Natural Product Synthesis

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# Differentiation of Nonconventional "Carbanions"—The Total Synthesis of Nemorosone and Clusianone**

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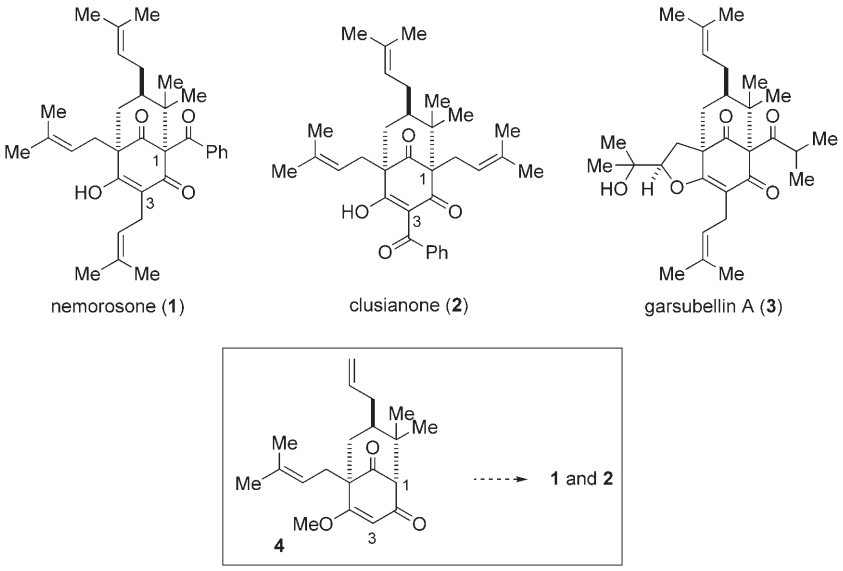
Recently, our research group described the total synthesis of the ChAT inhibitor garsubellin A (**3**) as its racemate.[1,2] The attainment of that goal required the crafting of novel methodology to accommodate the introduction of the three prenyl-like moieties. In garsubellin A, one of these "prenyl equivalents" appears in an oxidatively cyclized form. Also incorporated in the original synthesis of **3** was an isobutyryl group in the context of a non-enolizable β,β′-tricarbonyl setting. More recently, we noted with interest the appearance of a structurally related compound, nemorosone (**1**), which was isolated from the flowers of *Clusia rosea*.[3] In contrast to garsubellin A, nemorosone had been reputed to have significant cytotoxic activity, possibly associated with telomerase inhibition as well as inhibition of ERK-1/2. A previously isolated compound from the family of acylphloroglucinols was the compound clusianone (**2**; Scheme 1). Isolated originally from *Clusia congestiflora*, its structure was initially determined by McClandish et al. by X-ray crystallography.[4a] Subsequently, extensive 2D NMR analysis on the family of clusianones was described by Rastrelli and co-workers.[4b] Again, this structure belongs to a broad family, wherein polyprenyloids project from a carbobicyclo[3.3.1] framework. From a biological perspective, the anti-HIV properties claimed on behalf of clusianone were of interest as were the antitumor properties of nemorosone.




***Scheme 1.*** Nemorosone (**1**) and clusianone (**2**).

Given the subtle but important differences in the structures found in this class of natural products, and the range of their profiles of biological activity, it seemed that a program in total synthesis would be desirable to secure access to relevant probe structures which might help revise structure–activity relationship (SAR) patterns. In particular, we focused on nemorosone (**1**) and clusianone (**2**). Herein we describe the concise total syntheses of these targets.[5]

Influenced by the apparent similarity of these targets to garsubellin A, we started with the assumption that the hard-won lessons learned in our total synthesis of the latter would provide a clear-cut route to our new targets. The thought was to reach both targets from a common intermediate, **4**, which would be derived through extended teachings from our earlier garsubellin work. As matters transpired, nemorosone and clusianone emerged as much more difficult targets than garsubellin A. In retrospect, the existence of the fused tetrahydrofuran ring in garsubellin A, wherein one of the prenyl groups is uniquely presented at a higher oxidation level, served as a stabilizing device, which was used to good advantage in that total synthesis. Moreover, the chemical

