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Total Synthesis of (±)-Aplykurodinone-1: Traceless Stereochemical Guidance

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Abstract: The total synthesis of the highly degraded steroidal natural product, aplykurodinone-1 (**1**), has been accomplished. Key features include a one-flask hydrolysis/retro-aldol/iodolactonization sequence to excise the C_8 hydroxymethylene functionality with retention of stereochemistry and the stereoselective installation of the C_{13} methyl group through hydrogenation with homogeneous catalyst.

Of all of the classes of natural products, steroids have perhaps had the most enduring role in prompting new ideas in total synthesis.[1] A not insignificant body of organic chemistry has been discovered in the context of pursuits directed to the total synthesis of steroids. Apparently, this interest continues to the present day.[2]

One of the vexing problems in steroid total synthesis is that of exercising control of the configuration at C_{20}.[3] The challenge is that of correlating the configuration of the presumably "freely rotating" C_{20} with the resident stereochemistry of the polycyclic domain. Though ingenious solutions to the "C_{20} problem" have been advanced, it is still an interesting and thought provoking matter.

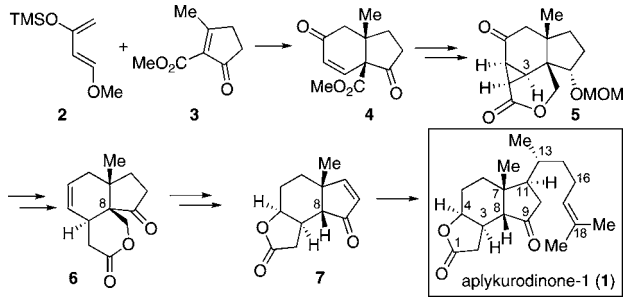
It was in this setting that we took particular note of the aplykurodines, isolated from marine mollusks of the genus Aplysia.[4] This family can well be viewed as a rare class of highly degraded marine steroids, where C_{13} in the aplykurodine setting corresponds to C_{20} in wild-type steroids. Also of note is the *cis* fusion of the hydrindane sector in contrast to the *trans* C−D fusion of hydrindanes, which is so prevalent in fully mature steroids.[5]

We note that various aplykurodines exhibit cytotoxic activity against a range of human cancer cell lines.[4] Notwithstanding the potential elements of chemistry and medicinal chemistry-based points of interest, surprisingly little attention at the level of synthesis has been directed to the aplykurodines.[6] Our laboratory took particular note of a recently isolated member of the family, aplykurodinone-1 (**1**).[7] Following its isolation from the sea hare *Synphonota geographica* in 2005, the structure of aplykurodinone-1 (**1**) was elucidated through a combination of spectroscopic methods, X-ray crystallography, and chemical correlation. As shown in Scheme 1, **1** was found to possess a *cis*-fused C−D ring with epimeric C_8 (steroidal numbering) and an unsaturated side chain (as compared to cholesterol).

On the basis of considerations advanced above, a total synthesis effort directed to this "degraded" steroid was undertaken. Below is described the inaugural total synthesis of (±)-**1**, resulting from this initiative. As will be seen, the program potentially encompassed several chemistry-level initiatives of broader heuristic value.

Using ideas stemming from analysis by pattern recognition,[8] we envisioned that, in principle, the hypothetical hydrindanone **4** contains an array of coordinated functionality, which could well enable access to the eventual target system, **1**. The plan envisioned halolactonization as the instrumentality for fusing the γ-lactone to the *cis*-fused hydrindanone, thereby creating a ladder-like topography. Accordingly, we needed to gain secure control over the configurational relationship between strategic carbons 3 and 7 in **1** (vide infra). It occurred to us that an otherwise unnecessary quaternary function at C_8 could orchestrate the required relationship of the angular methyl group at C_7 with a soon-to-be-installed acetic acid moiety at C_3 (see structures **5** and **6**). Iodolactonization leading to the γ-lactone could then follow in the wake of excision of the now traceless C_1 fragment.

