Total Synthesis of (+)-Erogorgiaene and the Pseudopterosin A–F Aglycone via Enantioselective Cobalt-Catalyzed Hydrovinylation

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Dedicated to Martin F. Semmelhack on the occasion of his approaching 80th birthday.

Abstract: Due to their pronounced bioactivity and limited availability from natural resources, metabolites of the soft coral Pseudopterogorgia elisabethae, such as erogorgiaene and the pseudopterosines, represent important target molecules for chemical synthesis. We have now developed a particularly short and efficient route towards these marine diterpenes exploiting an operationally convenient enantioselective cobalt-catalyzed hydrovinylation as the chirogenic step. Other noteworthy C–C bond forming transformations include diastereoselective Lewis acid-mediated cyclizations, a Suzuki coupling and a carbonyl ene reaction. Starting from 4-methyl-styrene the anti-tubercular agent (+)-erogorgiaene (>98% ee) was prepared in only 7 steps with 46% overall yield. In addition, the synthesis of the pseudopterosin A aglycone was achieved in 12 steps with 30% overall yield. In addition, the synthesis of the pseudopterosin A aglycone. Marine organisms in general and the soft coral Pseudopterogorgia elisabethae in particular represent a rich source of bioactive natural products, some of which are of high pharmaceutical interest.[1] Prominent examples are (+)-erogorgaene (1) and the pseudopterosins (e.g. 2, 3 and 4), the latter being biosynthetically derived from 1.[6] While 1 shows promising activity against Mycobacterium tuberculosis H37Rv,[2] the pseudopterosins have received outstanding scientific and even commercial[3–5] attention due to their strong anti-inflammatory and analgesic properties.[4–6] More recently, the unique bioactivity of the pseudopterosins was attributed to their ability to block the NFκB pathway through activation of the glucocorticoid receptor.[7] Moreover, these compounds also reveal interesting cytotoxic and antibacterial properties,[8] and pseudopterosin A (3) was identified as a potent broad-spectrum antibiotic agent against different pathogenic strains.[9] The same compound (3) was also shown to protect synaptic function and to exhibit neuromodulatory properties while being well distributed within mammalian tissues.[10]

Due to their promising biological activity and the scarcity of material from natural sources, both erogorgaene (1) and the pseudopterosins represent relevant target molecules for chemical synthesis. Actually, total synthesis currently appears to be the most sustainable way to provide substantial amounts of these compounds for possible pharmaceutical development. Accordingly, several research groups have elaborated synthetic routes towards erogorgaene,[11] the pseudopterosins[12] and other structurally related marine diterpenes.[13] However, a

Figure 1. Structure of (+)-erogorgaene (1) and selected members of the pseudopterosin family of marine diterpene glycosides.
careful analysis of the reported syntheses reveals that most (if not all) of the known approaches do not reach the required levels of overall efficiency (number of steps, yield, and stereoselectivity). We here disclose a particular short and efficient access to both (+)-erogorgaene (1) and the pseudopterins A–F aglycone following a general strategy which exploits an enantioselective Co-catalyzed hydrovinylation\[14,15\] as chirogenic step - in combination with diastereoselective cationic cyclization steps.

Our strategy, sketched in Scheme 1, is based on the consideration that ring C of the tricyclic pseudopterins can be formed by a late (“biomimetic”)\[14\] cationic cyclization. Thus, all target molecules shown in Figure 1 can retrosynthetically be traced back to precursors of type 5, which in turn should be accessible from calamenenes of type 6 through diastereoselective double bond functionalization. In a previous study we had already shown that compound 6b can be obtained from 7b by trans-selective Lewis acid-catalyzed cyclization under prototransfer conditions.\[16\] However, our original method for the preparation of 7b (by enantioselective hydroboration of 9b followed by double Matteson homologation and Suzuki coupling) turned out to be little attractive from an operational point of view and difficult to be scaled up.\[16\] Therefore, we sought to apply our operationally convenient protocol for the asymmetric cobalt-catalyzed hydrovinylation\[14\] to enantioselectively convert the vinyl-arenes 9a and 9b into the chiral olefins 8a and 8b, respectively. Intermediates of type 7 should then be accessible in a single step by hydroboration of 8 and subsequent Suzuki cross-coupling.\[17\]

