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Gold-Catalyzed Synthesis of Icetexane Cores: Short Synthesis of Taxamairin B and Rosmaridiphenol

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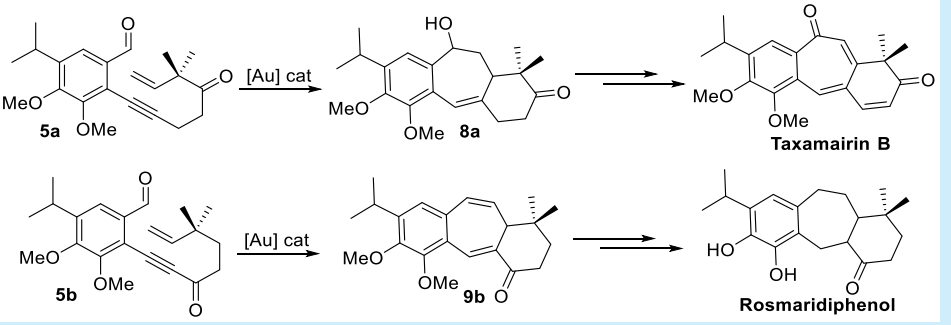

ABSTRACT: We report the short synthesis of two natural products, rosmaridiphenol and taxamairin B, from key intermediates **5a** and **5b**, which were prepared from enynals **8a** and **9b**, respectively, by using a gold-catalyzed cyclization reaction. This approach can be widely applied in the synthesis of [6,7,6]-fused tricyclic compounds found in many icetexane diterpenoids.

Icetexanes are natural diterpenoid products that have been isolated from a variety of Salvia species.[1] These compounds contain a [6,7,6]-tricyclic core that is supposed to be constructed via natural rearrangement of more common [6,6,6]-fused abietane diterpenoids.[2]

The icetexane diterpenoid shows potential biological activity such as antibacterial,[3] antifungal,[4] and antioxidant[5] activity and anti-HIV[6] and anticancer[7] effects. The syntheses of these natural products have attracted research groups to the development of efficient synthetic methods.[8]

Rosmaridiphenol was isolated from leaves of *Rosmarinus officinalis* L in 1984 and showed antioxidant activity approaching that of BHT.[9] The structure of rosmaridiphenol was revised by NMR analysis and single-crystal X-ray study of rosmaridiphenol diacetate.[10] In 2016, Matsushita's group reported the semisynthesis of (+)-rosmaridiphenol from (+)-pisiferic acid in 13% yield (nine steps).[11] There has been no further report of the synthesis of this compound.

Along with rosmaridiphenol, taxamairins A and B were first isolated in 1987 from the bark of *Taxusmairei*, a plant that grows in Fujiang Province, China. The structure of taxamairin was determined by X-ray crystallographic analysis with its oxygenated derivative at both C^1 and C^8 (Figure 1). Taxamairins A and B show inhibitory activity against hepatoma (liver tumor) cells in vitro, with IC_{50} values of 30.21 and 26.78 μg/mL, respectively.[12] Attracted by the structural characteristics and biological activity of taxamairins, several groups have attempted to synthesize taxamairins and related compounds. Pan's research group reported the first total synthesis of

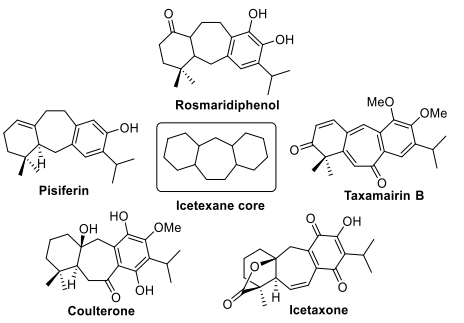

Figure 1. Icetexane diterpenoids.

taxamairin B in 1995,[13] and a second-generation synthesis was published in 1999.[14]

In recent years, new processes based on intramolecular transition-metal cyclization led to diverse products in good yields. In 2005, Padwa reported the construction of komaroviquinone using a Rh-catalyzed cyclization/cyclo-addition cascade of an *o*-carbomethoxyaryl diazo.[15] One year later, Sarpong and co-workers achieved total synthesis of

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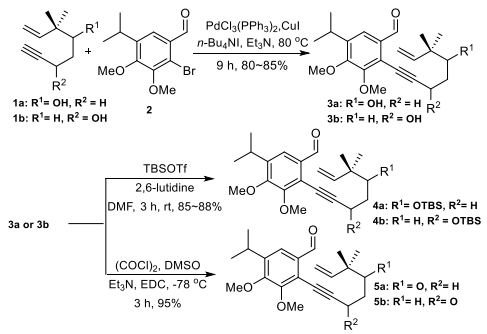
Org. Lett. XXXX, XXX, XXX−XXX

