyst for cross-coupling since it can suppress the reduction of halides.[11] After exchanging the catalyst to $Pd(dppf)Cl_2$, the yield of desired product was significantly increased to 91% (entry 5). The amount of catalyst and other reaction concentrations were further optimized. We eventually found that the optimal condition was 5 mol% $Pd(dppf)Cl_2$ in THF (C = 0.1 M), which provided the desired 1,6-enyne ester **10** in 95% yield (entry 6).

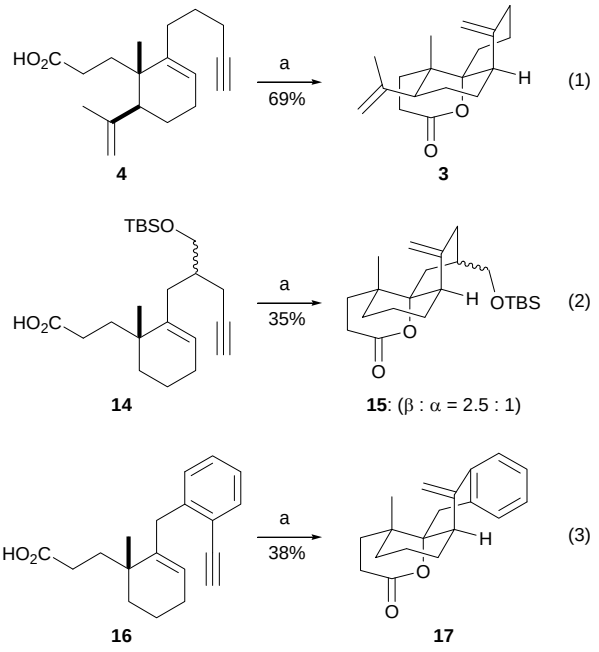


Scheme 3 Synthesis of the tricyclic skeleton of crotobarin and crotogoudin. *Reagents and conditions*: (a) LiOH, THF/H_2O = 3:1, rt, 16 h, quantitative; (b) [$AuCl(Ph_3P)$], AgOTf, CH_2Cl_2, rt, 1 h, 70%; (c) O_3, MeOH, -78 ºC, then Me_2S, 6 h, 75%; (d) PhSeCl, *p*-TsOH, EtOAc, 0 ºC, 2.5 h, then rt, 1.5 h; (e) H_2O_2, CH_2Cl_2, rt, 45 min, 53% (steps d and e).

Hydrolysis of methyl ester and deprotection of trimethylsilyl group of **10** with LiOH furnished the 1,6-enyne acid **6** in quantitative yield. With the key intermediate **6** in hand, we set out to investigate the gold-catalyzed cycloisomerization reaction. Treatment of **6** with [$AuCl(Ph_3P)$] and $AgSbF_6$ in CH_2Cl_2 could provide the desired product **5** in 50% yield. Further optimization of the reaction conditions showed that the silver salt played an important role. When AgOTf was used, the desired product **5** could be obtained in 70% yield. Control experiment indicated that this cycloisomerization reaction is "pure" Au(I)-promoted reaction.[12] The structure of **5** was unequivocally confirmed by X-ray crystallography analysis. Ozonization of the terminal olefin **5** in methanol afforded ketone **12** in 75% yield. Finally, treatment of ketone **12** with PhSeCl and *p*-TsOH in EtOAc followed by oxidation with H_2O_2 afforded the conjugated ketone **13** in 53% overall yield.[13]

After the success of model reaction, we set out to investigate the synthesis of the tricyclic skeleton **3** via this gold-catalyzed cycloisomerization reaction of compound **4** (Scheme 4, eqn (1)). Gratefully, the reaction also showed good compatibility with the isopropenyl side chain, and the desired product **3** was obtained in 69% yield, which could lay the groundwork to achieve the total synthesis of crotobarin and crotogoudin. Furthermore, 1,6-enyne

acids **14** and **16** with functionalized side chains including aryl and alkyl groups gave the corresponding products **15** and **17** in moderate yields, respectively. Compound **15** could be used as the model to construct the bridge ring of these natural products.



Scheme 4 *Reagents and conditions*: (a) [AuCl(Ph$_3$P)], AgOTf, CH_2Cl_2, rt, 1 h.

