

Total Synthesis of Neurymenolide A Based on a Gold-Catalyzed Synthesis of 4-Hydroxy-2-pyrones**

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Bioassay-guided fractionations of the extracts of the red alga *Neurymenia fraxinifolia* harvested off Fiji island afforded two polyunsaturated α -pyrone derivatives, dubbed neurymenolide A (**1**) and B (**3**).^[1] These metabolites exhibit appreciable activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), and show moderate cytotoxicity against 12 human cancer cell lines.^[1] What makes them really unique, however, is their unusual carbon skeleton, which is thought to derive from eicosapentaenoic acid by diketide chain extension followed by macrocyclization/pyrone formation as the key steps (Scheme 1).^[2–5] The resulting cyclophane framework of the narrower sibling **1** carries a chiral center of as yet unknown absolute configuration and shows an element of planar chirality as well. Therefore, the two atropisomers are diastereomeric to each other. After acetylation of the

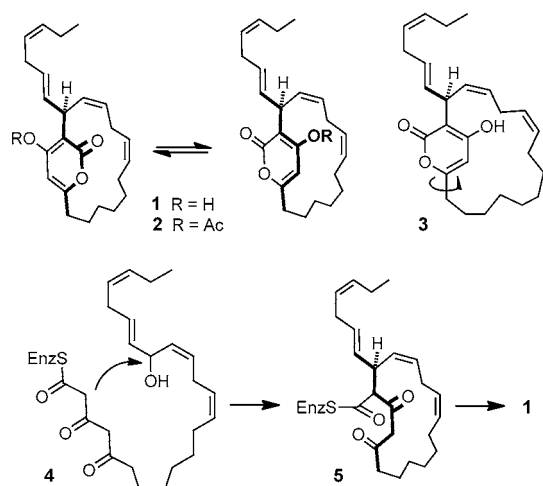
4-hydroxy group on the pyrone ring, the individual isomers of **2** are stable enough to be separated by HPLC, even though they equilibrate in solution on a time scale of hours.^[1,6]

The skipped array of the four double bonds in **1**, two of which may also migrate into conjugation with the pyrone ring, renders neurymenolide A exceptionally labile. Whereas an attempted purification of **1** on normal-phase silica led to rapid isomerization,^[1] the derived acetate **2** seems somewhat more manageable. The fragile character transpiring from these data imposes serious constraints upon any synthetic approach. As outlined below, however, we were able to meet this challenge with the aid of new methodologies developed in this laboratory, which capitalize on the ability of transition metal catalysts to rigorously distinguish between alkynes and alkenes under exceptionally mild conditions.^[7,8]

To this end, it seemed necessary to revisit the methodology for the formation of 4-hydroxy-2-pyrones. Although many procedures for the preparation of this heterocyclic motif are known in the literature,^[9] the biomimetic cyclization of tricarbonyl precursors (see compound **5**) is still most widely practiced. However, previous experiences led us to doubt that this particular transformation qualifies for the very demanding neurymenolide A case.^[10] Yet, we anticipated that substrates of type **6** might be an attractive alternative, since alkynes are carbonyl equivalents that can be activated under exceptionally mild conditions with the aid of carbophilic catalysts.^[11,12]

In fact, the readily available substrate **6a** ($R^1 = H$, $R^2 = Et$)^[13] was transformed into the corresponding pyrone derivative **7a** in excellent yield on treatment with 1 mol % of [(SPhos)AuNTf₂] (**8**; Tf = trifluoromethanesulfonate)^[14] at ambient temperature (Scheme 2). Although the cyclization proceeded well in a variety of solvents, the use of either nitromethane or acetic acid resulted in the highest reaction rates.^[15] A series of control experiments showed that neither HOAc alone nor in combination with HNTf₂ effected this transformation well. AgNTf₂ exhibits some activity, even though it is much less effective than gold complex **8**.^[16]