Following this plan, we first investigated the hydrovinylation of 9a employing chiral ligands L1 and L2, which had given the best results with other substrates in our previous study.\[14\] In addition, we tested the more electron-rich new ligand L3, which differs from L1 by a methoxy group at the ligand backbone.\[18\]

The air-stable pre-catalysts (L*CoCl\(_2\)) were prepared by stirring CoCl\(_2\) and the respective chiral ligand in THF for 16 h at room temperature. After solvent removal and re-dissolution in dichloromethane the mixture was cooled to the specified temperature under an atmosphere of ethylene (1.2 bar) before stirring CoCl\(_2\) and Et\(_2\)AlCl (as an activator) were injected. As reaction conditions: L*CoCl\(_2\) (0.03 mol %) to reproducibly afford \((R)-8a\) with 98–99% ee.

| Entry | L\(^*\) | Temp. [°C] | 8a\(^{ee}\) [%] | ee\(^{abs}\) [%] | abs. config.\[21\] |
|-------|---------|------------|----------------|----------------|------------------|
| 1     | L1 (1 mol %) | −40       | 100            | 89             | R                |
| 2     | L2 (1 mol %) | −40       | 97             | 89             | R                |
| 3     | L3 (1 mol %) | −40       | 93             | R              |                  |
| 4     | L3 (1 mol %) | −60       | 100            | 97             | R                |
| 5     | L3 (1 mol %) | −78       | 0              | −              |                  |
| 6     | ent-L3     | −65       | 98\(^{b}\)     | 98–99\(^{a}\)  | S                |

Reaction conditions: 9a (1.0 eq), CH\(_2\)Cl\(_2\), ethylene (1.2 bar), CoL*Cl\(_2\), Et\(_2\)AlCl (Co:Al = 1:6). \[a\] GC yield of 8a as determined by FID-GCMS; \[b\] Determined by FID-GC on a chiral stationary phase; \[c\] Determined by comparison of the optical rotatory values with those given in Ref. [19]. \[d\] Isolated yield (gram scale); \[e\] The reaction was performed several times to reproducibly afford \((S)-8a\) with 98–99% ee.

Within 2–3 h to give the \((R)-8a\) in high yield (entries 1–3).\[16\] While L1 and L2 behaved similarly (89% ee), the methoxy-substituted ligand L3\[18\] proved to be even more active in this case and selectively afforded \((S)-8a\) with 93% ee. By lowering the temperature to −60 °C the enantioselectivity could be further improved (entry 4). Under optimized conditions (using only 0.03 mol% of the ent-L3-based catalyst at −65 °C) the reaction could be reliably performed on a multi-gram scale (5 g) to afford the desired \((S)-8a\) in almost quantitative isolated yield and 98–99% enantiomeric excess.\[20\]

According to the chosen strategy, the next task was the elongation of the side chain to convert \((S)-8a\) into the allylic acetate 7a (Scheme 2). For this purpose, \((S)-8a\) was first hydroborated with 9-BBN and the in situ formed intermediate \(8a\) could be diastereomers could be separated by preparative HPLC to give the stereochemically

