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Biomimetic Cyclization of Ambliofuran and Analog By Using Mercury(II) Triflate/*N,N*-Dimethylaniline Complex: Synthesis of (±)-Ambliol-A

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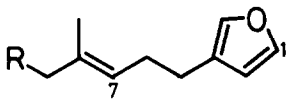
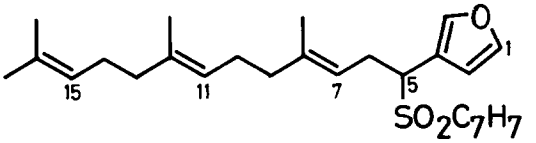
Summary: Biomimetic cyclization of ambliofuran with mercury(II) triflate/*N,N*-dimethylaniline complex is initiated from the internal double bond (Δ^7) in high selectivity, whereas the corresponding sulfone is cyclized from terminal (Δ^{15}) olefin to give marginatan skeleton.

Although a biomimetic cyclization of some acyclic furanoterpenoids[1] such as perillene (**1a**) and dendrolasin (**1b**) has been intensively studied,[2] similar attempts with a higher homologues have never been reported. We wish to describe herein a novel biomimetic cyclization study of ambliofuran (**1c**)[3] and its sulfonyl derivative **2** with mercury(II) triflate/*N,N*-dimethylaniline complex (**3**).[4] To our surprise, cyclization of **1c** with **3** is initiated from internal double bond to give a bicyclic product **4** in high selectivity. In striking contrast to the behavior of 1c, the corresponding sulfone **2** affords tetracyclic products, marginatane skeleton,[5] according to the normal mode of cyclization. The first total synthesis of (±)-ambliol-A (**19**)[3] by means of the analogous cyclization of **2** with **3** in aqueous media[6] is also disclosed.



1a R = H
1b R = $CH_2CH{=}C(CH_3)_2$
1c R = $CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$



2

$Hg(OSO_2CF_3)_2 \cdot C_6H_5N(CH_3)_2$

3

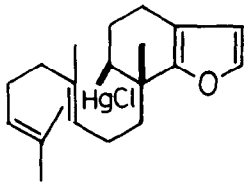
A variety of methods for the preparation of 3-substituted furanoterpenoids have been reported,[7,8,9] however they usually produce hardly separable isomeric mixtures. Therefore, we employed Masaki's procedure[10] for the preparation of ambliofuran (**1c**). The lithio derivative of 3-furfuryl *p*-tolyl sulfone was condensed with (*E,E*)-farnesyl bromide in the presence of HMPA to give sulfone **2** in 86% yield along with a dialkylation product (9%). Reductive desulfrization (Li/NH_3, -78 °C, 10 min) afforded ambliofuran (**1c**) as a colorless oil in 61% yield. The products **1c** and **2** thus obtained are stereochemically pure on the basis of HPLC, ^1H NMR and ^{13}C NMR analysis.

Since the internal double bond (Δ^7) of **1c** is likely more reactive than the external one (Δ^{15}) according to a preliminary investigation,[11] we have employed a reverse addition method for the cyclization condition. The reagent **3** (1.2 equiv, nitromethane solution) was slowly added to a solution of **1c** in nitromethane and dichloromethane (3:2) at -20° C, and the mixture was stirred for 2 h at the same temperature. After treatment with brine, an organomercuric product **4** was isolated in 38% yield along with a doubly cyclized product **5a** (diastereomeric mixture, 15%) and a tetracyclic **6** (13%). At least to our knowledge, this is the first observation that the olefin cyclization is initiated from an internal double bond in high selectivity. Upon treatment of **4** with $NaBH_4$, four isomeric cyclization products **7a** ~ **7d** were obtained by HPLC separation. These products should be formed via a radical intermediate generated by BH_4^- reduction of mercury compound **4**,[12] supporting the assigned structure of the latter. The diastereomeric mixture **5a** was converted to a single product **5b** by the $NaBH_4$ reduction.[13] The tetracyclic product **6** was subjected to Li/NH_3 reduction to give **8**. Although a skeletally related diterpenoid, marginatafuran (**9**), has been reported quite recently as a constituent of a nudibranch,[5] the cyclization mode to give **4** or **5** are not observed in nature yet.

Analogous cyclization of dendrolasin (**1b**) with **3** (1 equiv) under the reverse addition condition was also mainly initiated from the internal double bond (Δ^7) to give **10** in 53% yield along with tricyclic **11** (10%) and recovered **1b** (32%).