Scheme 1. Synthetic Strategy toward Aplykurodinone-1 (**1**)



Given the general line of thinking adumbrated above, and a long-term proclivity for Diels−Alder reactions, we hoped to advance along such lines. In the event, it was discouraging to find that attempted cycloaddition between **2**[9] and **3**[10] failed under various thermal and Lewis acid mediated conditions. However, reaction of **2** with methyllithium generated an operational lithium enolate,[11] which did undergo effective cycloaddition with **3**, thereby providing a 73% yield of **4**. It is well recognized that realization of the required cycloaddition does not, in and of itself, inform as to the limiting, mechanistic, extremi (two sequential Michael additions or an anionically mediated Diels−Alder reaction).[12]

The enone was regioselectively masked as a thioketal.[13] The C_9 ketone was then reduced, as shown, and the resultant alcohol was protected as a MOM ether. Upon reduction of the ester and removal of the dithiane ketal,[13a,14] compound **10** was in hand. The primary alcohol was next converted to its diazoacetyl derivative, **11**. As shown in Scheme 2, intramolecular cyclopropanation onto the electron-deficient enone afforded the activated cyclopropane, **5**, though only in moderate yield (40%).[15]

The next phase entailed the opening of the cyclopropane ring, with concomitant installation of unsaturation at C_4−C_5. Toward this end, the C_5 ketone was converted to an iodide through a two-step sequence, commencing with Luche reduction,[16] which provided a 2:1 (β:α) epimeric mixture of alcohols.[17] These compounds were readily converted to iodide **12**. In the event, upon exposure of **12** to SmI_2,[18] it readily suffered the hoped-for reductive cyclopropane

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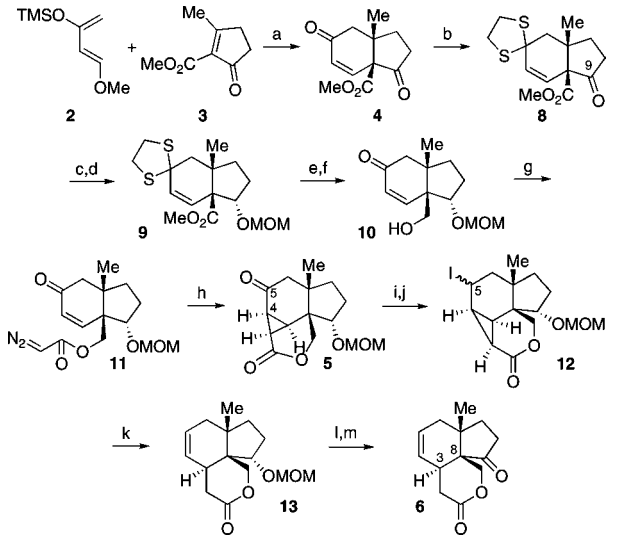
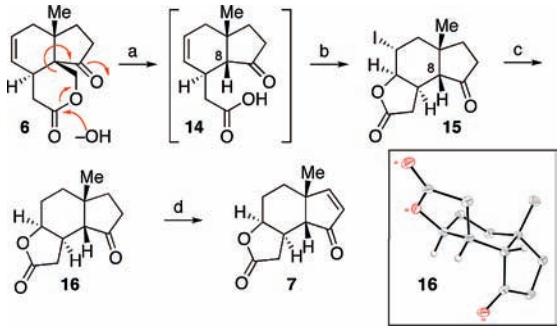
Scheme 2. Synthesis of **6** en Route to Aplykurodinone-1 (**1**)



[a] Key: (a) MeLi, DME/THF, −50 °C; TFA, $CHCl_3$, reflux, 73%; (b) $HSCH_2CH_2SH$, AcOH, *p*-TSA, 74%; (c) $NaBH_4$, CH_2Cl_2/MeOH, −78°→ −40 °C; (d) MOMCl, iPr_2NEt, CH_2Cl_2, 84% over two steps; (e) DIBAL-H, CH_2Cl_2, −78 °C; (f) $Tl(NO_3)_3$, MeOH/THF/H_2O, 95% over 2 steps; (g) TsNHN=CHCOCl, $PhNMe_2$, Et_3N, CH_2Cl_2, 0 °C, 88%; (h) bis-(*N-tert*-butylsalicylaldiminato) copper(II), PhMe, reflux, 40%; (i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$; (j) I_2, PPh_3, imidazole, PhMe, reflux, 78% over two steps; (k) SmI_2, THF/MeOH, 85%; (l) HCl, THF/H_2O; (m) DMP, CH_2Cl_2, 80% over two steps.

