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Total Synthesis of Aplysiasecosterol A

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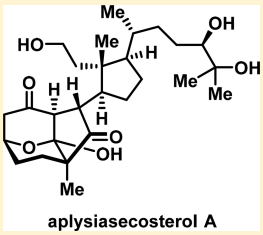
Supporting Information

ABSTRACT: Aplysiasecosterol A (**1**) is a structurally unusual 9,11-secosteroid isolated from the sea hare *Aplysia kurodai*. We have accomplished the first and asymmetric total synthesis of **1** in a convergent fashion. The left-hand segment bearing three adjacent stereocenters was constructed through desymmetrizing reduction, ketalization, and radical cyclization. A strategy of asymmetric 2-bromoallylation followed by spontaneous desymmetrizing lactolization enabled a more expeditious access to this segment. The right-hand segment was prepared through two different approaches: one featuring Myers alkylation and Suzuki−Miyaura coupling and the other relying upon Aggarwal lithiation−borylation and Zweifel−Evans olefination. The two fragments were coupled by a Reformatsky type reaction. The three consecutive stereocenters embedded in the central domain of **1** were generated by an iron-mediated, hydrogen atom transfer based radical cyclization reaction.



INTRODUCTION

Steroids are a large family of physiologically and pharmaceutically important natural products.[1] They often serve as signaling molecules for activation of steroid hormone receptors.[2] The additional biological functions of structurally unusual steroids remain to be explored. Studies toward the chemical synthesis of steroids have facilitated the development of steroid based drugs[1,3] and the evolution of the strategies and methods for the construction of polycyclic molecules.[4] In the past decade, the renaissance in this area resulted in a series of elegant syntheses of structurally and biologically interesting steroids, such as batrachotoxinin A,[5] cephalostatins,[6] cortistatins,[7] cyclocitrinol,[8] cyclopamine,[9] dafachronic acid A,[10] 19-hydroxysarmentogenin,[11] nakiterpiosin,[12] and ouabagenin.[13] However, secosteroids, a subclass of steroids featuring a ring cleavage of the original tetracyclic framework, have received less attention from both chemical and biological perspectives.[14] In 2015, Kigoshi, Kita, and Kawamura reported the isolation of aplysiasecosterol A (**1**, Figure 1) from the sea hare *Aplysia kurodai*.[15] This 9,11-secosteroid possesses an unprecedented tricyclic γ-diketone core attached by a densely substituted cyclopentane moiety. The same team also discovered two congeners of **1**, aplysiasecosterols B and C (**2** and **3**), the former of which was proposed as the biogenetic precursor of **1**.[16] In 2016, Sung, Sheu, Wu, and co-workers reported the isolation of pinnigorgiols A, B, D, and E (**4**−**7**) from the gorgonian *Pinnigorgia* sp., which share an aplysiasecosterol A type scaffold and vary slightly in their side chains.[17] Interestingly, **4** was found to induce apoptosis of hepatic stellate cells via the ROS−ERK/JNK−Caspase-3 signaling pathway.[18] However, the biology of **1** has not been sufficiently explored, presumably due to its natural scarcity.[19] The heavily reconstructed skeleton of **1** hampers a semisynthetic approach starting from a readily available precursor, and the eight consecutive stereogenic centers pose a considerable challenge for a de novo synthesis. Herein, we report the first and asymmetric total synthesis of **1**.

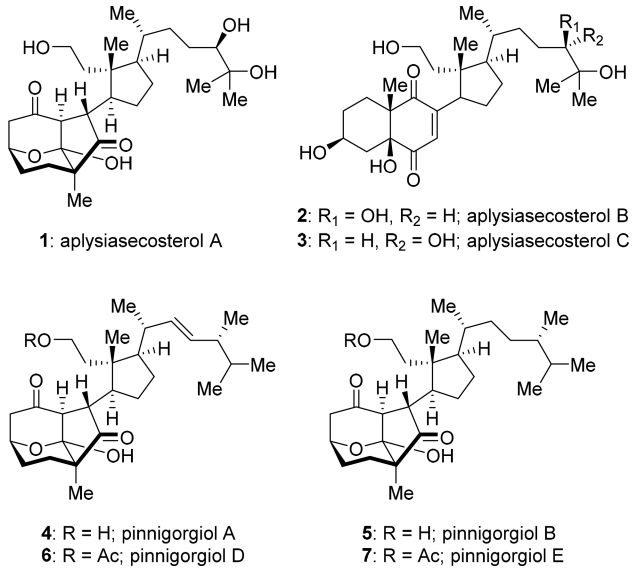


Figure 1. Aplysiasecosterol A (**1**) and related secosteroids.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. The structural features of **1** led to a retrosynthetic analysis depicted in Figure 2. The construction of the attached C and D rings[20] would be a key issue of the synthesis. The hidden structural symmetry of the C ring (highlighted in red) beckoned for a desymmetrization strategy[21,22] to establish the stereochemistry of quaternary C10

