Natural Product Synthesis

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A Concise Route to the Strongylophorines

*Wanwan Yu, Per Hjerrild, Jacob Overgaard, and Thomas B. Poulsen**

Abstract: *An efficient eight-step semisynthesis of strongylophorine-2 from the abundant building block isocupressic acid is reported. The route represents the first synthetic entry into this class of natural products and provides access to six additional family members. A novel iron(III)-mediated rearrangement–cyclization cascade and a directed photochemical sp^3 C–H δ-lactonization are the key transformations that enable concise assembly of these bioactive polycyclic meroterpenoids.*

Studies of terpenoid natural products continue to drive advances within structure determination,[1] biosynthesis,[2] and molecular pharmacology.[3] In addition, complex terpenoids are important synthetic targets, enabling biological investigations and subsequent discoveries.[3,4] Meroterpenoids are a terpenoid subclass resulting from hybrid biosynthetic pathways that fuse terpene substructures with polyketide or alkaloid components.[5,6]

Our laboratory takes an interest in natural products with challenging structural features and unclarified biological activities.[7] The strongylophorines (STRs, Figure S1 in the Supporting Information) are a family of meroditerpenoids initially isolated from the marine sponges *Strongylophora durissima* and *Petrosia cortica*,[8,9b] with members displaying diverse biological activity, including neuroprotective effects (STR-8),[9a] anti-invasive activity (STR-26),[9b–d] and inhibitory activity against HIF-1 (STR-2, 3, and 8).[9e] To date, no syntheses of any of the strongylophorines have been reported. Structurally, STR-2 (**1**, Figure 1) occupies a central position within the STR-family since this compound provides a favorable point of diversification and contains the synthetically challenging bicyclic δ-lactone functionality at the A–B ring junction found in most of the bioactive STRs. Similar or inverted δ-lactone substructures can be found in, for example, the recently isolated leonepetaefolin A,[10] members of the C20-gibberelin plant hormones,[11] and the HIV-RT inhibitors (neo)tripterifordin[12]—total syntheses of C20-gibberelins[11] and neotripterifordin[12c] have been reported.

To facilitate biological investigations of the strongylophorines, as well as the preparation of analogues, we set out to develop a route to several members of the STR family, with STR-2 as the primary objective. We initially considered strategies for an asymmetric total synthesis of STR-2, which inevitably resulted in lengthy sequence designs, mainly as a consequence of the manipulations required to install the bicyclic lactone. We then realized a potentially powerful semisynthetic approach starting from the labdane diterpene isocupressic acid (**2**; Figure 1)—a major constituent of the bark and needles of the *Ponderosa* pine tree. When viewed in combination with a monoprotected hydroquinone, the functionalities present in **2** map convincingly onto the STR-2 structure, however, despite the strong visual appeal, it was also clear that the required transformations (regioselective phenolic coupling, cyclization of the C and D rings, sp^3 C–H δ-lactonization) presented a substantial synthetic challenge (Figure 1). Herein, we report a sequence that delivers STR-2 in just 8 steps from isocupressic acid, with a novel iron(III)-mediated rearrangement–cyclization cascade and a directed photochemical sp^3 C–H δ-lactonization as the key steps. Our route thus far has enabled the synthesis of seven members of the STR family.

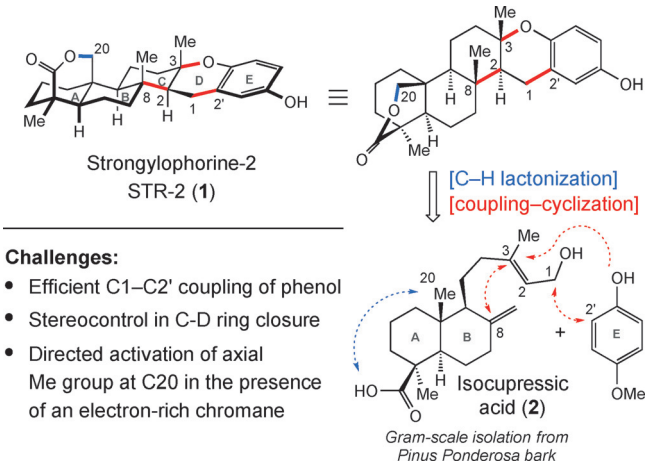

Figure 1. Chemical structure of strongylophorine-2 and proposed semisynthesis from isocupressic acid.

