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Synthesis of 17-Deacetoxyl Chromodorolide B Based on a Gold-Catalyzed Alkoxycyclization Reaction

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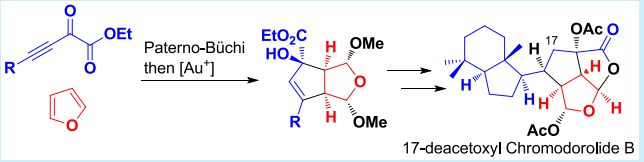
ABSTRACT: A novel strategy to construct the highly oxidized 3-oxabicyclo[3.3.0]octane skeleton was developed via a gold-catalyzed cascade cyclization with 2,7-dioxabicyclo[3.2.0]hept-3-ene as the substrate. We utilized this methodology as the key reaction to synthesize 17-deacetoxyl chromodorolide B.



Rearranged spongiane diterpenoids are small molecules isolated exclusively from sponges and marine shell-less mollusks (nudibranchs), which could play a key role as ecophysiological mediators and are of interest for potential applications given their wide range of bioactivities.[1] In particular, the Golgi-modifying properties of the rearranged spongian diterpenes norrisolide and macfarlandin E have been well established,[2] which inspired the development of a simplified analog (*t*-Bu-MacE) that led to similar phenotypes.[3] In comparison, (−)-chromodorolide B (Figure 1, **1**), one of

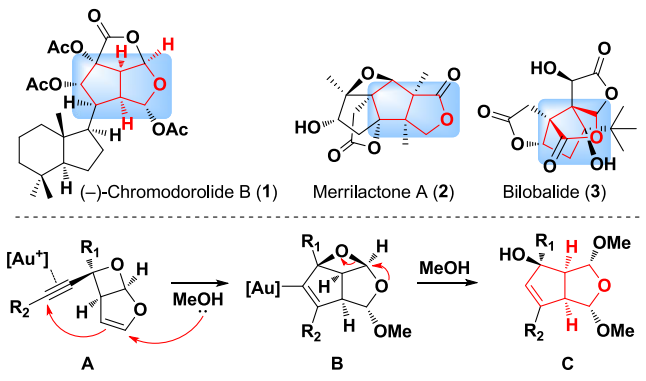


Figure 1. Representative natural products containing a 3-oxabicyclo[3.3.0]octane moiety and the hypothesized gold-catalyzed alkoxycyclization.

the most complex members within this family of natural products, was isolated from the tropical dorid nudibranch *Chromodoris cavae*, but the limited quantity of this natural product prevented in-depth biological investigation.[4] The only total synthesis of chromodorolide B to date was reported by the Overman group, which featured a bimolecular radical addition/cyclization/fragmentation cascade reaction to construct the key stereocenters.[5] A challenging structural feature of chomodorolide B is the presence of a 3-oxabicyclo[3.3.0]-octane skeletal motif, which is shared by a number of other natural products, such as merrilactone A (**2**)[6] and bilobalide (**3**).[7] To efficiently construct this unique subunit, we envisaged a gold-catalyzed alkoxycyclization: The activation of alkyne in substrate **A** by Au(I) catalysis would enable an intramolecular alkene attack (5-*endo-dig* cyclization),[8] followed by the nucleophilic trapping of the resulting oxocarbenium to obtain a highly strained tricycle, intermediate **B**;[9] the subsequent opening of the strained oxetane ring would ensue in situ to form the 3-oxabicyclo[3.3.0]octane skeleton, **C**. The bicyclic substrate (**A**) could, in turn, be easily prepared by alkynone and furan or furan derivatives via the Paternò−Büchi reaction.[10]

We commenced our work by evaluating the cascade reaction of oxetane **4a** (Figure 2, R^1 = −COOEt, R^2 = −^{i}Pr, R^3 = −H), the relative stereochemistry of which was determined by the X-ray of its derivative (Figure S1; see the Supporting Information (SI) for details). In the presence of 2 equiv of MeOH, the commonly used gold catalysis system (5 mol % Ph_3PAuCl/$AgSbF_6$) successfully converted **4a** to the desired product (**5a**) in dichloromethane (DCM) at room temperature; the structure of **5a** was confirmed by the X-ray diffraction (XRD) of its derivative (Figure S2). Even though the isolation yield was moderate (53%), the reaction was completed within 10 min, and elongation of the reaction time did not lead to an improved yield.