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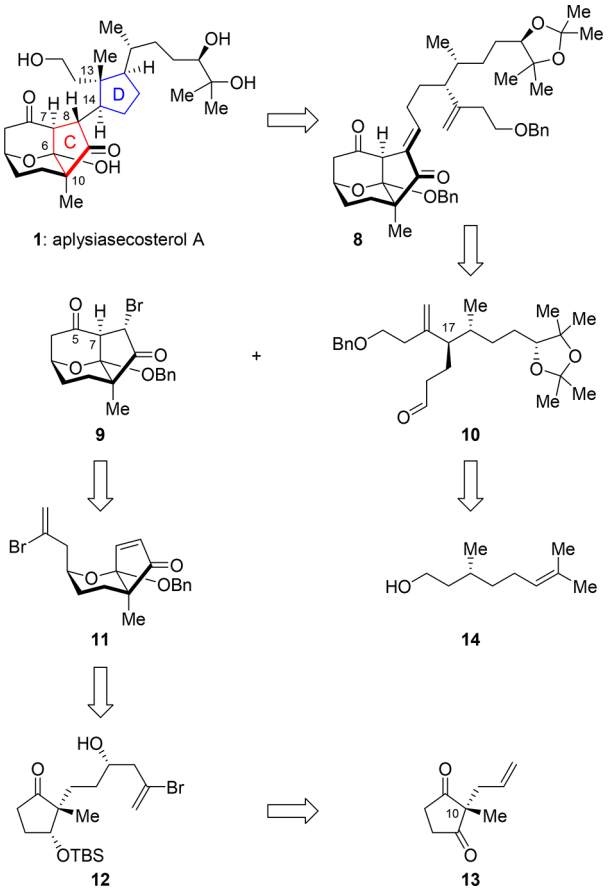
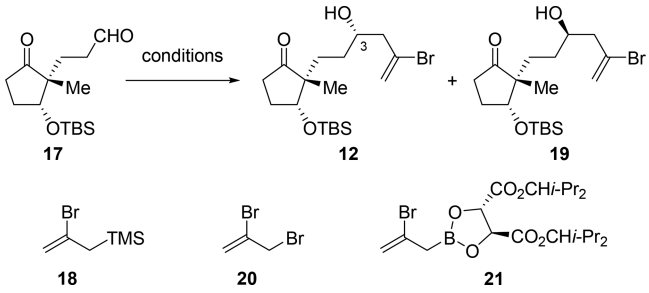


Figure 2. Retrosynthetic analysis of aplysiasecosterol A (**1**).

and subsequently secure the desired configurations at C6 and C7. A disconnection at the C13−C14 bond was then considered to address the D ring (highlighted in blue) and the linkage problems together. Hydrofunctionalization of unactivated alkenes via metal-mediated hydrogen atom transfer (HAT) has proven to be a powerful tool in organic synthesis.[23−32] Thus, we envisaged an HAT based alkene cyclization reaction[25,27b,28−31] for the construction of consecutive C13, C14, and C8 stereocenters. This strategy revealed α,β-unsaturated enone **8** as a late intermediate in the synthesis. Disassembly of **8** gave two segments **9** and **10**, which could be coupled through a Reformatsky type reaction. Cleavage of the C5−C7 bond of **9** led to a cyclization precursor **11**. Further simplification provided ketone **12**, which was then traced back to symmetrical diketone **13**.[33] Differentiation of the two carbonyls of **13** would render quaternary C10 chiral. The right-hand segment **10** may arise from (+)-citronellol (**14**); the tertiary C17 could be introduced through Myers asymmetric alkylation[34] or sequential Aggarwal lithiation−borylation[35] and Zweifel−Evans olefination.[36]

Preparation of the Left-Hand Segment 9. A sequence of desymmetrizing reduction, diastereoselective allylation, and radical cyclization was exploited to assemble the tricyclic skeleton of **9** (Scheme 1). Corey−Bakshi−Shibata (CBS) reduction of diketone **13** with oxazaborolidine (*S*)-**15** and catecholborane afforded β-hydroxy ketone **16** in 72% yield and 92% ee,[37] along with its C10 epimer in 11% yield. Compound **16** underwent sequential silylation, hydroboration/oxidation (Cy_2BH; aq. $NaBO_3$), and Dess−Martin oxidation to furnish ketoaldehyde **17** with good overall efficiency. We examined a variety of conditions for the 2-bromoallylation of this aldehyde (Table 1). Hosomi−Sakurai reaction with 2-bromoallylsilane