We were able to routinely isolate gram quantities of **2** from powdered *Pinus Ponderosa* bark through slight modification of reported conditions.[13] Following conversion into the benzyl ester (**3**; Scheme 1), we initially investigated direct C–C coupling between C1 of **3** and C2′ of monoprotected hydroquinone derivatives. Despite the apparent simplicity of this transformation, the established methods are surprisingly inefficient. Lewis acids such as $BF_3{\cdot}OEt_2$ or $Sc(OTf)_3$ are known to effect dehydrative C–C coupling between phenols and allylic alcohols but in low yields even for simple substrates while using an excess of the allylic alcohol.[14] When evaluated in our system, we maximally achieved around 30% yield in the presence of a large excess (20 equiv) of the phenol to partially suppress competing diene formation from **3** (Table S1 in the Supporting Informa-

[*] W. Yu, P. Hjerrild, Dr. J. Overgaard, Prof. Dr. T. B. Poulsen
Department of Chemistry, Aarhus University
Langelandsgade 140, 8000 Aarhus C (Denmark)
E-mail: thpou@chem.au.dk

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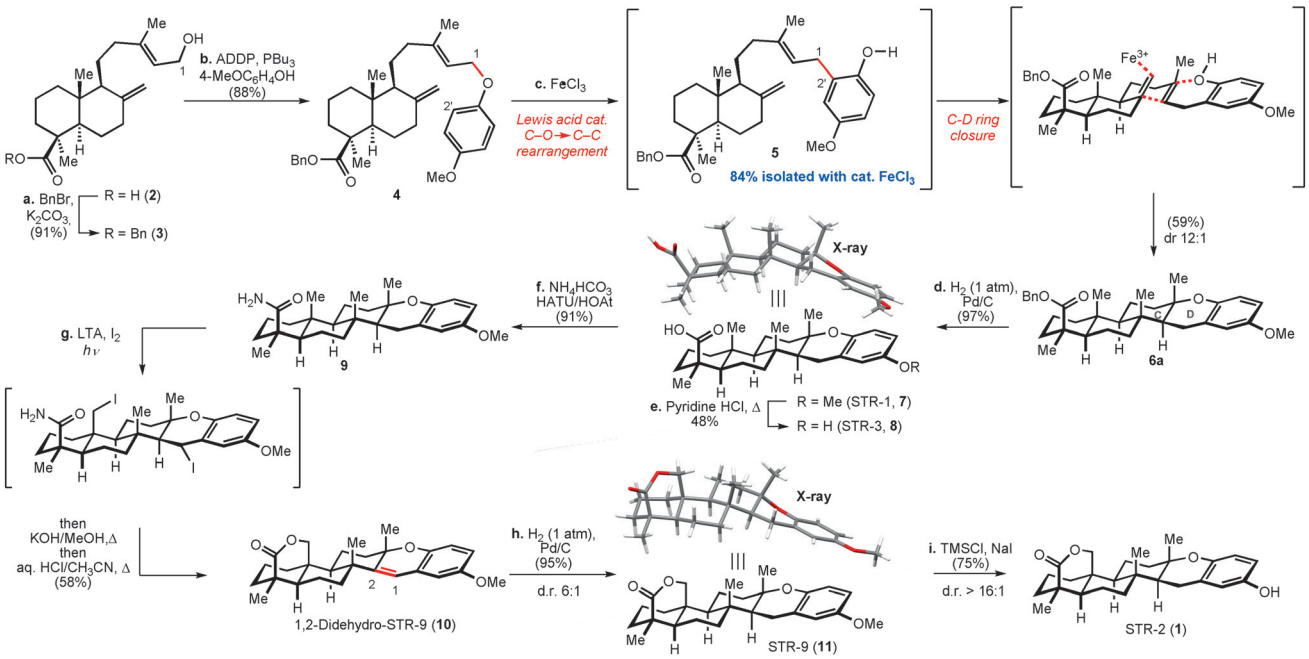
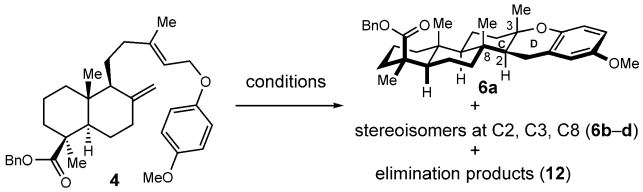