The substrate scope was preliminarily explored, indicating that desired products could be obtained in moderate yield (40−50%) for substrates with R^2 = −^{t}Bu, −Ph, or −Br (**5b**−**d**). In comparison, substrate **4e** with R^2 = −H afforded product **5e** in 34% yield, suggesting that other side reactions might be invoked in the presence of the terminal alkyne. Increasing the substitution at R^3 (−Me, **4f**) also led to deteriorated results

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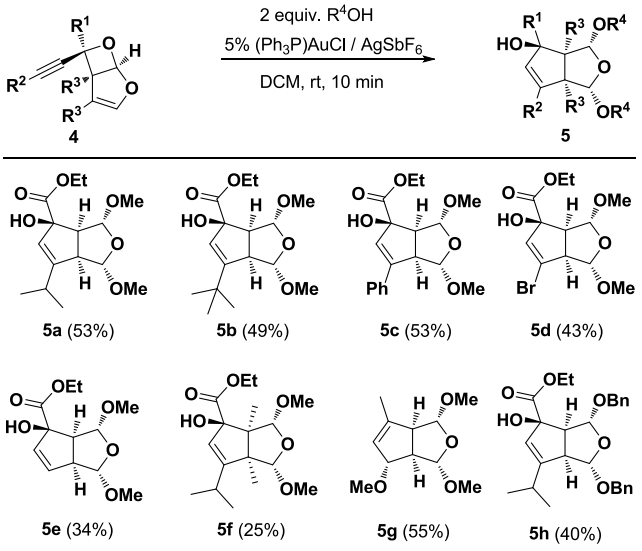
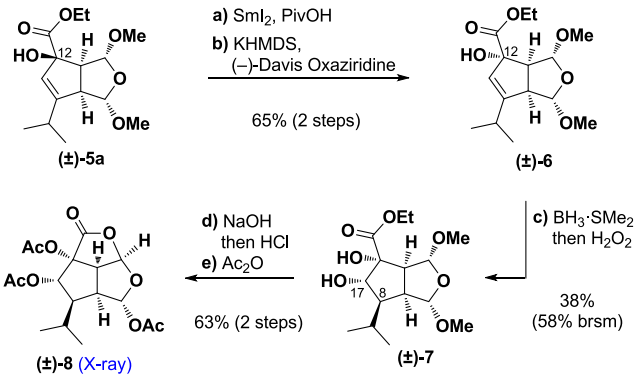


Figure 2. Synthesis of 3-oxabicyclo[3.3.0]octanes by the gold-catalyzed alkoxycyclization.

(25% isolation yield of the desired product), presumably due to the increased steric hindrance on the alkenyl nucleophile. Interestingly, with substrate **4g** (R^1 = −Me, R^2 = −H, R^3 = −H), product **5g** was obtained in 55% yield instead of the direct cascade product, the stereochemistry of which was determined by a nuclear Overhauser effect spectroscopy (NOESY) experiment. (See the SI.) This observation could be rationalized by the facile gold-catalyzed allylic ether formation from the allylic alcohol.[11] Replacing the methanol with benzyl alcohol also smoothly provided the corresponding 3-oxabicyclo[3.3.0]octane in a similar yield (**5h**).

On the basis of our retrosynthetic analysis of chromodorolide B (Figure S3), we first carried out a model study using 3-oxabicyclo[3.3.0]octane **5a** in hand (Scheme 1). The inversion of the C12 stereogenic center was achieved by (1) using excess SmI_2/pivalic acid in THF−HMPA to reductively remove the hydroxyl group[12] and (2) deprotonation of the resulting ester, followed by treatment with Davis oxaziridine.[13] The desired

Scheme 1. Model Study of Chromodorolide B[a]