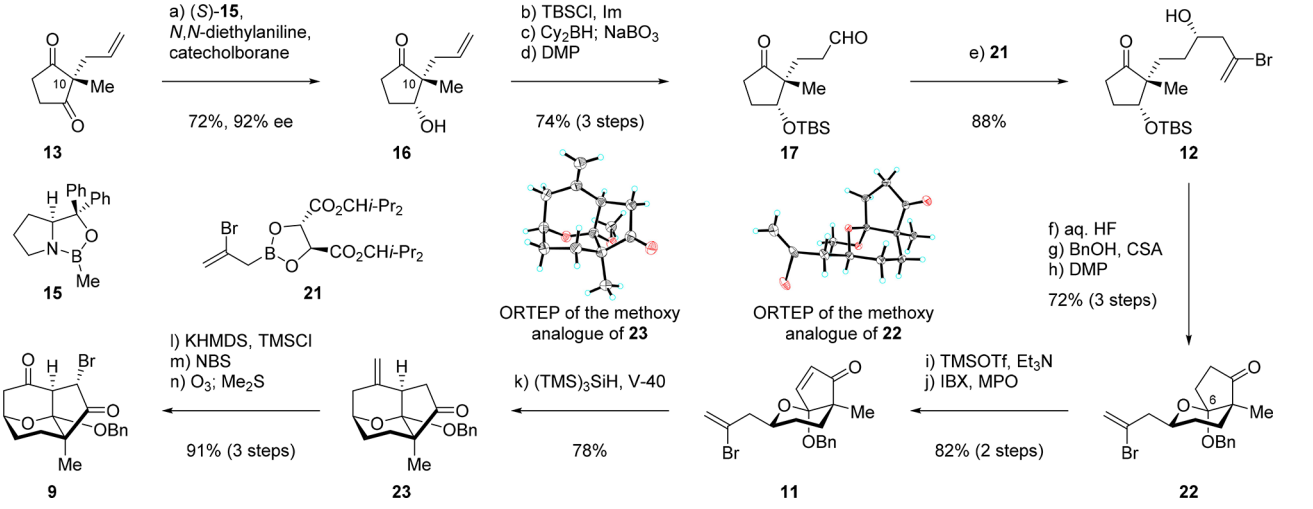
Table 1. Studies of 2-Bromoallylation of Aldehyde 17



entry	conditions	yield of **12**	yield of **19**
1	$TiCl_4$, **18**, CH_2Cl_2, −78 to 22 °C, 3 h	13%	14%
2[a]	$CrCl_2$, LiI, **20**, THF, 22 °C, 2.5 h	16%	18%
3[b]	In, $La(OTf)_3$, **20**, aq. NH_4Cl, 22 °C, 5 h	18%	18%
4	Sn, **20**, TBAI, aq. HCl, Et_2O, 22 °C, 3 h	31%	33%
5[a]	**21**, toluene/pentane, −95 °C, 2 h	88%	9%

[a]4 Å molecular sieves. [b]Sonication.

Scheme 1. Preparation of the Left-Hand Segment 9



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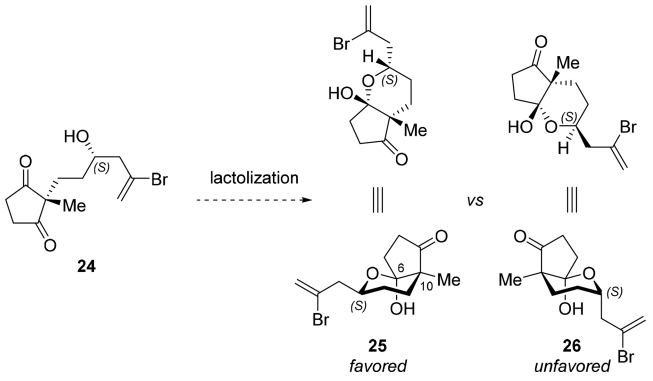
18 in the presence of $TiCl_4$ provided the desired homoallylic alcohol **12** in 13% yield, along with its C3 epimer **19** in an essentially equal amount (entry 1).[38] Under the modified Nozaki–Hiyama conditions [$CrCl_2$, LiI, 2,3-dibromopropene (**20**)],[39] **12** and **19** were obtained in 16% and 18% yields, respectively (entry 2). Indium-mediated Barbier type allylation in aqueous media was of similar efficiency and diastereoselectivity (entry 3).[40] In these cases, severe decomposition of **17** was observed. The combination of tin powder, **20**, and TBAI in Et_2O/aq. HCl significantly improved the yield of the homoallylic alcohols,[41] despite lack of stereocontrol at C3 (entry 4). Notably, the two epimers **12** and **19** can be readily separated by column chromatography, and the latter was converted into the former with good efficiency via sequential Mitsunobu and hydrolysis reactions (see the SI for details). To address the diastereoselectivity issue, we made recourse to chiral reagent based asymmetric allylation. Hara and coworkers developed a bis(2,4-dimethyl-3-pentyl) tartrate modified 2-bromoallylboronate reagent for Roush type enantioselective allylation.[42] To our delight, treatment of **17** with boronic ester **21** at low temperature gave **12** in 88% isolated yield (entry 5), along with a small quantity of **19** (9% yield). Desilylation of **12** with aq. HF followed by ketalization in the presence of CSA and BnOH furnished a bicyclic alcohol, which was oxidized with Dess–Martin periodinane to afford ketone **22** in 72% yield and >99% ee over the two steps. This ketone was then converted into α,β-unsaturated enone **11** by using the Nicolaou protocol (TMS enol ether formation/IBX oxidation; 82% overall yield).[43] For the radical cyclization, the conventional conditions (Bu_3SnH, AIBN, 100 °C) gave the desired product **23** in 23% yield; reductive debromination and enone conjugate reduction turned out to be severe side reactions. The combination of 1,1′-azobis(cyclohexanecarbonitrile) (V-40) and $(TMS)_3SiH$ significantly improved the annulation efficiency,[44] providing **23** in 78% yield. The structures of **22** and **23** were corroborated by X-ray crystallographic analysis of their methoxy analogues, respectively (Scheme 1). Exposure of the silyl enol ether derived from **23** to NBS effected face-selective α-bromination, and subsequent ozonolysis of the exocyclic C=C bond rendered diketone **9** in 91% overall yield.[45]