Scheme 1. Semisynthesis of Strongylophorines-1, 3, 9, and 2. Reagents and conditions: a) Benzyl bromide (1.2 equiv), K_2CO_3 (1.5 equiv), CH_2Cl_2/DMF (1:1), 0 °C, 40 h; b) 4-MeO-PhOH (6.0 equiv), P(*n*Bu)$_3$ (1.5 equiv), PhMe, 0 °C, 15 min, then ADDP (1.5 equiv), RT, 24 h; c) $FeCl_3$ (3.0 equiv), CH_2Cl_2 (3.6 mM), −15 °C, 15 min; d) Pd/C (20% w/w), H_2 (1 atm), MeOH, RT, 12 h; e) Pyridine-HCl, 200 °C, 20 min; f) NH_4HCO_3 (12 equiv), HATU (1.2 equiv), HOAt (1.2 equiv), NEt_3 (15 equiv), CH_2Cl_2/DMF (5:1), RT, 72 h; g) LTA (5.0 equiv), I_2 (3.0 equiv), *hν* (6W, 254 nm), PhH, RT, 12 h then 10% KOH in MeOH, reflux, 2 h then 2 M aq. HCl/CH_3CN (1:1), 100 °C, 4 h; h) H_2 (1 atm), Pd/C (250% w/w), EtOAc/AcOH (1:1), 40 °C, 12 h; i) NaI (100 equiv), TMSCl (100 equiv), CH_3CN, RT, 30 min, then **11** (1.0 equiv), PhMe/CH_3CN (1:1), 40 °C, 18 h. DMF = *N*,*N*-Dimethylformamide, ADDP = 1,1′-(Azodicarbonyl)-dipiperidine, HATU = 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, HOAt = 1-Hydroxy-7-azabenzotriazole, LTA = Lead(IV)acetate, TMS = trimethylsilyl.

tion). Alternative methods require multistep protection of both phenolic OH groups to enable the preparation of organometallics such as Grignard or lithium reagents, organocuprates, or organostannanes to allow coupling with allyl halides or allyl sulfonates.[15] Faced with these limitations, we hypothesized that access to the desired C1−C2′-linked phenol intermediate could be feasible by Lewis acid promoted [1,3]-shift[16] of the corresponding allyl ether derivative **4**, which in principle could allow a cascade rearrangement–double-ring annulation to construct the C and D rings of STR-2 in a single operation. To the best of our knowledge, this type of cascade reaction is unprecedented.

Contrary to the dehydrative C−C coupling, we found that direct dehydrative C−O coupling can be performed in excellent yield under modified Mitsunobu conditions (Scheme 1).[17] To our delight, we obtained validation for the cascade transformation through exposure of allyl ether **4** to $BF_3{\cdot}OEt_2$ (Table 1, entry 1), which resulted in direct formation of pentacycle **6a** as the major component, along with significant amounts of stereoisomeric products (**6b–d**) and side products (**12**), the latter originating from an elimination pathway from **4**. An extensive screening was undertaken (Table S2), with representative results shown in Table 1. In general, coordinating solvents completely shut down the reactivity (Table S2). Alternative Lewis acids strongly influenced the reaction outcome, for example, $SnCl_4$ mainly resulted in elimination–decomposition of the starting material (entry 2) and $TiCl_4$ afforded no compounds

Table 1: Screening of conditions for the rearrangement and C−D ring annulation.



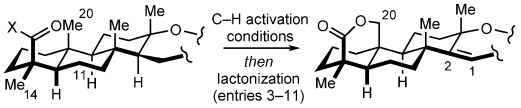
Entry	Conditions	(6a/6b–d/12)[a,b]
1	$BF_3{\cdot}OEt_2$ (5 equiv), CH_2Cl_2, 0 °C, 30 min	46:40:14
2	$SnCl_4$ (2 equiv), CH_2Cl_2, 0 °C, 30 min	21:19:60
3	$TiCl_4$ (2 equiv), CH_2Cl_2, 0 °C, 30 min	–[c]
4	$InBr_3$ (2 equiv), CH_2Cl_2, 0 °C, 30 min	66:23:11
5	$FeCl_3$ (2 equiv), CH_2Cl_2, 0 °C, 30 min	48:24:28
6	$InBr_3$ (2 equiv), CH_2Cl_2, −15 °C, 30 min	–[d]
7	$FeCl_3$ (3 equiv), CH_2Cl_2, −15 °C, 30 min	65:19:16
8	$FeCl_3$ (3 equiv), CH_2Cl_2, −15 °C, 5 min	77:19:4
9	$FeCl_3$ (3 equiv), CH_2Cl_2, −40 °C, 5 min	–[e]

