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Total Synthesis and Complete Assignment of the Stereostructure of a Cytotoxic Bromotriterpene Polyether (+)-Aurilol

Yoshiki Morimoto,* Yoshihiro Nishikawa, and Mamoru Takaishi

Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi-ku, Osaka 558-8585, Japan

Received January 8, 2005; E-mail: morimoto@sci.osaka-cu.ac.jp

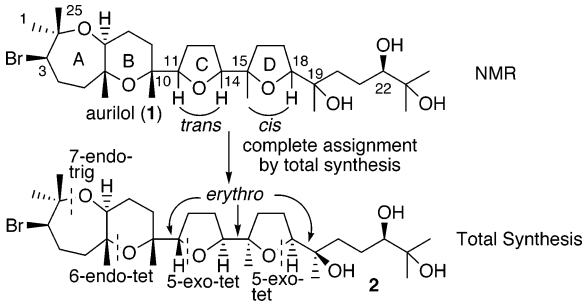
A bromotriterpene polyether aurilol (**1**) was isolated from the sea hare, *Dolabella auricularia*, by Yamada et al. in 1998 and exhibited cytotoxicity against HeLa S_3 cells with IC_{50} of 4.3 μg/mL (Chart 1).[1] Although the plane structure and partial stereochemistry of **1** were elucidated by spectroscopic and chemical analyses, determination of the entire stereochemistry has not been reached. There have also been many other types of triterpene polyethers (oxasqualenoids);[2] however, it is often difficult to determine their stereostructures even by the current highly advanced spectroscopic methods, especially in acyclic systems including quaternary carbon centers such as C10−C11, C14−C15, and C18−C19 in **1**. In such cases, it is effective to predict and synthesize the possible stereoisomers.[3] **1** also possesses a synthetically challenging 2,8-dioxabicyclo[5.4.0]undecane A,B ring system with a bromine atom at the neopentylic position and 1,3-diaxial dimethyl substituents on the B ring. These contexts have made oxasqualenoids, including bromotriterpene polyethers,[4] attractive targets for many synthetic organic chemists.[3] In this paper, we report that the total assignment of the incomplete stereostructure of (+)-aurilol (**1**) to **2** has been achieved through its first asymmetric total synthesis featuring biogenetic-like regioselective ether ring formations to secure the stereochemical pathway.

In the course of our structural studies on oxasqualenoids, which could biogenetically be derived by epoxide-opening cyclizations of squalene polyepoxides,[3b,4b] we predicted the unknown stereochemistry to be *erythro* configuration as shown in **2**. In the retrosynthetic analysis of **2**, we planned to straightforwardly construct all of the A−D ether rings by biogenetic-like cyclizations. The oxepane A ring would be constructed by 7-endo-trig[5] bromoetherification of the corresponding trishomoallylic alcohol, and the B−D rings would be formed by 6-endo-tet, 5-exo-tet, and 5-exo-tet[5] epoxide openings of the corresponding bishomoepoxy alcohols, respectively (vide infra).

The synthesis of target molecule **2** began with SEM protection of the hydroxy group in the known optically active epoxy alcohol **3** (98% ee)[6] (Scheme 1). Selective deprotection of the TBDMS ether in **4** and Sharpless' epoxidation[7] of the allylic alcohol **5** using L-(+)-DET afforded diepoxide **6**. The C ring formation from **6** under the alkaline condition stereoselectively proceeded via a regioselective 5-exo-tet epoxide opening of the intermediate **A** to provide triol **7** in 88% yield.[8] The following sequence, (1) mesylation; (2) epoxidation; (3) chain extension with the C_{10} unit **8**;[9] and (4) desulfurization,[3b] uneventfully yielded diol **9** from **7**. Shi's epoxidation of **9** catalyzed by chiral ketone **10**[10] diastereoselectively gave labile bishomoepoxy alcohol **11**. Treatment of **11** with a protic acid underwent a regioselective 5-exo-tet cyclization to produce diol **12** in 98% yield.[11]

With the highly stereocontrolled **12** in hand, we embarked on the elaboration of the formidable A,B-ring system. Deprotection