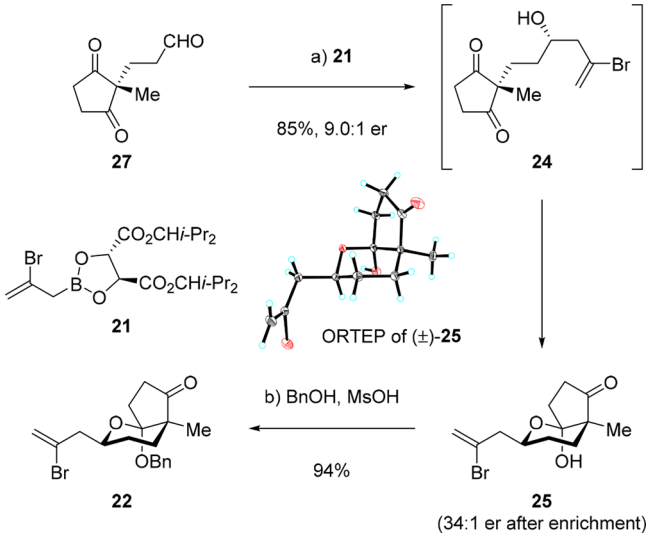
Expeditious Desymmetrizing Lactolization Approach to the Key Intermediate 22. In the presented route to **22**, the desymmetrization (the CBS reduction) was carried out prior to the ketalization, and therefore the C10 and C6 configurations were completely secured. However, the functional/protecting group manipulation markedly decreased the overall efficiency. To streamline the synthesis of **22**, we envisioned a desymmetrizing lactolization reaction of enantioenriched alcohol **24**, which would establish the C10 and C6 stereochemistry in a single step (Scheme 2).[46] The most stable conformations of lactols **25** and **26** were postulated (Scheme 2), respectively, based on X-ray crystallographic analysis of the methoxy analogue of **22** (Scheme 1), which suggested that **25** bearing an equatorial alkyl substituent should be thermodynamically more favorable than **26**.

Taking advantage of the desymmetrizing lactolization strategy (Scheme 2), we developed a two-step synthesis of **22** from known compound **27** (Scheme 3).[47] Chemo- and enantioselective allylation of the tricarbonyl compound with boronic ester **21** at −95 °C afforded the desired lactol **25** (85% yield) directly, presumably via the intermediacy of **24**. This lactol can be converted into the Mosher ester of **24** under

Scheme 2. Devised Desymmetrizing Lactolization Process



Scheme 3. Two-Step Synthesis of 22



standard acylation conditions, and the enantiomeric ratio was measured to be 9.0:1 by ^{19}F NMR analysis. Crystallization of this material from EtOAc/hexane (1:27) gave the crystals of (±)-**25**, and the enantiopurity of the mother liquid was elevated to an excellent level (34:1 er).[48] Thus, highly enantioenriched **25** was obtained in 64% overall yield from the prochiral starting material **27**. Similarly, tin-mediated 2-bromoallylation of **27** (under the conditions shown in Table 1, entry 4) provided (±)-**25** exclusively, which indicated that the tartrate-containing species in the asymmetric allylation had no bearing on the desymmetrization process. The structure of (±)-**25** was confirmed by X-ray crystallographic analysis (Scheme 3). We then tested a variety of conditions for the *O*-benzylation of **25**. Treatment with Yamada–Yu reagent (benzyl 2,2,2-trifluoro-*N*-phenylacetimidate)[49] furnished **22** in 56% yield, along with *O*-benzyl-**24** in 17% yield, whereas the more conventional benzylating reagent benzyl trichloroacetimidate did not react with **25**. The combination of BnOTf and 2,6-di-*tert*-butylpyridine[50] resulted in an increasing amount of *O*-benzyl-**24**. The ketalization conditions (BnOH, CSA, 4 Å molecular sieves) used in the first-generation preparation of **22** were ineffective for this substrate. To our delight, replacing CSA with more powerful MsOH led to the formation of **22** in 94% yield in 5 min. Notably, an inseparable side product emerged when an excess of BnOH was used. The ee of **22** was determined to be 93% by HPLC, which is consistent with the enantiopurity of its precursor **25**.