[a] Determined by ^{1}H-NMR. [b] For the structure of **12**, see the Supporting Information. [c] Decomposition. [d] 34% conversion into compound **5** (Scheme 1), no cyclization. [e] No conversion.

that could be readily identified (entry 3). Protic acids (CSA or HCl) were not productive (Table S2). Further screening revealed that both $InBr_3$ and $FeCl_3$ exhibited increased stereoselectivity (entries 4 and 5). Only $FeCl_3$ maintained

reactivity at −15 °C (entries 6 and 7), and by limiting the reaction time to 5 minutes, the selectivity could be increased further (entry 8). At even lower temperatures, the reactivity with $FeCl_3$ was also drastically reduced (entry 9). In the end, we were able to generate benzyl-protected STR-1 (**6a**) on a preparative scale in 59% yield as a 12:1 mixture of diastereomers (Scheme 1).[18] Debenzylation of **6a** delivered STR-1 (**7**) in 97% yield (confirmed by X-ray analysis),[19] and demethylation of **7** by heating in neat pyridine-HCl afforded STR-3 (**8**). STR-3 provides a convenient starting point for several other family members, such as STR-5 (**18**) and STR-12 (**19**; see the Supporting Information). With an efficient route to the pentacyclic compounds in place, our focus shifted towards the sp^3 C–H activation at the axial methyl group at C20 to construct the bicyclic δ-lactone motif of STR-2. Given the locked conformation of **7** and the axial orientation of the carboxylic acid (see X-ray crystal structure of **7**), the geometry presented an opportunity for achieving a directed transannular δ-C–H activation. Our first attempts to directly construct the lactone under Shilov-type conditions[20] using STR-1 (**7**) only returned starting material (Table 2, entry 1).

Table 2: Optimization of the C–H lactonization.



Entry	X	Conditions/ Variations	Results (% **10**)[a]
1	OH/OK	K_2PtCl_4/K_2PtCl_6 H_2O, 160 °C, 20 h	No conv.
2	NHOMe	$Pd(OAc)_2/CuCl_2/AgOAc$ DCE, 100 °C, 14 h	40% conv. (complx mix)
3[b]	NH_2	I_2, $PhI(OAc)_2$, *hν* (6W UV) PhH, 20 °C, 24 h	100% conv. (complx mix)
4[b]	NH_2	I_2, $Pb(OAc)_4$, *hν* (6W UV) PhH, 20 °C, 24 h	44
5[c]	NH_2	300W UV instead of 6W UV lamp	20
6[c]	NH_2	Sunlamp instead of 6W UV lamp	12
7[c]	NH_2	Sonication instead of irradiation	No conv.
8[c]	NH_2	3 equiv I_2 instead of 5 equiv	45
9[c]	NH_2	Irradiation: 4 h/**12 h**/ 16 h	25/**58**/51
10[c]	NH_2	$Hg(OAc)_2$ instead of $Pb(OAc)_4$	24
11[c]	NH_2	Solvent: $PhCF_3/CHCl_3$/cHex-CH_2Cl_2	23/25/43

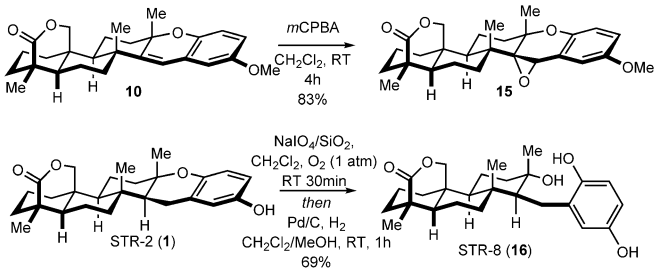
[a] Yield of isolated product. [b] Conditions: I_2 (5 equiv), $Pb(OAc)_4$/ $PhI(OAc)_2$ (5 equiv) then 10% KOH in MeOH, reflux, 2 h then 2 M aq. HCl/CH_3CN (1:1), 100 °C, 4 h. [c] Conditions otherwise as in entry 4.