The examples compiled in Scheme 2 indicate a substantial scope for this convenient new entry into 4-hydroxy-2-pyrones, which also scales well (see the Supporting Information). Various substituents at the 3- and the 6-position are well tolerated. Even substrates **6d,e** ($R^1 = Br$, F), which carry labile bromide or fluoride substituents on their β -keto ester subunit, reacted cleanly to the corresponding 2-halogenated pyrones **7d,e**. Only the silylated derivative **7f** was formed in modest yield, which echoes previous experiences with silylated alkynes in gold catalysis.^[17] The current synthesis of pseudopyronine A (**7g**), an antibiotic interfering with microbial fatty acid biosynthesis, also favorably compares to an

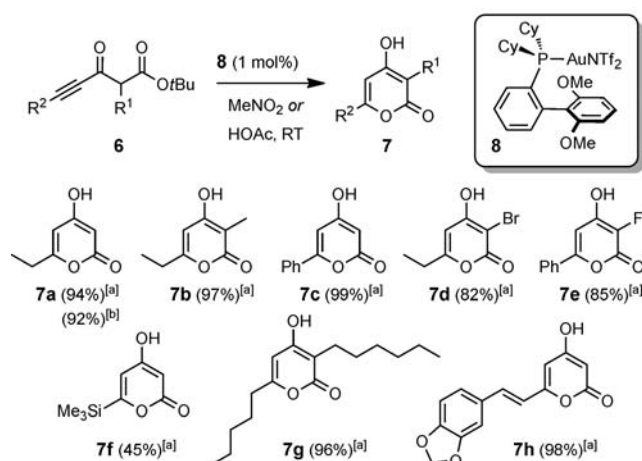


Scheme 1. Neurymenolide A (**1**, $R = H$), an atropisomeric cyclophane of marine origin, and its ring-expanded homologue neurymenolide B (**3**). Proposed biosynthetic pathway toward **1** by cyclization of an eicosapentaenoic acid-derived precursor.^[1,3] Enz = enzyme.

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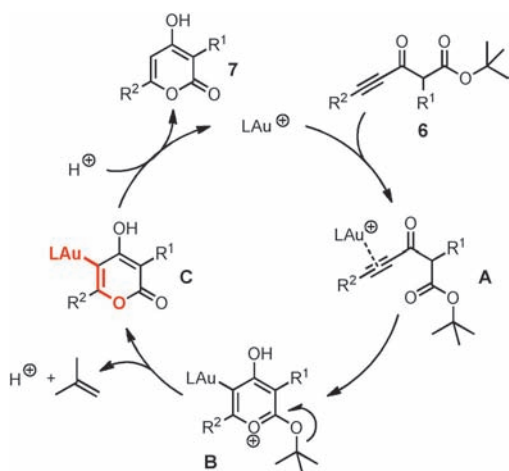
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Scheme 2. Gold-catalyzed synthesis of 4-hydroxy-2-pyrones. [a] In HOAc. [b] In MeNO₂. Cy = cyclohexyl, Tf = trifluoromethanesulfonate.

earlier approach.^[18] Product **7h**, representing a protected form of hispidine, which is the first pyrone derivative isolated from natural sources,^[19] suggests that the new method leaves pre-existing alkenes uncompromised and may hence qualify for the projected total synthesis of neurymenolide A.

A plausible catalytic cycle is depicted in Scheme 3. As this mechanism suggests, the ready cleavage of the *tert*-butyl group off of putative intermediate **B** is critical for the release of the α -pyrone ring. Previous studies from this laboratory, however, showed that alkenylgold species carrying oxygen substituents at the β -position are biased to react with a second gold atom to give *gem*-diaurated intermediates, which are surprisingly stable (Scheme 4).^[20] This pathway may seriously compete with proto-deauration and hence retard the catalytic turnover. It is of note that the proposed intermediate **C** contains this characteristic structural element (Scheme 3, color coded in red).^[21] Although it yet remains to be seen whether *gem*-diauration interferes in the pyrone series or not, this side track could explain why HOAc is a particularly favorable (co)solvent for this transformation.