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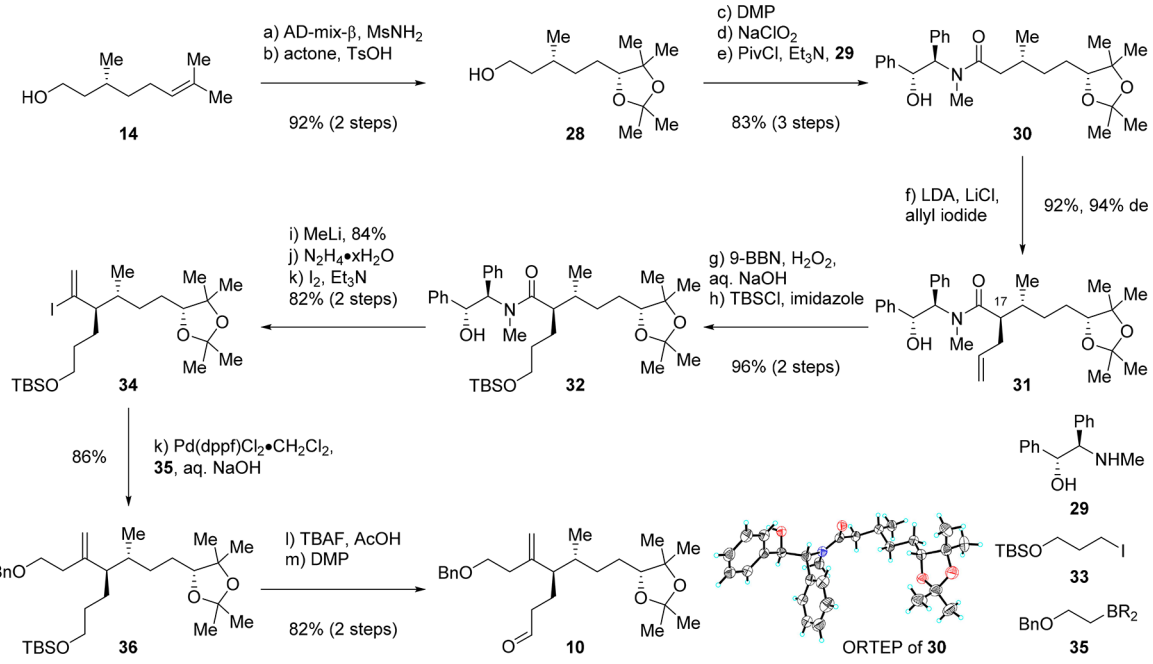
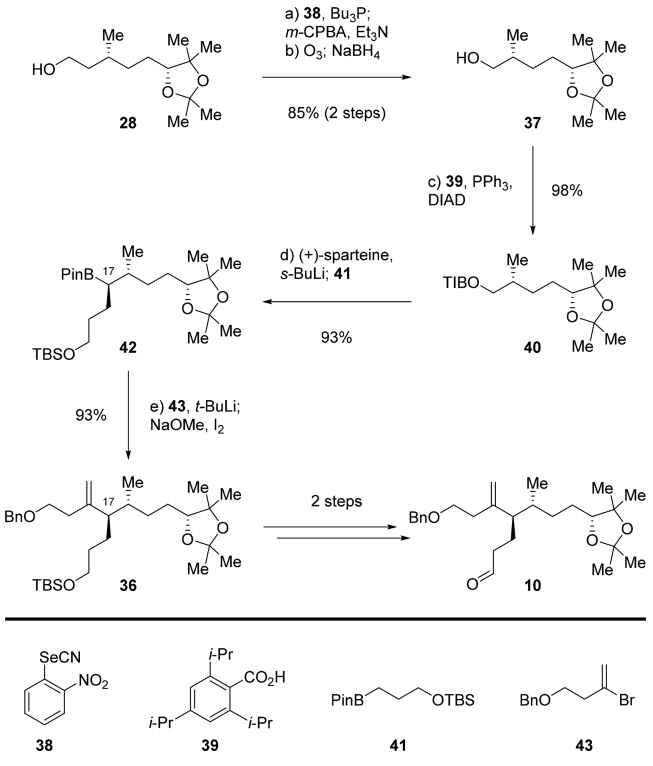
Scheme 4. First Route to the Right-Hand Segment 10



First Route to the Right-Hand Segment 10. The vicinal tertiary carbons of **10** posed a challenge for stereoselective synthesis. (+)-Citronellol (**14**) containing a desired tertiary center was exploited as the starting material of this route, and Myers alkylation[34] was responsible for the construction of the second tertiary center (Scheme 4). Sharpless asymmetric dihydroxylation of **14** (AD-mix-β, $MsNH_2$) followed by protection of the resultant 1,2-diol furnished acetonide **28** as a single stereoisomer in 92% overall yield. This compound was subjected to sequential Dess–Martin and Lindgren–Krauss–Pinnick oxidation to afford the corresponding carboxylic acid, which was condensed with (+)-(1*R*,2*R*)-pseudoephenamine (**29**) to give amide **30** with good efficiency.[34b] The structure of **30** was verified by X-ray crystallographic analysis (Scheme 4). Under the Myers conditions (LDA, LiCl, allyl iodide),[34] alkylation of **30** proceeded smoothly to provide olefin **31** in 92% yield and 94% de (measured by HPLC). Hydroboration/oxidation and silylation of the resultant alcohol afforded compound **32** in 96% yield over the two steps. Of note, the lower reactivity of iodide **33** (compared with that of allyl iodide) for alkylation hindered a direct path from **30** to **32**. The elaborated amide **32** underwent a sequence of MeLi addition, hydrazone formation, and iodination[51] to furnish alkenyl iodide **34** with good overall efficiency. Suzuki–Miyaura coupling of this iodide with alkylborane **35** (generated in situ from benzyl vinyl ether and 9-BBN) using $Pd(dppf)Cl_2$ as a catalyst gave alkene **36** in 86% yield. In this particular case, the triflate counterpart of **34** was not a suitable substrate for the cross-coupling reaction due to its tendency of elimination.[52] Desilylation with buffered TBAF followed by oxidation with Dess–Martin periodinane rendered aldehyde **10** in 82% overall yield.