(±)-salviasperanol using Ga(III)-catalyzed cycloisomerization.[16] In previous research, we have synthesized faveline and komaroviquinone using a Pt-catalyzed hydrative cyclization reaction.[17] Recently, we reported the total synthesis of taxamairin B (six steps from *o*-bromobenzyl bromide) in good yield under mild conditions. The [6,7,6]-tricyclic core was constructed by an intramolecular hydrative Heck strategy.[18] The catalysts provide an efficient synthetic method for many natural products and useful building blocks in organic synthesis.

In this research, we focus on use of gold catalysts to construct the corresponding [6,7,6]-tricyclic skeletons as key intermediates for the synthesis of taxamairin B and rosmaridiphenol.

We first prepared a substrate for gold-catalyzed cyclization from starting materials **1a**, **1b**, and **2** via Sonogashira reaction with $PdCl_2(PPh_3)_2$, CuI, and *n*-Bu_4NI at 80 °C in triethylamine for 9 h to produce alcohols **3a** and **3b** in 85% and 80% yields, respectively. Then, TBS-protected alcohols **3a** and **3b** under a basic condition gave compounds **4a** and **4b** in 88% and 85% yields, respectively. Swern oxidation of **3a** and **3b** afforded compounds **5a** and **5b**, respectively, in excellent yield (95%) (Scheme 1).

Scheme 1. Synthesis Substrate for Gold-Catalyzed Cyclization



On the basis of previous work in our laboratory using gold-catalyzed cycloisomerization of diynals and enynals to synthesize [6,7,*n*]-tricyclic compounds, we chose $AuBr_3$ as a catalyst for this cyclization reaction.[19]

First, we treated compound **3a** with $AuBr_3$ in EDC at 60 °C for 1 h. Unfortunately, our desired compound was not formed, although compound **6a** was synthesized in 90% yield. The formation of this dihydronaphthofuran ring system by gold-catalyzed cascade annulation has been reported by Hammond's group.[20] Next, enynal **4a** underwent cyclization to afford **7a** in 70% yield. The structure of **7a** was confirmed as a diastereomeric mixture by spectroscopic analysis. Compound **7a** is a pseudoisomer of **7a′**, which was the compound previously isolated from Pt-catalyzed hydrative cyclization of **4a′** during the synthesis of komaroviquinone (Scheme 2).[17a]

Searching for a suitable intermediate for synthesis of taxamairin B, we tested substrate **5a** with various metal catalysis conditions, and the results are summarized in Table 1. Treatment of compound **5a** with silver triflate in toluene caused decomposition of the starting material. With $PtCl_2$ as a catalyst, only hydration of the triple bond of **5a** was achieved. However, performing the reaction with $AuBr_3$ (30 mol %) in EDC led to the formation of compound **10a** in 60% yield, the same product produced when compound **5a** was treated with

Scheme 2. Gold-Catalyzed Cyclization of 3a and 4a

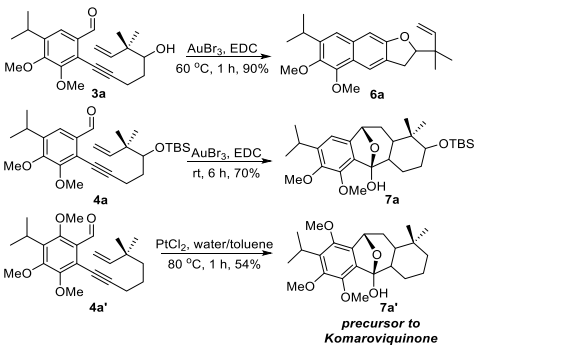
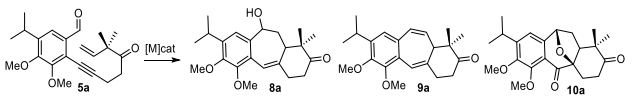


Table 1. Optimization of the Gold-Catalyzed Cyclization of 5a



entry	catalyst (mol %)	solvent	temp (°C)	product	yield (%)[a]
1	$AuBr_3$ (30)	EDC	60	**10a**	65
2	$AuBr_3$ (10)	EDC	80	**9a**	42
3	$PPh_3Au(NTf)_2$ (5)	EDC	80	**9a**	50
4	$NaAuCl_4$ (5)	EDC	60	**10a**	70
5	COAuCl (5)	EDC	60	**8a**	55
6	COAuCl (5)	toluene	60	–	nr[b]
7	COAuCl (5)	THF	60	–	nr[b]

[a]Isolated yields of indicated products. [b]No reaction.