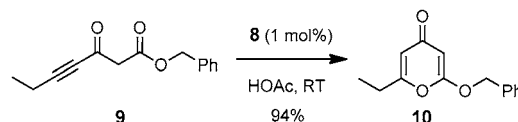


Scheme 3. Proposed catalytic cycle.



Scheme 4. Documented example of a highly favorable diauration of a β -alkoxy-alkenylgold intermediate.^[20]

In line with the proposed mechanism, the formal replacement of the *tert*-butyl groups in **6** by other ester functions should allow this methodology to be diverted to the preparation of isomeric γ -pyrone derivatives. This notion is corroborated by the clean conversion of benzyl ester **9** into the stable benzyl derivative **10** shown in Scheme 5.

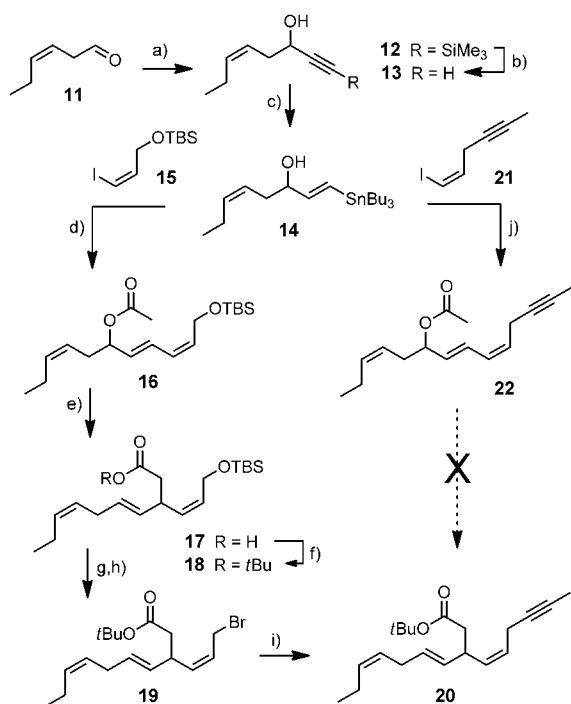


Scheme 5. Extension to the preparation of γ -pyrone derivatives.

These encouraging results notwithstanding, the total synthesis of neurymenolide A as the biologically more relevant and synthetically more challenging of the two sister compounds presents a much more rigorous test for the performance of the new methodology. As shown in Scheme 6, freshly distilled (*Z*)-3-hexenal (**11**) served as our entry point,^[22] which reacted with lithio trimethylsilylacetylide to give propargyl alcohol **13** after standard proto-desilylation. A palladium-catalyzed hydrostannylation then provided **14**, which was cross-coupled with the known alkenyl iodide **15**.^[23] This Stille-type reaction was best promoted by copper thiophene-2-carboxylate (CuTC) in the absence of palladium;^[24] under these conditions, compound **16** was secured in excellent yield after acetylation of the primary product. This ester was then subjected to a remarkably high yielding, deconjugative Ireland–Claisen rearrangement^[25,26] to set three of the four skipped unsaturated sites with the correct *Z,E,Z*-pattern, as contained within the neurymenolide tether.

After conversion of acid **17** into the corresponding *tert*-butyl ester **18**, the yet missing unsaturation was installed by cleavage of the primary *tert*-butyldimethylsilyl group and conversion of the resulting alcohol into the *Z*-configured allylic bromide **19**. Gratifyingly, a copper-catalyzed reaction with propynylmagnesium bromide in THF/HMPA (HMPA = hexamethylphosphoramide) allowed the required alkyne moiety to be introduced without any noticeable scrambling of the allylic double bond or competing S_N2' substitution.^[27] The success of this route stands out against the failure of the slightly more elaborate compound **22** to undergo an analogous Ireland–Claisen rearrangement in preparatively meaningful yields.

