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Mercuric Triflate-Catalyzed Tandem Cyclization Leading to Polycarbocycles

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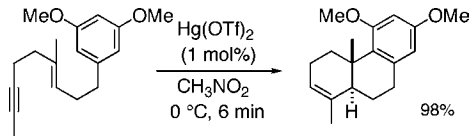
ABSTRACT



We developed $Hg(OTf)_2$-catalyzed cyclization of (*E*)-1,3-dimethoxy-5-(4-methyl-3-nonen-7-ynyl)benzene leading to the formation of (4a*S,10a*S**)-3,4,4a,9,10,10a-hexahydro-5,7-dimethoxy-1,4a-dimethylphenanthrene in 98% yield with up to 100 catalytic turnovers. This is the first mercuric salt-catalyzed biomimetic tandem cyclization.**

Biomimetic olefin cyclization is an efficient process of preparing polycarbocycles that has been investigated for many years.[1] We have developed mercury(II) trifluoromethanesulfonate, so-called mercuric triflate [hereafter $Hg(OTf)_2$], as a highly efficient olefin cyclization agent[2] and applied it to the synthesis of polycyclic terpenoids.[3] Recently, we found that the $Hg(OTf)_2$ and $Hg(OTf)_2$−tetramethylurea (hereafter TMU) complex showed highly efficient catalytic activity for the hydration of terminal alkynes to give methyl ketones,[4] hydroxylative 1,6-enyne cyclization to give exomethylene five-membered ring products,[5] cyclization of 1-alkyn-5-ones leading to 2-methylfurans,[6] and ω-arylalkyne cyclization leading to dihydronaphthalene derivatives.[7] The reaction involves a protodemercuration step of the vinylmercury intermediate[8] induced by TfOH that is generated in situ. We describe herein $Hg(OTf)_2$-catalyzed tandem cyclization of a nonenylbenzene derivative and dodecadienyl substrates to give polycarbocycles with an efficient catalytic turnover. Although Yamamoto and co-workers have demonstrated Brønsted−Lewis acid-induced asymmetric biomimetic olefin cyclization,[9] the present procedure is the first mercuric salt-catalyzed biomimetic tandem cyclization leading to poly-

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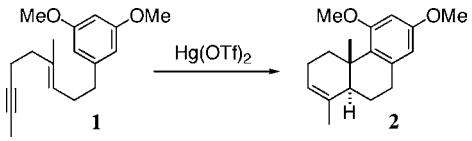
carbocycles in the vast history of mercuric salt-mediated biomimetic olefin cyclization.[3,10]



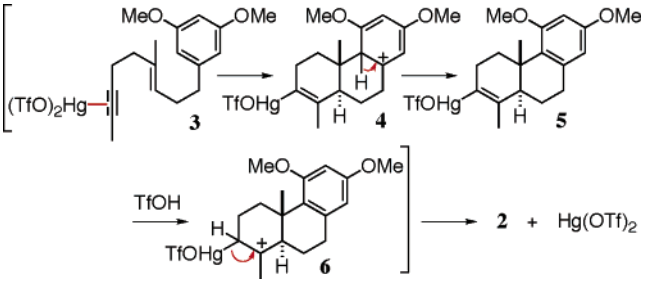
When (*E*)-1,3-dimethoxy-5-(4-methyl-3-nonen-7-ynyl)-benzene (**1**)[11] was treated with 5 mol % $Hg(OTf)_2$ in CH_3CN at 0 °C for 15 min, a tricyclic compound **2** was obtained in 94% yield after aqueous workup and column chromatography on silica gel (Table 1, entry 1). Structure **2** was confirmed by two-dimensional NMR experiment. A lower concentration of catalyst could also be used with comparable success. For instance, 1.0 mol % catalyst resulted in a 93% yield of the product in 3 h (entry 2). However, the reaction was too slow with 0.1 mol % catalyst to be of practical use. The reaction was very slow with $Hg(OTf)_2$−TMU complex (entry 4). CH_3CN and CH_2Cl_2 were employed as solvents for the reaction with almost equal efficiency. The use of CH_3NO_2 as a solvent was, however, discovered to be the solvent of choice, as it allowed a complete reaction in 6 min and furnished the product in near quantitative yield (entry 7). Further, 0.1 mol % catalyst was also effective and furnished the product in 86% yield after 24 h at room temperature (entry 8). The high degree of suitability of CH_3NO_2 as a solvent is also evident from the observation that the reaction with $Hg(OTf)_2$−TMU was also complete in 3 h with a 90% yield of the product (entry 9). $Hg(OAc)_2$ did not show any catalytic activity (entry 10). Mercuric trifluoroacetate [$Hg(OTFA)_2$] (1 mol %) also afforded **2** in 80% yield after 24 h in CH_3NO_2 at room temperature (entry 11).