Reaction of the sulfone **2** with **3** at -20 °C was initiated at the terminal double bond (Δ^{15}) selectively as usual mode to give tetracyclic products **12** and **13** (42% yield) in 3:1 ratio, which was based on the ^1H NMR analysis of C-15 proton signals (**12** δ 6.52; **13** δ 6.00). A mixture of bicyclic products **14** ($\Delta^{7,8}$:$\Delta^{8,9}$:$\Delta^{8,17}$ = 9:4:3)[14] was accompanied in 19% yield. Pure **12** was isolated by careful crystallization. Sodium borohydride reduction of the mixture of **12** and **13** gave **15** and **16** in 70% and 24% yield, respectively.

The cyclization of **2** with **3** in the presence of water (30 equiv)[6] afforded mono- and bicyclic *tert*-alcohols **17** and **18** (both diastereomeric mixtures) in 16% and 18% yields, respectively, along with 25% of tetracyclic **12** and **13**, and



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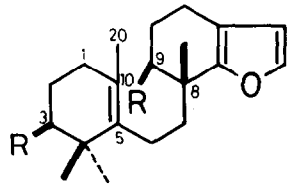
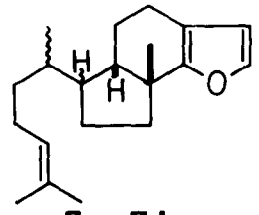
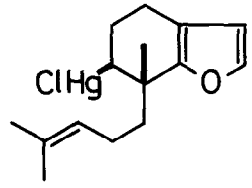


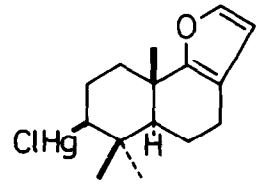
5a R = HgCl
5b R = H



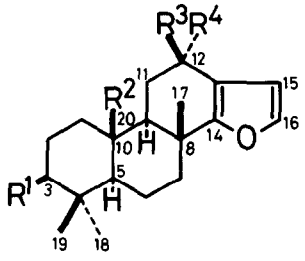
7a ~ 7d

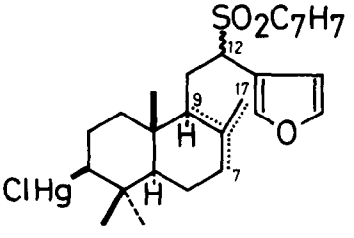


10



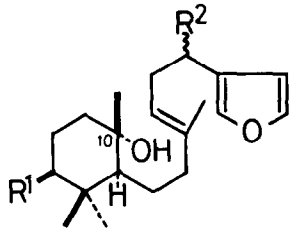
11



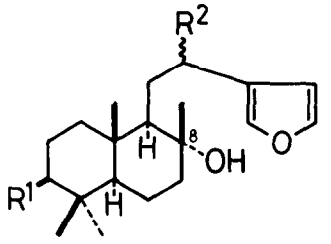


14

6 R^1 = HgCl, R^2 = CH_3, R^3 = R^4 = H
8 R^1 = H, R^2 = CH_3, R^3 = R^4 = H
9 R^1 = H, R^2 = CO_2H, R^3 = R^4 = H
12 R^1 = HgCl, R^2 = CH_3, R^3 = $SO_2C_7H_7$, R^4 = H
13 R^1 = HgCl, R^2 = CH_3, R^3 = H, R^4 = $SO_2C_7H_7$
15 R^1 = H, R^2 = CH_3, R^3 = $SO_2C_7H_7$, R^4 = H
16 R^1 = H, R^2 = CH_3, R^3 = H, R^4 = $SO_2C_7H_7$



17 R^1 = HgCl, R^2 = $SO_2C_7H_7$
19 R^1 = R^2 = H



18 R^1 = HgCl, R^2 = $SO_2C_7H_7$
20 R^1 = R^2 = H

bicyclic olefin **14** (15%).[15] The alcohols **17** and **18** were reduced with Li/NH_3 to give desulfurization products **19** (52% yield) and **20** (66%). respectively. The monocyclic product **19** showed entirely superimposable spectral properties (IR, ^1H NMR, ^{13}C NMR) with those of natural ambliol-A.[3]

The stereochemistry of each cyclization product was established by ^{13}C NMR chemical shifts analogy with our previous results.[4,6]

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10. Masaki, Y.; Hashimoto, K.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Perkin* I **1984**, 1289.
11. When **1c** was treated with **3** in the usual manner (ref 4), a complicated mixture was obtained including double cyclization products **5**.
12. Giese, B.; Heuck, K. *Chem. Ber.* **1979**, *112*, 3759.
13. Ca 10% of isomeric olefin ($\Delta^{1,10}$ and $\Delta^{10,20}$) was incorporated and these were separated by HPLC.
14. The ratio was determined by the HPLC analysis of the demercuration products.
15. The starting material (24%) was recovered in this reaction.

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