The use of C–H activation methodology developed in the Yu laboratory[21] also did not result in activation of the C20 methyl group in this system (entry 2). Following conversion of **7** into amide **9** (Scheme 1), we turned to the classical photochemical lactonization chemistry developed by Barton,[22a] and Petterson,[22b] building on the work by Hoffmann, Löfler, and Freytag.[23] This type of transformation, which proceeds through the intermediacy of an N-haloamide, has only seldom been employed for constructing δ-lactones ([1,6]-hydrogen abstraction) and typically with low efficiency even with simple substrates.[22,24] Besides the unpredictable steric factors, successful use of this reaction in the STR scaffold is challenged by the lability of the electron-rich chromane system, which may be prone to undergo side reactions during the required halogenation conditions or upon photochemical radical formation. These concerns were legitimized when we attempted the formation of an N-bromoamide derivative from **9** to enable stepwise C20 bromination. Even with stoichiometric quantities of the mild brominating agent dibromoisocyanuric acid (DBI),[25] we only isolated compounds that were brominated on the aromatic ring (**13** and **14**, see the Supporting Information for details).

Next, we tested conditions for the in situ formation of IOAc with concomitant photolysis followed by lactonization (Table 2, entries 3–11). Suárez-type conditions[26] using Bis-(acetoxy)iodobenzene in combination with iodine and irradiation with a 6W UV lamp (standard TLC lamp) were not successful, and although we did not attempt to fully decipher the products formed, we again noted undesired reactivity in the chromane moiety, with no indications of activation at C20. Changing the oxidant to lead(IV) acetate resulted in activation at C20, and we were able to isolate products with a clear spectroscopic signature from the bicyclic δ-lactone. Further analysis of the NMR spectra revealed that the only product that we could isolate from this reaction (**10**, 44% yield, entry 4) also contained a C1=C2 double bond, presumably the result of photolytic benzylic iodination and subsequent dehydrohalogenation during the lactonization. Importantly, we saw no indications of modification to the chromane moiety or activation at other positions (e.g., C11 or C14). Further investigation (entries 5–11) revealed several interesting aspects of this reaction. A simple TLC lamp (6W output, 254 nm) constitutes an optimal light source since both a high-powered (300W) UV lamp and a UV-free sunlamp resulted in diminished yields of **10** (entries 5–6). Sonication was unsuccessful and amide **9** was recovered unchanged following aqueous work-up (entry 7). The amount of iodine could be reduced to 3 equivalents and shortening the irradiation period to 12 hours further increased the yield (entry 8–9). Mercury-(II) acetate proved inferior as an activating agent (entry 10) and alternative solvents did not further improve the outcome (entry 11).

Although we were unable to suppress oxidation at C1–C2, the formation of **10** provides an unexpected opportunity for modifying the STR scaffold, as exemplified by the preparation of epoxide **15** (Scheme 2, top). With access to **10**, we initiated the final synthetic operations towards STR-2 (Scheme 1). Diastereoselective hydrogenation under heterogeneous conditions proceeded in excellent yield to afford a 6:1 mixture of diastereomers. The structure of the major isomer (STR-9, **11**)[8e] was confirmed by X-ray crystallography.[19]

Finally, we sought conditions for carrying out a demethylation of STR-9 to form STR-2 (**1**). This transformation is challenging due to the sensitive nature of the chromane system and the propensity for regioisomeric reactivity. Ultimately, we found that in situ generation of TMS iodide effected selective ether cleavage to afford STR-2 in 75% isolated yield as a single isomer (d.r. > 16:1). Our synthetic



Scheme 2. Modification of the STR scaffold.

material matched all spectroscopic data reported for the natural product[8b] (see the Supporting Information). In one subsequent operation, we were able to perform oxidative opening of the chromane system[6a] to afford another family member, STR-8[8b] (**16**, Scheme 2, bottom).

In conclusion, we have developed the first syntheses of members of the strongylophorine family of marine meroterpenoids. An iron(III)-promoted allylic rearrangement–cyclization cascade and a strategic sp^3 C–H activation are the key reactions to enable highly efficient semisynthesis from isocupressic acid, as exemplified by the preparation of STR-2 in 17% yield over 8 steps. Our current focus is the preparation of additional STRs as well as unnatural analogues in order to fuel systematic biological studies of this family of natural products.

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[18] On a preparative scale, the reaction time needed is longer than for small-scale screening (15 minutes vs. 5 minutes, see support-

ing information). Use of catalytic quantities of $FeCl_3$ allows isolation of the uncyclized phenol **5** in high yield. See the Supporting Information for details.
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