$NaAuCl_4$ (Table 1, entries 1 and 4). However, when the same reaction was performed at 80 °C with $AuBr_3$ (10 mol %) as a catalyst, compound **9a** was isolated in 42% yield (Table 1, entry 2). Another gold catalyst, $PPh_3Au(NTf)_2$, was tested, where compound **9a** was also isolated as a major product in 50% yield (Table 1, entry 3).

Finally, treatment of **5a** with COAuCl in EDC at 50 °C led to the desired product **8a** as a key intermediate for further synthesis (Table 1, entry 5). When the same reaction was performed in toluene and tetrahydrofuran, no reaction has occurred (Table 1, entries 6 and 7).

We next examined gold-catalyzed cyclization of compounds **3b**, **4b**, and **5b**. When compound **4b** was treated with $AuBr_3$ in EDC at room temperature for 8 h, compound **7b** was produced in 73% yield. Surprisingly, oxidative cyclization of compound **7b** with PCC at room temperature for 6 h gave compound **8b**. The structure of **8b** was determined by X-ray diffraction. The X-ray structures of compound **8b** showed that this PCC oxidation reaction formed one C−O−C bridge between positions C^8 and C^{11} and a carbonyl group in position C^{12} (Figure 2). On the basis of this X-ray analysis, we could confirm this structure. Compound **8b** also was the cyclic product when compound **3b** was treated with $AuBr_3$ at 60 °C for 2 h and then oxidized by PCC at room temperature for 3 h. Fortunately, when we treated compound **5b** with $AuBr_3$ at 80 °C for 2 h, intermediate **9b** was formed in 80% yield and was used for subsequent synthesis of rosmaridiphenol (Scheme 3).

Mechanistically, we proposed that the formation of **9b** is initiated by activation of alkyne by Au(III) species to generate zwitterion **A** or **B** that would undergo cycloaddition to form Au-carbene species **C**. The deprotonation from **C** by a base (likely solvent or another source) led to the formation of **D**,

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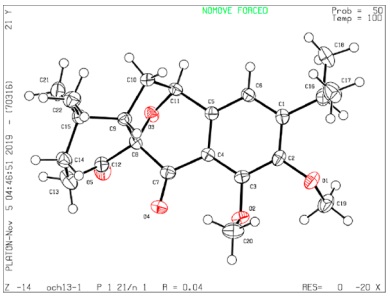
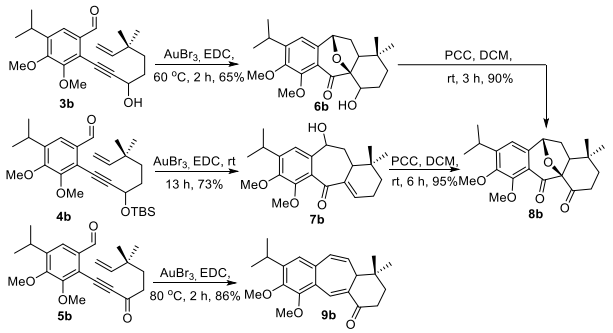


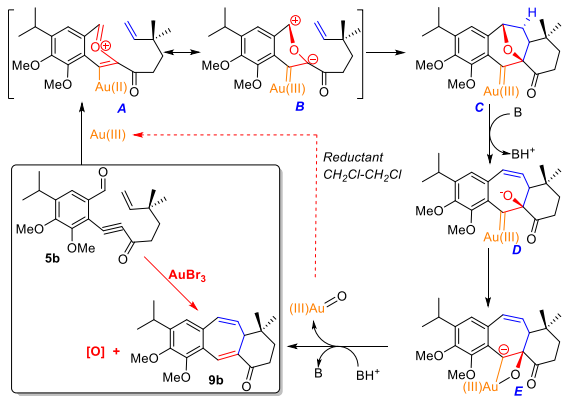
Figure 2. X-ray spectra of compound **8b** with ellipsoids shown at the 50% contour percent probability level (CCDC 2033257).