Second Route to the Right-Hand Segment 10. Although Myers' alkylation chemistry provided an efficient means to establish the C17 stereochemistry, the tedious modifications after the alkylation significantly lowered the overall efficiency of the route described herein. Aggarwal and colleagues have developed lithiation–borylation chemistry[35] for the construction of consecutive stereocenters and showcased its power by a series of elegant syntheses of natural products.[53] Taking advantage of this method, we installed the tertiary C17 with good stereocontrol and minimized efforts of functional group manipulation (Scheme 5). Alcohol **28** was degraded into its one-carbon lower homologue **37** through a sequence of dehydration (Bu_3P, selenocyanate **38**; then *m*-CPBA) and ozonolysis (O_3; then $NaBH_4$). Mitsunobu reaction of **37** with 2,4,6-triisopropylbenzoic acid (**39**) afforded TIB

Scheme 5. Second Route to the Right-Hand Segment 10



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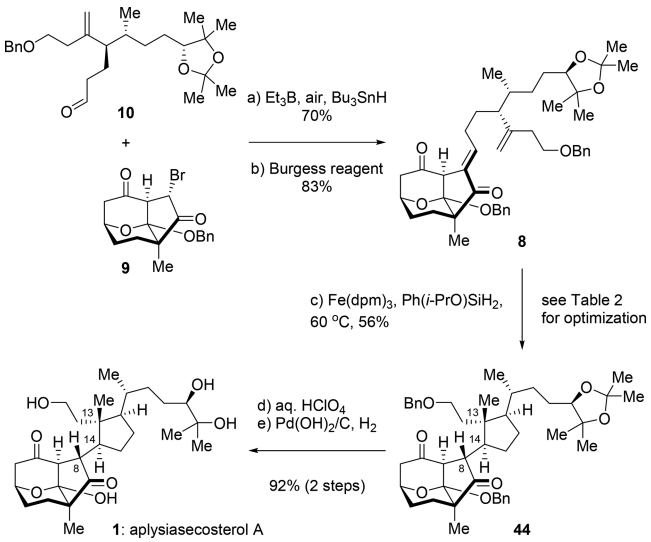
ester **40** (98% yield) as a precursor for lithiation.[54] Exposure of **40** to *s*-BuLi and (+)-sparteine led to stereoselective lithiation, and the resultant lithium species reacted with alkylboronate **41** to give secondary boronate **42** in excellent yield (93%) and diastereoselectivity (>40:1 at C17).[55] The *N*,*N*-diisopropylcarbamate (OCb) derivative of **37** turned out to be a poor substrate for this transformation. Treatment of alkenyl bromide **43** with *t*-BuLi generated an alkenyl lithium species, which underwent Zweifel–Evans olefination[36] with **42** in the presence of NaOMe and I_2 to furnish the key intermediate **36** in 93% yield, albeit with slightly diminished stereoselectivity (15:1 dr at C17). **36** was converted into the subtarget **10** through the two-step sequence used in the first route, and the minor diastereomer can be removed by column chromatography. This concise and flexible route also enabled convenient preparation of the analogues of **10** with various protecting groups of the primary hydroxyl, which served as building blocks for the syntheses of radical cyclization substrates (*vide infra*).

Studies of the HAT Based Radical Cyclization and Completion of Synthesis of Aplysiasecosterol A. *α*,*β*-Unsaturated enone **8** was assembled from the two segments and employed as a substrate for the key radical cyclization (Scheme 6). Under the Oshima conditions (Et_3B, air, Bu_3SnH),[56] *α*-bromoketone **9** and aldehyde **10** underwent a Reformatsky type reaction to afford an *anti* aldol product[57] in 70% yield, although reductive debromination of **9** occurred as a side reaction. Dehydration of the *β*-hydroxy ketone with Burgess reagent defined the *E*-geometry of the C=C bond of **8** (see the NOE study in the SI). Mesylation conditions (MsCl, Et_3N) gave the same dehydration product with lower efficiency.

Scheme 6. Completion of the Synthesis of Aplysiasecosterol A (1)



With a large quantity of **8** in hand, we directed our attention to the HAT based radical cyclization (Table 2). In most cases, four cyclization products were generated. We first managed to obtain each product in its pure form and elucidate the structure. One of the four can be separated from the other three by column chromatography, which turned out to be the desired product **44** stereochemically corresponding to **1** on the basis of 2D NMR analysis. The inseparable mixture of the rest three products were subjected to acetonide hydrolysis (aq. $HClO_4$). The resultant diols can be separated by column chromatography, the structures of which were determined by 2D NMR analysis as follows: 13-*epi*-6-*O*,11-*O*-bisbenzyl-**1**, 14-*epi*-6-*O*,11-*O*-bisbenzyl-**1**, and 13,14-bis-*epi*-6-*O*,11-*O*-bisbenzyl-**1**. These diols were reprotected as acetonides, providing the original cyclization products **45**–**47**, respectively. With the individual ^1H NMR spectra of **44**–**47** as references, we were able to evaluate the stereochemical outcomes of the cyclization under various conditions, by the integration in the ^1H NMR spectra of a mixture of the four products (see the ratios shown in Table 2). The excellent stereocontrol at C8 was noteworthy. When a proton approached the enolate species[29a] generated from the radical cyclization, the bulky cyclopentane moiety may preferentially occupy the opposite orientation against the sterically hindered 6-6-bicyclic domain fused to the cyclopentanone core.