![Scheme 1. A general strategy towards marine diterpenoids related to erogorgaene and the pseudopterins.](image)
pure alcohol 13a in 86% isolated yield. Introduction of the side chain stereocenter was then achieved by diastereoselective hydrogenation of 13a using the Ir-catalyst 14 developed by Pfaltz and coworkers.\textsuperscript{[7]} The crude product (containing 4% of the undesired diastereomer) could be readily purified through flash chromatography to afford pure 15a in 89% yield. With this compound in hand, the synthesis of the target molecule was then efficiently concluded in only two steps, i.e. by flash chromatography to afford pure the undesired diastereomer) could be readily purified through column chromatography; (h) Me$_3$Al, THF, r.t., 6 h.; (i) 9-BBN, THF, r.t., 6 h.; (j) AlCl$_3$, CH$_2$Cl$_2$, 0°C–r.t., 1.5 h.; separation of diastereomers by preparative HPLC; (k) Pfaltz catalyst 14 (2 mol%), H$_2$, cat. 14 (35 bar), CH$_2$Cl$_2$, r.t., 2 d; separation of diastereomers by column chromatography; (l) Li$_2$PPh$_2$, imidazole, CH$_2$Cl$_2$, r.t., 30 min; (m) isocrotyl-lithium, THF, –78°C–r.t., 18 h; 9-BBN = 9-borabicyclo[3.3.1]nonane; DMAP = 4-N,N-dimethylaminopyridin.

Following the same general strategy (Scheme 1), we next tackled the synthesis of the pseudopterosterin A–F aglycone (20) as a second target molecule in this study (Scheme 3). Starting from the styrene derivative 9b, which is available from veratrole in three steps,\textsuperscript{[19]} the first task was to achieve the Co-catalyzed hydrovinylation to 8b.\textsuperscript{[19]} According to our previous experience, this proved to be more challenging (as compared to the hydrovinylation of 8a) due to the additional methoxy-substituent in ortho-position to the vinyl group.\textsuperscript{[14,26]} However, after careful optimization of the conditions (Table SI-2) the desired transformation could be successfully performed on a gram scale (2.7 g) using a L$_2$-derived catalyst to afford the alkene 8b (84% ee) in 87% isolated yield (after distillation). Noteworthy, ligand L2, prepared from (R,R)-Taddol afforded the desired (S)-configured product 8b, while the same ligand gave rise to the (R)-configured product when substrate 9a was employed (see Table 1).\textsuperscript{[27]}

The conversion of 8b into the allylic acetate 7b was achieved in 89% yield by hydroboration (9-BBN) and microwave-assisted Suzuki coupling of the resulting borane intermediate with the vinyl iodide 12. The following Friedel-Crafts-type cyclization of 7b (under strictly aprotic conditions to avoid the undesired disproportionation of the product)\textsuperscript{[19]} reproducibly afforded 6b with high yield and trans-diastereoselectivity (d.r. = 9:1) using Me$_3$AlCl as a Lewis acid in hexafluorobenzene as a solvent. As in the synthesis of 1 (Scheme 2) the diastereomers were not separable at this stage. However, after elongation of the side chain by Et$_3$AlCl-mediated carbonyl-ene reaction with paraformaldehyde under sonifiction, the isomers

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**Scheme 2.** Total synthesis of (+)-erogorgaeine (1). Reagents and conditions: (a) 9-BBN, THF, r.t., 6 h; (b) Me$_3$Al, Cp, ZrCl$_2$ (25 mol%), CH$_2$Cl$_2$, then I$_2$, THF, 0°C–r.t.; (c) NET$_3$, cat. DMAP, Ac$_2$O, CH$_2$Cl$_2$, 0°C–r.t.; (d) addition of 10a in THF to a suspension of 12, Cs$_2$CO$_3$, and Pd(PPh$_3$)$_4$ (5 mol%) in DMF, H$_2$O, 40°C, 18 h; (e) Me$_3$Al, CH$_2$Cl$_2$, –78°C–78°C, 6 h; (f) (CH$_2$O)$_2$, Et$_3$AlCl, CH$_2$Cl$_2$, –70°C, 1.5 h; separation of diastereomers by preparative HPLC; (g) Pfaltz catalyst 14 (2 mol%), H$_2$, cat. 14 (35 bar), CH$_2$Cl$_2$, r.t., 2 d; separation of diastereomers by column chromatography; (h) I$_2$, PPh$_3$, imidazole, CH$_2$Cl$_2$, r.t., 30 min; (i) isocrotyl-lithium, THF, –78°C–r.t., 18 h; 9-BBN = 9-borabicyclo[3.3.1]nonane; DMAP = 4-N,N-dimethylaminopyridin.