Scheme 3. Gold-Catalyzed Cyclization of 3b, 4b, and 5b



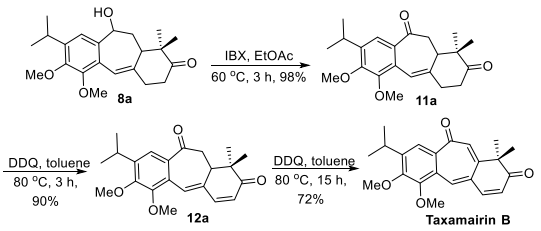
and then simultaneously to the formation of four-membered ring **E**. Then, reprotonation to **E** by liberated BH^+ followed by reductive elimination resulted in **9b** via the release of an unprecedented Au(III)═O species. This phenomenon might be proceeded by the action of solvent CH_2Cl-CH_2Cl as a reductant; thus, we tried this reaction in the presence of hydroquinone, where we found benzoquinone formation in ^1H NMR of the crude reaction mixture. Although reduction of Au(III)═O to Au(III) was not yet confirmed, we have carried out the following reactions to finish the synthesis of rosmaridiphenol (Scheme 4).

Scheme 4. Possible Mechanism for the Formation of 9b



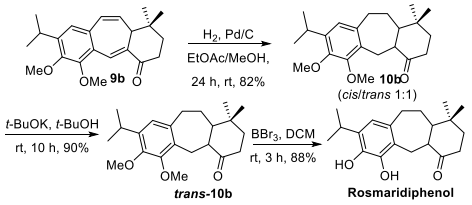
We next focused our attention on formation of taxamairin B. Mild conditions for oxidation of alcohol **8a** afforded ketone **11a** in 98% yield. Selective dehydrogenation using 3 equiv of DDQ at 80 °C for 3 h gave compound **12a** in 90% yield. Further reaction beyond 3 h produced taxamairin B in 72% yield (Scheme 5).

Scheme 5. Synthesis of Taxamairin B



Hydrogenation of **9b** (Scheme 6) afforded **10b** in 82% yield (1:1 *cis*:*trans* ratio). Compound **10b** then was treated with *t*-

Scheme 6. Synthesis of Rosmaridiphenol



BuOK to achieve complete isomerization and yield the *trans* isomer of **10b**. Finally, cleavage of the methyl ethers using BBr_3 gave rosmaridiphenol in excellent yield.

In conclusion, we successfully performed gold-catalyzed cyclization of **5a** and **5b** to generate [6,7,6]-tricyclic compounds **8a** and **9b**, respectively, in moderate yields. These were subsequently transformed into taxamairin B and rosmaridiphenol, respectively. This method could allow application of gold-catalyzed cyclization to the synthesis of various natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03415.

Experimental procedures and spectroscopic data for adduct compounds (PDF)

Accession Codes

CCDC 2033257 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chen, H. L.; Lin, K. W.; Gan, K. H.; Wang, J. P.; Won, S. J.; Lin, C. N. *Fitoterapia* **2011**, *82*, 219. (b) Esquivel, B.; Calderon, J. S.; Sanchez, A. A.; Ramamoorthy, T. P.; Flores, E. A.; Dominguez, R. M. *Rev. Latinoam. Quim.* **1996**, *24*, 44. (c) Esquivel, B.; Calderon, J. S.; Arano, M. G.; Hernandez, P. M.; Sanchez, A. A. *Rev. Latinoam. Quim.* **2005**, *33*, 82. (d) Esquivel, B. *Nat. Prod. Commun.* **2008**, *3*, 989. (e) Suresh, G.; Babu, K. S.; Rao, V. R. S.; Rao, M. S. A.; Nayak, V. L.; Ramakrishna, S. *Tetrahedron Lett.* **2011**, *52*, 1273. (f) Suresh, G.; Suresh Babu, K.; Suri Appa Rao, M.; Rama Subba Rao, V.; Ashok Yadav, P.; LakshmaNayak, V.; Ramakrishna, S. *Tetrahedron Lett.* **2011**, *52*, 5016.

(2) (a) Rodiguez-Hahn, L.; Esquivel, B.; Adela Sanchez, A.; Sanchez, C.; Cardenas, J.; Ramamoorthy, T. P. *Rev. Latinoam. Quim.* **1989**, *20*, 105. (b) Gonzalez, A. G.; Andres, L. S.; Luis, J. G.; Brito, I.; Rodriguez, M. L. *Phytochemistry* **1991**, *30*, 4067. (c) Fraga, B. M.; Diaz, C. E.; Guadano, A.; Gonzalez-Coloma, A. *J. Agric. Food Chem.* **2005**, *53*, 5200.

(3) (a) Kobayashi, K.; Nishino, C. *Agric. Biol. Chem.* **1986**, *50*, 2405. (b) Kobayashi, K.; Nishino, C.; Fukushima, M.; Shiobara, Y.; Kodama, M. *Agric. Biol. Chem.* **1988**, *52*, 77.