Scheme 3



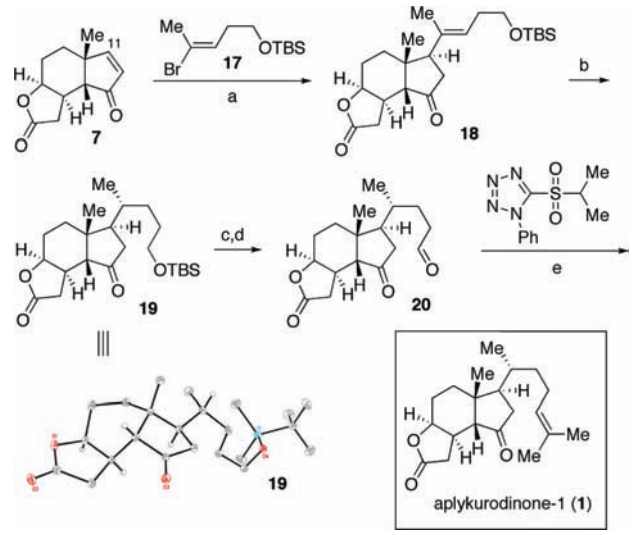
[a] Key: (a) K_2CO_3, H_2O, 100 °C; (b) NIS, CH_2Cl_2, 75%; (c) Ra−Ni, CH_2Cl_2/EtOH, 90%; (d) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; $Pd(OAc)_2$, CH_3CN, 76% (90% brsm).

opening, to deliver lactone **13** in good yield (85%). The latter was converted to **6** in a straightforward fashion, as shown.

The otherwise extraneous C_8 oxymethylene functionality had indeed been exploited as a very useful C_3 stereochemical linchpin (vide supra). Having served its function in mediating the stereoselective installation of the C_3 center, the C_1 fragment was cleaved via a hydrolysis−retro-aldol sequence following exposure of **6** to the action of K_2CO_3 in water at 100 °C. Subsequent iodolactonization[19] of the resultant carboxylic acid (**14**) was accomplished in the same flask, to provide **15** in 75% yield from **6**. The re-emergence of the *cis*-junction was confirmed through NOESY analysis of the methyl ester derivative of **14** and by X-ray diffraction of the subsequent deiodinated intermediate, **16**.[20] Finally, Saegusa oxidation[21] of **16** afforded **7**, presenting the tricyclic core of aplykurodinone-1, in the sense shown (Scheme 3).

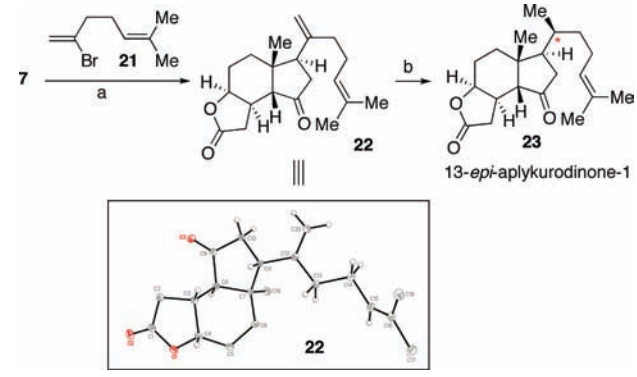
With compound **7** in hand, the synthesis entered its terminal phase, i.e. installation of the C_{11} side chain. A stepwise strategy was set in place. As outlined in Scheme 4, BF_3-mediated conjugate addition of the cuprate derived from vinyl bromide **17**[22] was

Scheme 4



[a] Key: (a) **17**, *t*-BuLi, CuCN, $BF_3 \cdot OEt_2$, −78 °C→−98 °C, 73%, 10:1 dr; (b) Crabtree catalyst, H_2, CH_2Cl_2, 75% conversion, 50% yield (pure); (c) HF, CH_3CN/THF; (d) DMP, CH_2Cl_2, 87% over two steps; (e) THF, LiHMDS, −78 °C, 68%.