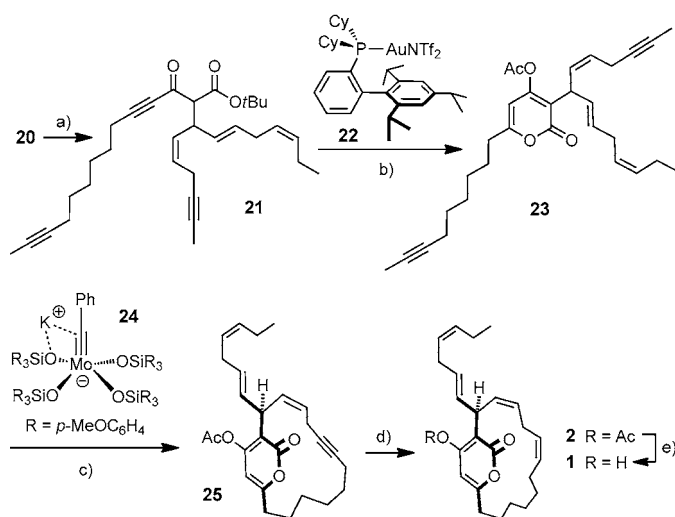
Next, compound **20** was deprotonated at low temperature and the resulting lithium enolate condensed with methyl dodeca-2,10-diynoate^[28] to give product **21** in respectable yield (Scheme 7). With this highly sensitive material in hand, which contains six different non-conjugated sites of unsaturation (not counting the partial enol form of the β -ketoester



Scheme 6. a) $\text{Me}_3\text{SiC}\equiv\text{CH}$, $n\text{BuLi}$, THF, $-78^\circ\text{C}\rightarrow\text{RT}$, 84%; b) K_2CO_3 , MeOH, 98%; c) Bu_3SnH , $[\text{PdCl}_2(\text{PPh}_3)_2]$ (2 mol %), THF, 0°C , 59%; d) 1. CuTC , NMP, 0°C ; 2. Ac_2O , Et_3N , DMAP (5 mol %), CH_2Cl_2 , 0°C , 93%; e) 1. LDA, TBSCl, THF/HMPA, $-78^\circ\text{C}\rightarrow\text{RT}$; 2. K_2CO_3 , MeOH, 0°C , 93%; f) 2,4,6-trichlorobenzoyl chloride, Et_3N , DMAP (cat.), toluene, then $t\text{BuOH}$, 73%; g) TBAF, THF, 95%; h) CBr_4 , PPh_3 , CH_2Cl_2 , 0°C , 92%; i) propynylmagnesium bromide, CuI (20 mol %), THF, -10°C , 98%; j) 1. CuTC , NMP, 0°C ; 2. Ac_2O , Et_3N , DMAP (cat.), CH_2Cl_2 , 0°C , 74%. CuTC = copper thiophene-2-carboxylate, DMAP = 4-dimethylaminopyridine, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, NMP = *N*-methyl-2-pyrrolidinone, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

visible in the NMR spectra), the critical phase of the total synthesis was reached, in which the heterocyclic ring and the cyclophanic frame had to be forged. From a conceptual viewpoint, it seemed reasonable to perform the gold chemistry prior to the macrocyclization, as the resulting pyrone might impart some stability onto the very fragile polyunsaturated material. To this end, however, it is mandatory that the catalyst is able to rigorously distinguish between the different π systems of **21**. However, since the acetylene in conjugation to the keto group is the least electron rich of the three alkynes and may therefore have the lowest affinity to an electrophilic gold fragment, it was by no means clear if this transformation would be successful, even if the alkenes do not get scrambled by the catalyst, which is also non-obvious. On top of this, one of the alkynes in **21** is perfectly set up for a gold-catalyzed 6-*exo-dig* Conia-ene cyclization,^[29] which has to be outperformed by the pyrone cyclization too.