Table 1. $Hg(OTf)_2$-Catalyzed Cyclization of **1**

entry	catalyst (mol %)	solvent	temp	time (h)	yield (%)[a] **2**	**1**
1	$Hg(OTf)_2$ (5)	CH_3CN	0 °C	0.25	94	0
2	$Hg(OTf)_2$ (1)	CH_3CN	0 °C	3	93	0
3	$Hg(OTf)_2$ (0.1)	CH_3CN	rt	24	58	40
4	$Hg(OTf)_2$−TMU (1)	CH_3CN	rt	24	88	10
5	$Hg(OTf)_2$ (1)	toluene	rt	24	62	36
6	$Hg(OTf)_2$ (1)	CH_2Cl_2	0 °C	1	93	0
7	$Hg(OTf)_2$ (1)	CH_3NO_2	0 °C	0.1	98	0
8	$Hg(OTf)_2$ (0.1)	CH_3NO_2	rt	24	86	10
9	$Hg(OTf)_2$−TMU (1)	CH_3NO_2	0 °C	3	94	0
10	$Hg(OAc)_2$ (1)	CH_3NO_2	rt	24	0	99
11	$Hg(OTFA)_2$ (1)	CH_3NO_2	rt	24	80	15

[a] Isolated yield.

The reaction is initiated by π-complexation of alkyne with $Hg(OTf)_2$ as shown in **3**. Stepwise cyclization of **3** leads to the cation **4**, which, following deprotonation, leads to the aromatic vinylmercuric species **5**. Protonation of **5** by the in situ-generated TfOH leads to the alternative cation **6**, which transforms into **2** and the regenerated catalyst $Hg(OTf)_2$ on subsequent demercuration.



Next, we examined the reaction of (2*E*,6*E*)-3,7-dimethyl-2,6-dodecadien-10-ynyltolyl sulfone (**7**) using 10 mol % $Hg(OTf)_2$ in CH_3NO_2 at 0 °C for 20 min. The bicyclic product **8** was obtained in 74% yield. The structure of **8** was confirmed by a single-crystal X-ray diffraction study.[13] Reaction using 5 mol % catalyst produced **8** in 54% yield. Cyclization of acetate **9** using 10 mol % $Hg(OTf)_2$ at 0 °C for 15 min gave **10** in 68% yield. On reaction with 5 mol % catalyst for 2 h, **10** was obtained in 61% yield. Reaction of the corresponding TBS ether **11** with 5 mol % $Hg(OTf)_2$ at 0 °C for 20 min afforded **12** in 81% yield selectively.

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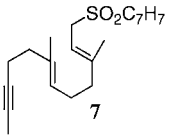
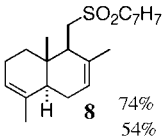
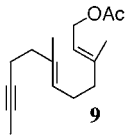
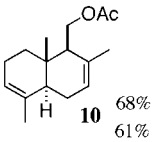
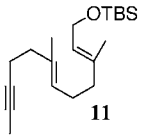
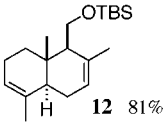
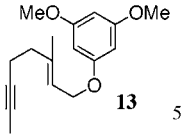
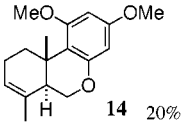
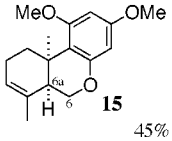
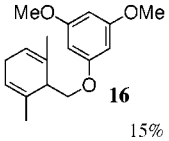
(11) Substrate **1** was prepared by the Pd complex-catalyzed coupling (see ref 15) of (*E*)-1-bromo-3-methyl-2-octen-6-yne (see ref 16) and dimethoxybenzylmagmesium bromide.