Scheme 5



[a] Key: (a) **17**, *t*-BuLi, CuCN, Et_2O, −78 °C, 51%; (b) Wilkinson catalyst, H_2, benzene, 67%.

accomplished with a high degree of facial selectivity (10:1 dr) to provide intermediate **18**. Given the difficulties surrounding the *heterogeneous* hydrogenation of the $C_{20}-C_{22}$ olefin as a means of installing the C_{20} stereocenter of *trans*-fused mature steroids,[23] it was hoped that *homogeneous* hydrogenation protocols may be more productive.[24] Thus, following exposure to Crabtree catalyst,[25] under an atmospheric pressure of H_2, the trisubstituted olefin was reduced in a diastereoselective fashion (>5:1) to furnish compound **19**, which bears all of the stereocenters of aplykurodinone-1 (**1**). A single crystal of this advanced intermediate was obtained, and X-ray crystallographic analysis was found to support the proposed structure. Elaboration of the side chain was accomplished in a straightforward fashion, as shown. Thus, cleavage of the TBS group[26] and subsequent oxidation[27] delivered aldehyde **20**, which readily underwent modified Julia olefination[28] to furnish the target compound, aplykurodinone-1 (**1**). Its spectroscopic properties were the same as those reported for the isolated natural product. In the course of these synthetic studies, we also investigated a different route for the emplacement of the C_{11} side chain. The fully elaborated dienyl fragment could be appended to the core (**7**) in a single step. It was hoped that the intermediate thus obtained could then be converted, in one step, to aplykurodinone-1 (**1**), through regio- and stereoselective hydrogenation. In the event, the conjugate addition

of **21**[29] to **7** was accomplished, to provide **22** in moderate yield. Upon exposure to Wilkinson's catalyst[30] under atmospheric H_2, the 13-*epi*-aplykurodinone-1 isomer (**23**) was selectively formed (>6:1 dr) (Scheme 5). Perhaps in each of the two hydrogenation transition states (**18**→**19**; **22**→**23**), the double bond projects from the β-face of the molecular backbone. The bulky catalyst then approaches the olefin from the unhindered portion of the olefin, to provide the observed stereochemical outcome.[31]

In summary, the total synthesis of aplykurodinone-1 (**1**) has been accomplished. A key feature of the effort involved an anionically mediated cycloaddition of a metallo-enolate derived from **2** with **3** (see formation of **4**). The seemingly extraneous oxymethyl C_1 function at C_8 was used to govern the configurational relationship between C_3 and C_7. The C_8 function is ultimately excised. The stereochemistry at C_{13} is managed with good stereoselectivity based on the suitable order of introduction of H and Me to this carbon.

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Note Added after ASAP Publication. The Supporting Information was published as .txt files rather than as .cif files. The correct Supporting Information files with an additional .cif file were posted to the web as an Addition and Correction on June 24, 2010.

Supporting Information Available: Experimental procedures, copies of spectral data, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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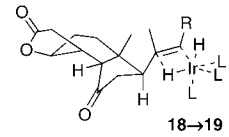
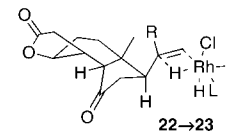
(31) Proposed transition states of the homogeneous hydrogenation with Crabtree and Wilkinson catalyst are shown below. In each case, the bulky catalyst is believed to approach the double bond from its less hindered face. However, as described above, different stereochemical outcomes were observed in these two systems.



18→19



22→23

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