Our initial attempts to close the required 4-hydroxy-2-pyrone **23** seemed to reflect these difficulties. Specifically, treatment of **21** under aprotic conditions with catalytic amounts of **8** in nitromethane resulted in rapid decomposition. After considerable experimentation it was found that recourse to gold complex **22**, which contains the even more



Scheme 7. a) LDA, THF, then methyl dodeca-2,10-dienoate, $-78^\circ\text{C}\rightarrow 0^\circ\text{C}$, 76%; b) (i) **22** (5 mol %), $\text{MeNO}_2/\text{HOAc}$ (4:1, 0.04 M); (ii) Ac_2O , Et_3N , CH_2Cl_2 , 0°C , 73%; c) **24** (5 mol %), toluene, 5 Å molecular sieves, 88%; d) H_2 (1 atm), Lindlar catalyst, quinoline (cat.), $\text{EtOAc}/1\text{-hexene}$, 84%; e) K_2CO_3 , MeOH, 0°C , see text for details. Cy = cyclohexyl, LDA = lithium diisopropylamide.

bulky Xphos ligand,^[30] allowed the desired product **23** to be isolated in modest 26% yield from a still quite complex mixture, together with unreacted starting material (37%). Gratifyingly though, the addition of HOAc as cosolvent, meant to accelerate the presumably critical protodeauration step within the catalytic cycle, resulted in a much cleaner transformation. Under these conditions, pyrone **23** was isolated in 73% yield after acetylation of the crude material. This *in situ* protection was mandatory to suppress fast isomerization of the lateral alkenes.^[31] It is believed that the selective activation of the least electron-rich acetylene group in **21**, which leads to pyrone formation, is kinetic in origin and the ensuing reaction is irreversible due to the gain of aromaticity.

The subsequent macrocyclization of this very delicate compound was effected with remarkable efficiency using the molybdenum alkylidyne ate-complex **24** as the arguably most active and selective catalyst for ring closing alkyne metathesis (RCAM)^[8,32] known to date. Specifically, the desired cyclophane **25** was obtained in 88% yield (as a 1:1 mixture of two atropisomers) within less than 30 min upon exposure of substrate **23** to catalytic amounts of **24** (5 mol %)^[33,34] in toluene at ambient temperature in the presence of molecular sieves to sequester the released 2-butyne. The fragile array of skipped olefins was not damaged at all, which proves that alkyne metathesis is strictly orthogonal in chemical terms to alkene metathesis;^[35] this feature is instrumental, since an analogous closure of the neurymenolide frame by conventional RCM seems inconceivable with any of the catalysts known to date^[36] in view of the four double bonds of *E*- and *Z*-configuration, each of which is disubstituted and needs to pass uncompromised.^[37,38]

Lindlar reduction of cycloalkyne **25** in the presence of 1-hexene as a sacrificial alkene provided neurymenolide A

acetate (**2**) in isomerically pure form without noticeable overreduction. Given the unstable nature of free neurymenolide A (**1**) itself, compound **2** served as a relay to ensure the identity of our synthetic samples with the authentic material. Compound **2** is reasonably stable and could be fully characterized; its spectroscopic data match those in the literature.^[1,6] In contrast, product **1**, when released from **2** with K₂CO₃ in MeOH at 0°C, was found to be highly unstable; it rapidly degraded upon contact with silica and neutral alumina alike.

In summary, the first total synthesis of neurymenolide A, a highly unusual α -pyrone of eicosanoid origin, was accomplished. The unusually sensitive character of this naturally occurring cyclophane constituted a stringent test for the efficiency and tolerance of the methodology developed in our laboratory. The challenge was ultimately met with the aid of a new gold-catalyzed pyrone synthesis in combination with an amazingly effective alkyne metathesis reaction.^[39] It is the ability to manipulate alkenes and alkynes in an orthogonal and selective manner in either step—with the aid of an early as well as with a late transition metal catalyst—which is at the heart of this success.

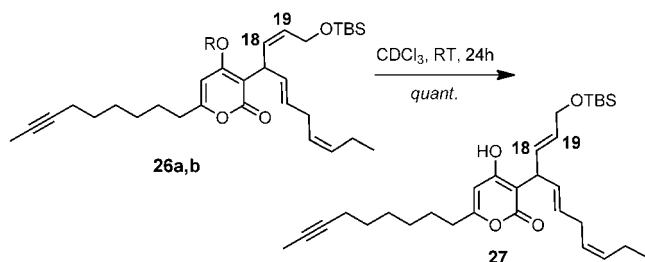
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