The results from the investigation of the cyclization conditions are summarized in Table 2. Under the conditions reported by Baran and co-workers for olefin cyclization [$Fe(acac)_3$, $PhSiH_3$, $EtOH/(CH_2OH)_2$, 60 °C],[29a] a mixture of the four cyclization products was isolated in 60% yield; however, **44** was only obtained in 25% yield due to the poor stereoselectivity (entry 1). Interestingly, one of the side products was identified as peroxide **48** on the basis of HRMS and 2D NMR analysis, which may result from the oxidation of the enolate intermediate corresponding to ketone **46** by O_2 remaining in the reaction system followed by hemiketal formation. Thus, we strictly degassed the solvents used for the cyclization by freeze–pump–thaw cycling (entries 2–9). The yields of the mixture and **44** both increased under the same conditions (entry 2), while the peroxides were not detected. We examined more reactive $Ph(i\text{-}PrO)SiH_2$ used by Shenvi and colleagues for HAT based reactions.[30b] The cyclization took place at room temperature and more preferentially generated **44**, despite a lower yield of the mixture (entry 3). As the reaction temperature rose from 22 to 60 °C, the cyclization efficiency was enhanced considerably, while the stereoselectivity remained similar [**44**:(**45**+**46**+**47**) ca. 1:1); entries 3–5]. However, the ratio dropped significantly at 70 °C, although the yield of the mixture reached 90% (entry 6). Thus, all reactions were performed at 60 °C in further studies. The survey of solvents, solvent ratios, and an analogous silane was not fruitful (see Table S1 in the SI). We then turned our attention to other iron complexes. The use of $Fe_2(ox)_3$ resulted in a complex reaction profile and thus a poor yield of **44** (entry 7).[27b] More bulky 1,3-diketone ligands compared to acetylacetonate (acac), such as diisobutyrylmethanate (dibm)[29b,58] and dipivaloylmethanate (dpm),[29b,30b,58b] were found to improve the stereoselectivity to 1.7:1 [**44**:(**45**+**46**+**47**); entry 8] and 2.5:1 (entry 9), respectively. In the latter case, DCE was used as a cosolvent to enhance the solubility of $Fe(dpm)_3$, and **44** was isolated in 56% yield. We are intrigued by the observation that the 1,3-diketone ligands of different steric hindrances led to different stereoselectivity of the radical cyclization at the same temperature and under essentially same conditions (entries 5, 8, and 9). This indicates that the iron complex was not completely innocent in the cyclization process.

We then prepared three analogues of **44** (Table 3) to study the steric effect of substrates upon the efficiency and stereochemical outcome of the cyclization. Compounds **49** and **50** arose from two analogues of **10** with more bulky 2,4,6-

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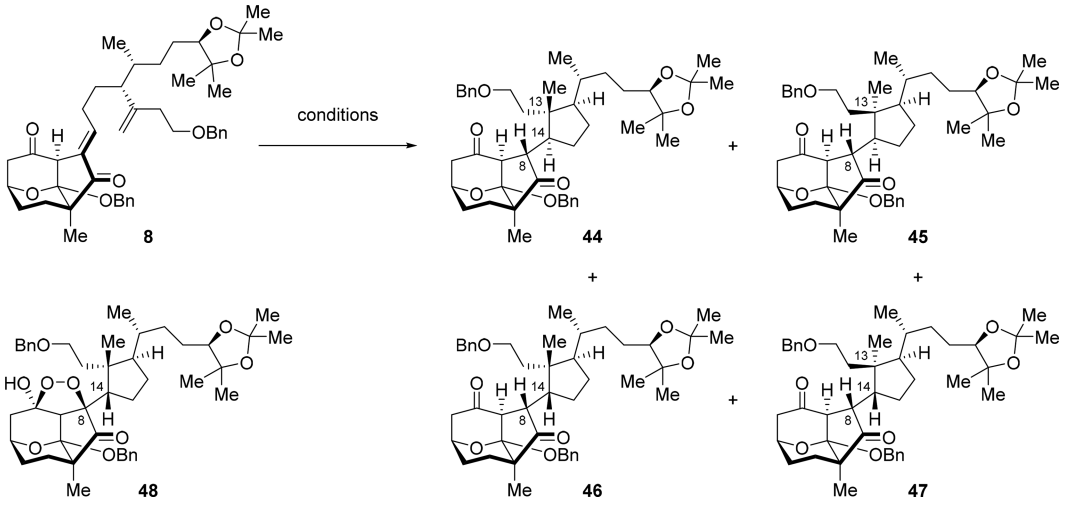
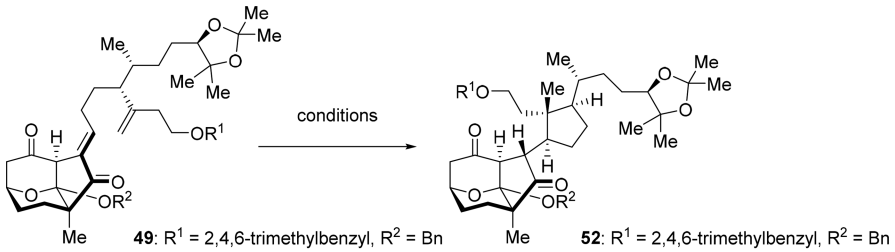
Table 2. Conditions for the HAT Based Radical Cyclization of 8