[a]Reagents and conditions: (a) SmI_2 (5.0 equiv), pivalic acid (4.0 equiv), HMPA, THF, rt; (b) KHMDS (1.1 equiv), (1*S*)-(+)-(10-camphorylsulfonyl oxaziridine (1.2 equiv), HMPA, THF, −78 °C, 65% (two steps); (c) BMS (2.5 equiv), DCE, 0 to 35 °C, then $NaHCO_3$, H_2O_2, THF, rt, 38% (58% brsm); (d) NaOH, THF, rt, then HCl, THF, rt; (e) DMAP (0.8 equiv), pyridine (17.0 equiv), Ac_2O (12.0 equiv), rt, 63% (two steps).

product, ester **6**, was obtained in 65% yield over two steps. Hydroboration of **6** from the convex face, followed by treatment with H_2O_2 afforded diol **7** in 38% yield (58% based on the recovery of starting material). Bicycle **7** was first hydrolyzed to the corresponding carboxylate, which formed the tricyclic lactone upon exposure to 5 M HCl in tetrahydrofuran (THF) at room temperature.[5] Subsequent acetylation delivered ^{i}Pr-chomodorolide B (**8**) in 63% yield over two steps, the structure of which was confirmed by XRD.

Encouraged by the successful model study, we carried out further synthetic studies toward chromodorolide B (Scheme 2). The *trans*-hydrindanone **9** was first prepared via the procedures reported by the Overman group[5] and underwent a Van Leusen reaction[14] followed by a DIBAL-H reduction to afford aldehyde **10** with a d.r. ratio of 5:1 in 60% yield over two steps. The Corey−Fuchs reaction converted aldehyde **10** to the corresponding dibromo compound,[15] and the subsequent addition of ^{n}BuLi generated lithium acetylide **12** that was trapped in situ by Weinreb amide **11** to afford alkynone **13** in 70% yield over two steps.[16] The Paternò−Büchi reaction of alkynone **13** and furan afforded inseparable diastereomeric oxetanes **14a** and **14b** (1:1) in 62% yield (91% brsm). The poor diastereoselectivity was expected given the distance between the chiral hydrindane and the ketone carbonyl group (reaction center). Gratifyingly, by screening a variety of reaction conditions (Table S1), we found that 5 mol % ^{t}Bu$_3$PAuCl/AgSbF$_6$ catalyzed the alkoxycyclization of **14a**/**b** to afford a pair of separable diastereomers **15a** and **15b** in 37 and 15% yield, respectively. The structure of **15b** was unambiguously determined by XRD, suggesting that the major product, **15a**, was the desired stereoisomer for the total synthesis of **1**. The epimerization of the C12 stereogenic center was accomplished by a similar two-step sequence shown in our model study, but we found the α-hydroxylation step worked better with O_2 as the oxidant, leading to **16** in 54% yield over two steps.

However, we encountered an insurmountable hurdle in the hydroboration of C8−C17 alkene. A variety of conditions screened did not afford compound **17** from **16**, and the decomposition of starting material (**16**) to unidentifiable products was observed. The difficulty of this hydroboration could be ascribed to two reasons: (1) The hydrindane motif created a stifling congestion on the convex face, preventing the rhombic transition state of hydroboration (**TS A**); (2) the transformations on the convex face of *cis*-bicyclo[3.3.0]octenes were torsionally unfavored.[17] Consequently, other side reactions, including the hydroxyl-directed reduction of ester[18] and the decomposition of ketals due to the Lewis acidity of borane reagents, predominated. Consistent with this explanation, even the hydrogenation of C8−C17 alkene turned out to be extremely sluggish, which was completed after 6 days at 35 °C in the presence of PtO_2. Compound **18** was isolated as a single diastereomer in 80% yield and subjected to a hydrolysis/acidification/acetylation sequence to afford 17-deacetoxyl chomodorolide B (**19**) in 66% yield over two steps, the structure of which was confirmed by XRD.