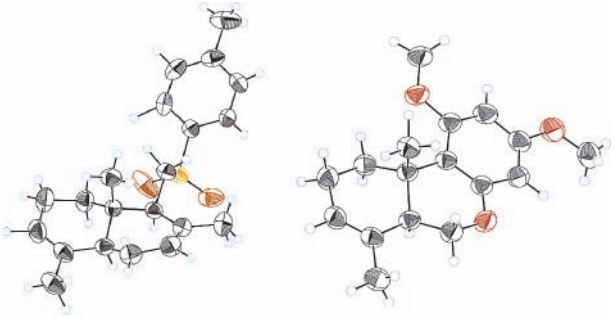
(12) Typical experimental procedure is as follows. A stock solution of $Hg(OTf)_2$ in CH_3CN (0.01 M solution, 0.37 mL, 0.0037 mmol) was transferred to a two-necked flask under an argon atmosphere, and the solvent was replaced with CH_3NO_2 (2 mL) after removal of CH_3CN under reduced pressure. To this was added a solution of (*E*)-1,3-dimethoxy-5-(4-methyl-3-nonen-7-ynyl)benzene (**1**) (100 mg, 0.37 mmol) in CH_3NO_2 (1.7 mL), and the mixture was stirred at 0 °C until all of the starting material was consumed. The reaction was quenched by the addition of an aqueous NaCl−$NaHCO_3$ solution, and the organic layer was extracted with Et_2O, dried over $MgSO_4$, and concentrated. The resulting crude material was purified by column chromatography on silica gel using hexanes−EtOAc as an eluent.

(13) Crystal data for **8**: $C_{21}H_{28}O_2S$, colorless cube, crystal dimension 0.65 × 0.60 × 0.55 mm, M_r = 344.517, orthorhombic $Pc2_1b$, a = 7.8410 (2) Å, b = 13.7550 (5) Å, c = 17.4400 (9) Å, V = 1880.96 (13) Å^3, Z = 4, r_{calcd} = 1.217 mg m^{-3}, m = 0.182 mm^{-1}, T = 298 K, 1859 measured reflections, 1709 independent reflections, 217 parameters, GOF = 1.193, R_1 (wR_2) = 0.0436 (0.1228). Crystal data for **14**: $C_{17}H_{22}O_3$, colorless plate, crystal dimension 0.4 × 0.2 × 0.1 mm, M_r = 274.360, triclinic $P1$, a = 7.2860 (4) Å, b = 10.5060 (7) Å, c = 10.5850 (9) Å, a = 107.314 (3)°, b = 99.739 (3)°, g = 102.947 (3)°, V = 729.25 (9) Å^3, Z = 2, r_{calcd} = 1.249 mg m^{-3}, m = 0.084 mm^{-1}, T = 298 K, 2591 measured reflections, 2519 independent reflections, 181 parameters, GOF = 1.092, R_1 (wR_2) = 0.0516 (0.1490). The measurements were carried out on a Mac Science (Bruker Nonius) dip image plate diffractometer using graphite-monochromated Mo Kα radiation (l = 071073 Å). The crystal structure was solved by the direct method with SIR-97. Refinement was performed by a full matrix least squares refinement on F^2 with SHELXL-97. CCDC 251539 (**8**) and CCDC 251540 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table 2. $Hg(OTf)_2$-Catalyzed Tandem Cyclization in CH_3NO_2 at 0 °C

substrate	$Hg(OTf)_2$, time	product
 **7**	10 mol%, 20 min 5 mol%, 20 min	 **8** 74% 54%
 **9**	10 mol%, 15 min 5 mol%, 2 h	 **10** 68% 61%
 **11**	5 mol%, 20 min	 **12** 81%
 **13**	5 mol%, 1 h	 **14** 20%
 **15** 45%		 **16** 15%

Reaction of (*E*)-1,3-dimethoxy-5-(3-methyl-2-octen-6-ynyloxy)benzene (**13**) with 5 mol % $Hg(OTf)_2$ gave trans product **14** in 20% yield and cis product **15** in 45% yield along with monocyclic **16** (15%). The structure of **14** was established by a single-crystal X-ray diffraction study,[13] and that of **15** was confirmed by detecting the NOE relationship between the C-6aα proton and the angular methyl group.



ORTEP Drawing of **8** ORTEP Drawing of **14**

The above development of the catalytic biomimetic tandem cyclization should open a new avenue for the catalytic preparation of the carbon skeleton of polycyclic natural products. We have initiated such studies, and the result will be described elsewhere.[14]

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Supporting Information Available: Experimental procedures and spectroscopic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We would like to mention the toxicity of mercury. While CH_3HgCl and $(CH_3)_2Hg$ are extremely dangerous, causing serious damage to the central nervous system, most organomercuric compounds with higher molecular weights such as phenylmercuric acetate and mercurochrome are not that toxic and are used in agrochemicals and medicine, respectively. The toxicity of most inorganic mercuric salts is moderate compared with that of Os, As, Tl, Cd, or Pb.

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