Chart 1. Structures of Aurilol



of the SEM ether in **12** afforded triol **13**, from which diene **15** was derived by the same sequence as that of **7** to **9** except for employing sulfide **14**.[12] Shi's epoxidation of the diene **15** with ***ent*-10**,[10] enantiomeric to **10**, proceeded in a regioselective manner to provide monoepoxide **16** with the terminal alkene intact. The construction of the desired B ring was regioselectively carried out by treating the bishomoepoxy alcohol **16** with TIPSOTf and 2,6-lutidine in CH_3NO_2 at 0 °C for 20 min. The unprecedented 6-endo-tet cyclization promoted by a silyl triflate against Baldwin's rule[5] would be very stimulating[14] because Brønsted acid-catalyzed cyclizations for these types of bishomoepoxy alcohols, such as **11**, generally afford 5-exo-tet regioselectivity, regardless of the relative configurations of the tertiary alcohol−epoxide substrates.[11]

After removal of the TIPS group in **17**, cross metathesis of olefin **18** with 2-methyl-2-butene using Grubbs' catalyst **19**[15] produced alkene **20** in 90% yield.[16] After many attempted experimentations,[17] it has been found that $(CF_3)_2CHOH$ with high polarity and non-nucleophilicity[18] is the solvent of choice to successfully form the A ring. The regio- and stereoselective 7-endo-trig bromoetherification of **20** was brought about under the optimal condition to give the A,B-ring system **21**,[19] wherein removal of the acetonide, finally furnished the target molecule **2**. The spectral characteristics (^{1}H and ^{13}C NMR) of the synthetic **2**, $[\alpha]^{19}_D$ +4.5 (*c* 0.21, $CHCl_3$), were identical to those reported for the natural product, $[\alpha]^{30}_D$ +4.6 (*c* 0.41, $CHCl_3$).[1] Thus, it has been found that the hitherto unknown relative configuration of (+)-aurilol (**1**) is *erythro* as indicated in **2**.

In conclusion, we have accomplished the first asymmetric total synthesis of a cytotoxic bromotriterpene polyether (+)-aurilol (4.74% overall yield in 21 steps from **3**) featuring the highly regio- and stereocontrolled biogenetic-like A−D ether ring formations. The total synthesis has realized the total assignment of the incomplete stereostructure of aurilol (**1**), which is difficult to determine the stereochemistry otherwise. Application of this synthetic strategy to other bromotriterpene polyethers is in progress.

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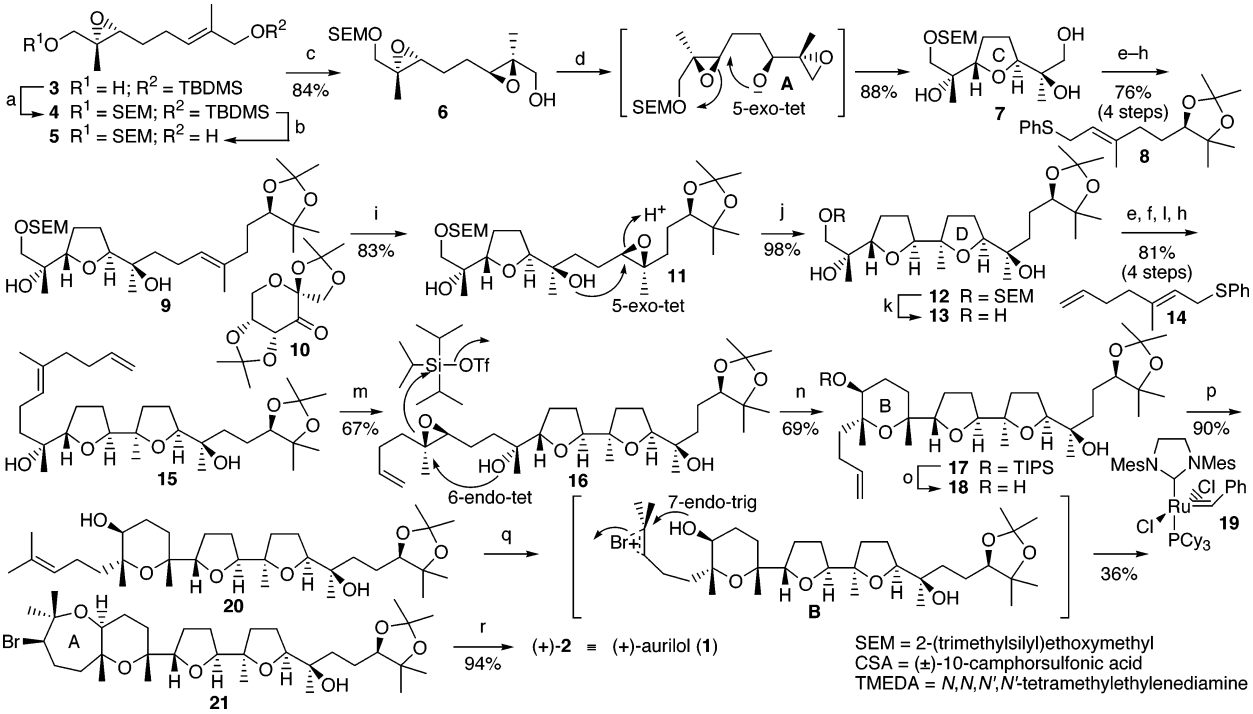
Scheme 1. Total Synthesis of Target Molecule **2**[a]