entry	conditions[a]	yield of mixture	yield of **44**	ratio[b] (**44**:**45**:**46**:**47**)
1[c]	$Fe(acac)_3$, $PhSiH_3$,EtOH/$(CH_2OH)_2$, 60 °C	60%	25%	1:0.33:0.47:0.58
2[c]	$Fe(acac)_3$, $PhSiH_3$,EtOH/$(CH_2OH)_2$, 60 °C	70%	30%	1:0.33:0.46:0.59
3[d]	$Fe(acac)_3$, Ph(*i*-PrO)SiH_2,EtOH/$(CH_2OH)_2$, 22 °C	41%	21%	1:0.33:0.21:0.39
4[d]	$Fe(acac)_3$, Ph(*i*-PrO)SiH_2,EtOH/$(CH_2OH)_2$, 50 °C	60%	27%	1:0.35:0.38:0.51
5[d]	$Fe(acac)_3$, Ph(*i*-PrO)SiH_2,EtOH/$(CH_2OH)_2$, 60 °C	84%	44%	1:0.29:0.29:0.32
6[d]	$Fe(acac)_3$, Ph(*i*-PrO)SiH_2,EtOH/$(CH_2OH)_2$, 70 °C	90%	36%	1:0.34:0.55:0.57
7[d]	$Fe_2(ox)_3{\cdot}6H_2O$,Ph(*i*-PrO)SiH_2,EtOH/$(CH_2OH)_2$, 60 °C	22%	17%	1:0.18:0:0.09
8[e]	$Fe(dibm)_3$, Ph(*i*-PrO)SiH_2,EtOH/$(CH_2OH)_2$, 60 °C	75%	47%	1:0.25:0.14:0.19
9[e,f]	$Fe(dpm)_3$, Ph(*i*-PrO)SiH_2,EtOH/DCE/$(CH_2OH)_2$, 60 °C	77%	56%	1:0.22:0.04:0.14

[a]The solvents were subjected to freeze−pump−thaw cycling except for entry 1. V_{EtOH}:$V_{(CH_2OH)_2}$ = 4:1, unless otherwise noted. All reactions were complete in 1 h. [b]Determined by ^1H NMR analysis of the mixture. [c]1.0 equiv. [Fe], 2.5 equiv. [Si]. [d]0.50 equiv. [Fe], 2.5 equiv. [Si]. [e]0.50 equiv. [Fe], 5.0 equiv. [Si]. [f]V_{EtOH}:V_{DCE}:$V_{(CH_2OH)_2}$ = 3:1:1.

Table 3. Cyclization of the Analogues of 8 under the Optimal Conditions[a]



entry	substrate	desired product	yield of mixture	yield of the desired product	ratio[b]
1	**49**	**52**	75%	55%	2.8:1
2	**50**	**54**	59%	45%	3.2:1
3	**51**	**53**	77%	56%	2.8:1

[a]The solvents were subjected to freeze−pump−thaw cycling. 0.50 equiv. [Fe], 5.0 equiv. [Si]. V_{EtOH}:V_{DCE}:$V_{(CH_2OH)_2}$ = 3:1:1, 60 °C. All reactions were complete in 1 h. [b]The ratio of the desired product and the other three isomers. Determined by ^1H NMR analysis of the mixture.

trimethylbenzyl and 1-naphthylmethyl protecting groups on their side chains, respectively, and compound **51** was obtained from the methoxy analogue of **9**. These substrates were subjected to the optimal conditions for the cyclization (Table 2, entry 9), and the results are shown in Table 3. Enones **49** and **51** were converted into the corresponding cyclization products **52** and **53**, respectively, with essentially same efficiency and stereoselectivity as those of the cyclization of **44** (entries 1 and 2). However, 1-naphthylmethyl was not a completely stable protecting group under these conditions, which resulted in a lower yield of cyclization product **54** from its precursor **50** (entry 3). The stereoselectivity was slightly improved in this case.

Finally, acetonide hydrolysis of **44** with aq. $HClO_4$ followed by double debenzylation via hydrogenolysis [$Pd(OH)_2/C$, H_2] afforded aplysiasecosterol A (**1**) in 92% yield over the two steps (Scheme 6). The spectra and physical properties of the synthetic sample were identical to those reported for the authentic natural product.[15]

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CONCLUSION

We have accomplished the first and asymmetric total synthesis of aplysiasecosterol A (**1**). Desymmetrization strategies were developed to introduce the three consecutive stereocenters of the left-hand segment, based on the recognition of the hidden structural symmetry of the molecule. The right-hand segment bearing two vicinal tertiary carbons was prepared through two approaches featuring Myers asymmetric alkylation and Aggarwal lithiation−borylation, respectively. A Reformatsky type reaction was responsible for coupling of the two segments under essentially neutral conditions. The strategic application of iron-mediated HAT based radical cyclization enabled expeditious construction of the three adjacent stereocenters at the central domain. This concise and convergent route paves the way for the synthesis of structurally relevant secosteroids and designed analogues thereof, which may facilitate studies of the biology of this fascinating class.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b05070.

Experimental procedures and spectroscopic data of compounds, NMR spectra of compounds (PDF)
CIF files (ZIP)

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Notes

The authors declare no competing financial interest.

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