(4) Kobayashi, K.; Nishino, C.; Tomita, H.; Fukushima, M. *Phytochemistry* **1987**, *26*, 3175.

(5) V. G. M., N.; Atmakur, H.; Katragadda, S. B.; Devabakthuni, B.; Kota, A.; S., C. K. R.; Kuncha, M.; M. V. P. S., V. V.; Kulkarni, P.; Janaswamy, M. R.; Sistla, R. *Phytomedicine* **2014**, *21*, 497.

(6) Berger, E. A.; Murphy, P. M.; Farber, J. M. *Annu. Rev. Immunol.* **1999**, *17*, 657.

(7) Giacomelli, E.; Bertrand, S.; Nievergelt, A.; Zwick, V.; Simoes-Pires, C.; Marcourt, L.; Rivara-Minten, E.; Cuendet, M.; Bisio, A.; Wolfender, J. L. *Phytochemistry* **2013**, *96*, 257.

(8) (a) Tuckett, M. W.; Watkins, W. J.; Whitby, R. J. *Tetrahedron Lett.* **1998**, *39*, 123. (b) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883. (c) Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189. (d) Wang, X.; Pan, X.; Zhang, C.; Chen, Y. *Synth. Commun.* **1995**, *25*, 3413. (e) Wang, X. C.; Pan, X. F. *J. Indian Chem. Soc.* **1996**, *73*, 497. (f) Ning, C.; Wang, X. C.; Pan, X. F. *Synth. Commun.* **1999**, *29*, 2115. (g) Jan, N. W.; Liu, H. J.; Hsieh, M. T.; Shia, K. S. *Eur. J. Org. Chem.* **2010**, *2010*, 4271. (h) Chen, D. L.; Liu, X. Y.; Cheng, H.; Wang, F. P. *Chin. Chem. Lett.* **2011**, *22*, 774. (i) Cortez, F. D. J.; Lapointe, D.; Hamlin, A. M.; Simmons, E. M.; Sarpong, R. *Tetrahedron* **2013**, *69*, 5665. (j) Simmons, E. M.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2705. (k) Jiao, Z. W.; Tu, Y. Q.; Zhang, Q.; Liu, W. X.; Zhang, S. Y.; Wang, S. H.; Zhang, F. M.; Jiang, S. *Nat. Commun.* **2015**, *6*, 7332. (l) Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189.

(9) Houlihan, C. M.; Ho, C. T.; Chang, S. S. *J. Am. Oil Chem. Soc.* **1984**, *61*, 1036.

(10) Muñoz, M. A.; Perez-Hernandez, N.; Pertino, M. W.; Schmeda-Hirschmann, G.; Joseph-Nathan, P. *J. Nat. Prod.* **2012**, *75*, 779.

(11) Nisigaki, E.; Sugamoto, K.; Nishida, M.; Matsushita, Y. *Chem. Lett.* **2016**, *45*, 746.

(12) (a) Liang, J.; Min, Z.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Chem. Pharm. Bull.* **1987**, *35*, 2613. (b) Liang, J.; Min, Z.; Tanaka, T.; Linuma, M. *Huaxue Xuebao* **1988**, *46*, 21.

(13) Wang, X.; Pan, X.; Zhang, C.; Chen, Y. *Synth. Commun.* **1995**, *25*, 3413.

(14) (a) Wang, X. C.; Pan, X. F. *J. Indian Chem. Soc.* **1996**, *73*, 479. (b) Ning, C.; Wang, X. C.; Pan, X. F. *Synth. Commun.* **1999**, *29*, 2115.

(15) Padwa, A.; Boonsombat, J.; Rashatasakhon, P.; Willis, J. *Org. Lett.* **2005**, *7*, 3725.

(16) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883.

(17) (a) Ho Oh, C.; Lee, S. M.; Hong, C. S. *Org. Lett.* **2010**, *12*, 1308. (b) Oh, C. H.; Piao, L.; Jung, J.; Kim, J. *Asian J. Org. Chem.* **2016**, *5*, 1237.

(18) Le, T. Q.; Karmakar, S.; Lee, S.; Chai, U.; Le, M. H.; Oh, C. H. *Chemistry Select.* **2019**, *4*, 11926.

(19) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289.

(20) Liu, L.-P.; Hammond, G.-P. *Org. Lett.* **2010**, *12*, 4640.

https://dx.doi.org/10.1021/acs.orglett.0c03415
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