In summary, we have developed a novel strategy to synthesize highly substituted 3-oxabicyclo[3.3.0]octanes by combining the Paternò−Büchi reaction of furan and a gold-catalyzed cascade reaction. Even though we were not able to accomplish chromodorolide B, the efficiency of the current approach to construct the skeleton of these rearranged spongian diterpenoids was noteworthy. The caveat of our

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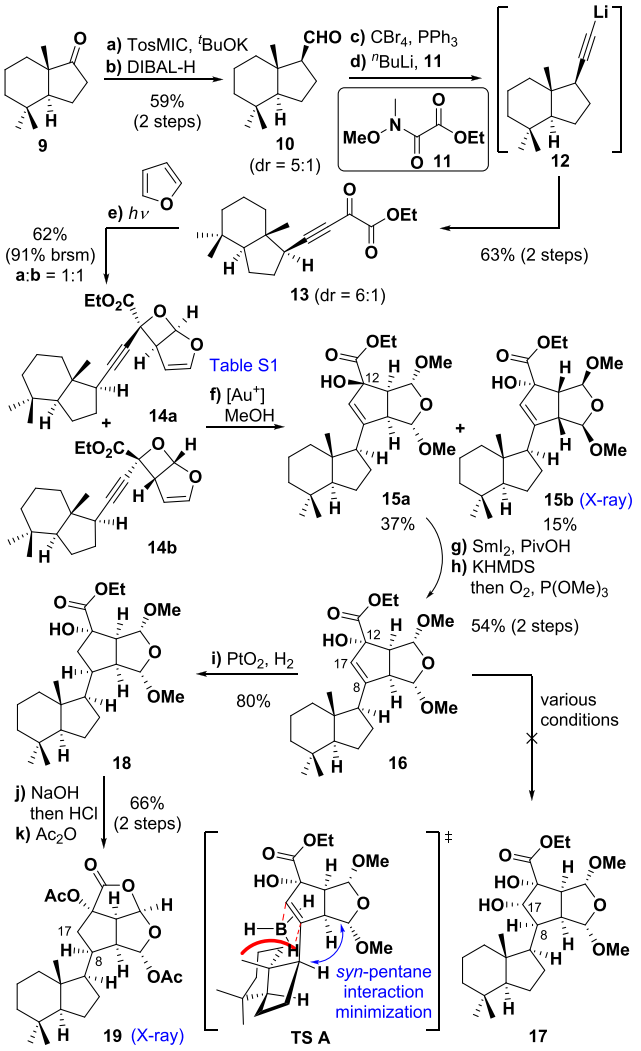
Scheme 2. Synthesis of 17-Deacetoxyl Chromodorolide B[a]



[a]Reagents and conditions: (a) TosMIC (1.4 equiv), ^{t}BuOK (6.0 equiv), ^{t}BuOH, DME, 0 °C to rt; (b) DIBAL-H (1.0 equiv), DCM, −78 °C, 60% (two steps, d.r. = 5:1) ; (c) PPh_3 (4.0 equiv), CBr_4 (2 equiv), DCM, 0 °C to rt; (d) ^{n}BuLi (2.2 equiv), **11** (1.1 equiv), −78 to 0 °C, 63% (two steps, d.r. = 6:1); (e) furan, *hν*, rt, 62%, (91% brsm, d.r. = 1:1); (f) $^{t}Bu_3PAuCl$ (0.05 equiv), $AgSbF_6$ (0.05 equiv), MeOH (2 equiv), DCM, rt; **15a**, 37%; **15b**, 15%; (g) SmI_2 (6.0 equiv), pivalic acid (5.0 equiv), HMPA, THF, rt, 88% (d.r. = 1.5:1); (h) KHMDS (1.2 equiv), $P(OMe)_3$ (1.4 equiv), O_2, THF, −78 °C, 63%; (i) PtO_2 (4 equiv), H_2 (1 atm), EtOH, 35 °C, 6 days, 80%; (j) NaOH, then HCl, THF, rt; (k) Ac_2O (10 equiv), pyridine (15 equiv), DMAP (1 equiv), DCM, rt, 66% (two steps). TosMIC, tosylmethyl isocyanide; DME, 1,2-dimethoxyethane.

unsuccessful late-stage hydroboration argued for the strategic importance of choosing the functionalization sequence in the synthesis of complex molecules.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00247.

Detailed experimental procedures, compound characterization data, and CIFs for **S2**, **S3**, **8**, **15b**, and **19** (PDF)

Accession Codes

CCDC 1979632−1979636 contain 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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