**Scheme 3.** Total synthesis of the pseudopterosterin A–F aglycone (20). Reagents and conditions: (a) ethylene (1.2 bar), Co(L$_2$Cl)$_2$ (5 mol%), Et$_3$AlCl (30 mol%), CH$_2$Cl$_2$, –20°C to 6°C, 6 h; (b) 9-BBN, THF, r.t., 24 h; then transfer to a suspension of 12, [Pd(dpdpf)Cl$_2$] (5 mol%), AsPh$_3$ (5 mol%) and Cs$_2$CO$_3$ in H$_2$O/DMF, then ωH (50 W), 40°C; 2 h; (c) Me$_3$AlCl, C$_6$F$_5$, 5°C, 1.5 h; (d) (CH$_2$O)$_2$, Et$_3$AlCl, CH$_2$Cl$_2$, 20°C, sonification, 4.5 h; separation of diastereomers by column chromatography; (e) 14 (1 mol%), H$_2$ (20 bar), CH$_2$Cl$_2$, r.t., 48 h; (f) DAIB, TEMPO (20 mol%), CH$_2$Cl$_2$, r.t., 1 h, separation of diastereomers by column chromatography; (g) methyl (2-methylallyl)phosphonate, n-BuLi, TPPA, THF, –78°C to r.t., 6 h; (h) [Pd(dpdpf)Cl$_2$] (5 mol%), AsPh$_3$ (5 mol%) and Cs$_2$CO$_3$ in H$_2$O/DMF, then ωH (50 W), 40°C; 2 h; (i) Li$_2$PPh$_2$, imidazole, DMF, 160°C, 3 h. dppf = 1,1'-bis(diphenylphosphino)ferrocene; TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl-oxy; DAIB = (diacetoxy)iodobenzene; TPPA = tripyrrolidinophosphoric acid triamide.

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As the final critical step of the synthesis of the pseudopter-
ose aglycone (20) we carefully investigated the diaster-
oselective cationic cyclization of 18 to the amphilectane 19. In
this context we first tested various acids and Lewis acids us-
ing 

In summary, we have developed a powerful, general
strategy for the stereoselective total synthesis of the marine
natural products erogorgiaene and the pseudopterosins. In the
chirogenic opening step, we exploited a Co-catalyzed enantio-
selective hydrovinylation, thus demonstrating the practicality
of this methodology in the context of total synthesis. The
synthetic sequences, mainly based on metal-catalyzed or
mediated transformations, also feature highly selective cationic
cyclizations and the diastereoselective elaboration of the
serulane side chain by substrate-controlled Pfaltz hydro-
genation of the carbonyl-ene products 15a and 15b, re-
spectively. Both target molecules were obtained in less than 10
steps with high overall yield. The efficient access to the
pseudopterosin aglycone (20) enabled us to also prepare iso-
pseudopterosin A, a novel anti-inflammatory compound, which
proved to be equally active as a mixture of natural pseudopter-

Figure 2. Structure of 19 in the crystalline state.

Figure 3. Anti-inflammatory activity of natural pseudopterosins A–D (mix-
ture) in comparison to the synthetic compounds 19, 20 (pseudopterosin A–F
aglycone), and iso-pseudopterosin A (iso-3/3 = 6:1) as reflected by the
inhibition of the NFκB pathway in LPS-stimulated MDA-MB-231 breast cancer
cells.
osins in the inhibition of the NFκB pathway. Thus, we are optimistic that this work will stimulate research into the pharmaceutical exploitation of pseudopterosins and related natural products in the future - without the need to harvest the corals.

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Conflict of Interest

The authors declare no conflict of interest.

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