[a] Reaction conditions: (a) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature, 12 h, 99%; (b) Bu_4NF, THF, 0 °C, 1 h, 100%; (c) *t*-BuO_2H, $Ti(Oi\text{-}Pr)_4$, L-(+)-DET, MS 4A, CH_2Cl_2, −25 °C, 16 h (>20:1); (d) 1 M aq NaOH, 1,4-dioxane, reflux, 5 h; (e) MsCl, Py, CH_2Cl_2, 0 °C to room temperature, 1 h; (f) K_2CO_3, MeOH, rt, 15 min; (g) **8**, BuLi, TMEDA, THF, −78 °C, 1 h; (h) Na, *i*-PrOH, THF, reflux, 4 h; (i) **10**, Oxone, $(MeO)_2CH_2/CH_3CN/H_2O$, pH 10.5, 0 °C, 2 h (>15:1); (j) CSA, CH_2Cl_2, rt, 10 min; (k) Bu_4NF, THF, reflux, 30 h, 92%; (l) **14**, BuLi, TMEDA, THF, −78 °C, 1 h; (m) ***ent*-10**, Oxone, $(MeO)_2CH_2/CH_3CN/H_2O$, pH 10.5, 0 °C, 2 h (>10:1); (n) TIPSOTf, 2,6-lutidine, CH_3NO_2, 0 °C, 20 min; (o) Bu_4NF, THF, 0 °C to room temperature, 15 h, 100%; (p) **19**, 2-methyl-2-butene, reflux, 12 h; (q) 2.5 equiv of NBS, MS 4A, $(CF_3)_2CHOH$, 0 °C, 10 min (>10:1); (r) 80% aq AcOH, rt, 14 h.

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Supporting Information Available: Characterization data for **2**−**7**, **9**, **11**−**13**, **15**−**18**, **20**, and **21**, and experimental procedures for synthesis of **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The C_{10} unit **8** was prepared from commercially available geranyl acetate by the following sequence: (1) AD-min-β, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 15 h, 80% (98% ee); (2) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 0 °C, 2 h, 97%; (3) K_2CO_3, MeOH, rt, 4 h, 98%; (4) $(PhS)_2$, Bu_3P, THF, rt, 4 h, 96%.

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(12) The sulfide **14** was prepared from the known (*E*)-6-acetoxy-4-methyl-4-hexenal (ref 13) by the following sequence: (1) $Ph_3P{=}CH_2$, 0 °C, 1 h, 99%; (2) K_2CO_3, MeOH, rt, 30 min, 95%; (3) $(PhS)_2$, Bu_3P, THF, rt, 4 h, 93%.

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(17) Bromoetherifications of **20** with NBS or 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) in CH_2Cl_2, CH_3CN, or CH_3NO_2 and TBCO in $(CF_3)_2CHOH$ resulted in complex mixtures. For 6-endo cyclizations in preference to 5-exo ones in bromoetherifications of unsaturated alcohols, see: Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982−2987 and refs 4b and c.

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(19) In this reaction, all of the starting material **20** has been consumed, and the products other than **21** were inseparable and unidentifiable complex mixtures.

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