In conclusion, we have succeeded in synthesizing the tricyclic skeleton **3** bearing most of the components of crotobarin and crotogoudin. The present synthesis features a chemo-selective enol triflate formation, a sterically hindered Negishi cross-coupling reaction, and a gold-catalyzed 1,6-enyne cycloisomerization reaction. We also examined this strategy with other substrates, they all gave good results. Further studies toward the total synthesis of crotobarin and crotogoudin using this strategy are currently ongoing in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and copies of ^{1}H & ^{13}C NMR. See DOI: 10.1039/b000000x/

1 O. L. Rakotonandrasana, F. H. Raharinjato, M. Rajaonarivelo, V. Dumontet, M. T. Martin, J. Bignon and P. Rasoanaivo, *J. Nat. Prod.*, 2010, **73**, 1730.

2 (a) S. Breitler and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2013, **52**, 11168; (b) D. M. Ushakov and M. E. Maier, *Synlett*, 2013, 705.

3 For selected reviews, see: (a) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **44**, 7896; (b) A. Fürstner and P.W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410; (c) A. Hoffman-Rgder and N. Krause, *Org. Biomol. Chem.*, 2005, **3**, 387; (d) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395; (e) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (f) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (h) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (i) N. Bongers and N. Krause, *Angew. Chem., Int. Ed.*, 2008, **47**, 2178.

4 For selected examples of synthetic applications: (a) Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.*, 2006, **128**, 10352; (b) L. Xin, J. J. Kennedy-Smith and F. D. Toste, *Angew. Chem., Int. Ed.*, 2007, **46**, 7671; (c) B. M. Trost, B. M. O'Boyle and D. Hund, *J. Am. Chem. Soc.*, 2009, **131**, 15061; (d) Q. Zhou, X. Chen and D. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 3513; (e) K. Molawi, N. Delpont and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2010, **49**, 3517; (f) H. Shi, L. Fang, C. Tan, L. Shi, W. Zhang, C. Li, T. Luo and Z. Yang, *J. Am. Chem. Soc.*, 2011, **133**, 14944; (g) O. F. Jeker and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3474; (h) H. Chiba, S. Oishi, N. Fujii and H. Ohno, *Angew. Chem., Int. Ed.*, 2012, **51**, 9169; (i) R. Nakajima, T. Ogino, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2010, **132**, 1236; (j) K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda and H. Tokuyama, *Angew. Chem., Int. Ed.*, 2013, **52**, 7168; (k) A. W. Gregory, P. Jakubec, P. Turner and D. J. Dixon, *Org. Lett.*, 2013, **15**, 4330; (l) C. Fang, Y. Pang and C. J. Forsyth, *Org. Lett.*, 2010, **12** , 4528.

5 (a) A. Fürstner and L. Morency, *Angew. Chem., Int. Ed*., 2008, **47**, 5030; (b) S. G. Sethofer, T. Mayer and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 8276.

6 (a) M. Pfau, G. Revial, A. Guingant and J. d'Angelo, *J. Am. Chem. Soc.*, 1985, **107**, 273; (b) D. Desmäele, F. Dumas, A. Guingant and J. d'Angelo, *Tetrahedron: Asymmetry*, 1992, **3**, 459; (c) C. Cavé, D. Desmaële and J. d'Angelo, *J. Org. Chem.*, 1996, **61**, 4361.

7 A. Padwa, S. K. Bur and H. Zhang, *J. Org. Chem.*, 2005, **70**, 6833.

8 (a) L. A. Paquette, T. Z. Wang and N. H. Vo, *J. Am. Chem. Soc.*, 1993, **115**, 1676; (b) M. C. Carreno, M. Gonzalez-Lopez, A. Latorre and A. Urbano, *J. Org. Chem.*, 2006, **71**, 4956.

9 (a) P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390; (b) P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117; (c) J. A. Enquist and J. B. M. Stoltz, *Nature*, 2008, **453**, 1228; (d) A. Krasovskiy and B. H. Lipshutz, *Org. Lett*., 2011, **13**, 3822.

10 E. Negishi, L. F. Valente and M. Kobayashi, *J. Am. Chem. Soc.*, 1980, **102**, 3298.

11 (a) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158; (b) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417.

12 D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012.

13 (a) X.-S. Xu, Z.-W. Li, Y.-J. Zhang, X.-S. Peng and H. N. C. Wong, *Chem. Commun.*, 2012, 8517; (b) H. J. Reich, *Acc. Chem. Res.*, 1979, **12**, 22; (c) A. F. Barrero, S. Arseniyadis, J. F. Quílez del Moral, M. M. Herrador, M. Valdivia and D. Jiménez, *J. Org. Chem.*, 2002, **67**, 2501.