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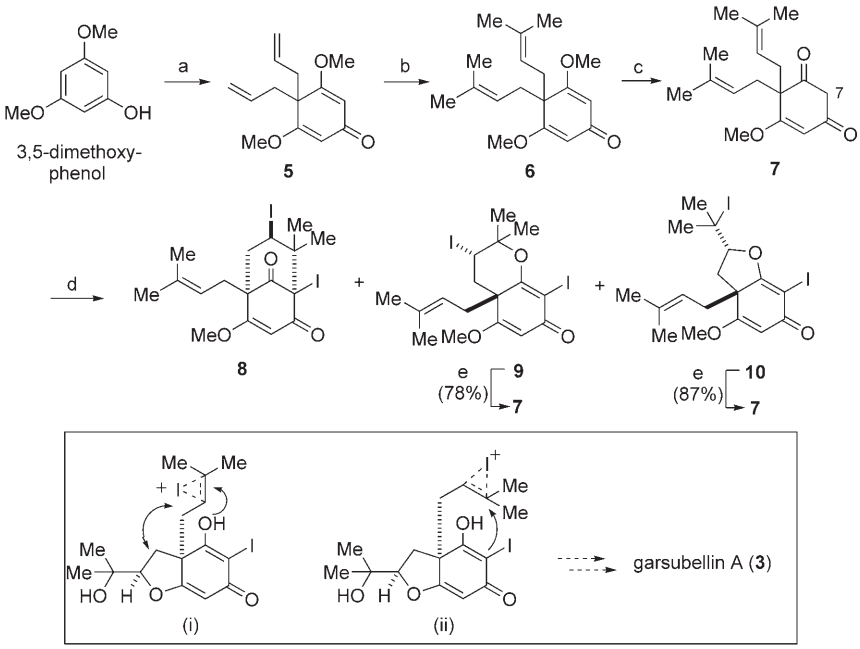
frailty of nemorosone had not been anticipated, until we were attempting to complete its total synthesis. Nonetheless, after considerable travail, the total syntheses of **1** and **2** were accomplished very concisely. Indeed, both targets were reached from the common intermediate **4**. The differentiation of the C1 and C3 sites in **4** involved some novel chemistry.

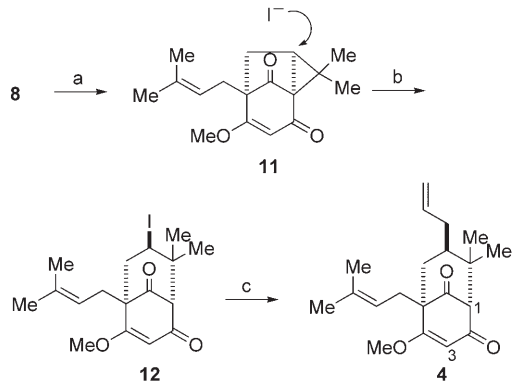
Our route to **4** commenced with twofold allylation of commercially available 3,5-dimethoxyphenol, through the use of π-allylpalladium chemistry, as shown in Scheme 2.[6] At this stage, both allyl groups in **5** were converted into prenyl functions through twofold cross-metathesis (see **6**, Scheme 2).[7] In our prospective vision of the total synthesis, we hoped to use one of the two "enantiotopic" prenyl functions to provide the wherewithal for building the all-carbon bicyclo[3.3.1] nonane latticework in a particularly direct fashion. Happily, it proved possible to cleave a single methoxy function of **6** through the agency of lithium iodide in *sym*-collidine (see **7**).[8–10] However, a significant complication arose in our envisioned iodonium-induced carbocyclization reaction on substrate **7**.[11] Given the centrality of this step to our aspirations of high convergency, a variety of protocols for its realization were surveyed. However, under all the conditions studied, in addition to the desired **8** (obtained in only 32% yield), there were also obtained substantial quantities (namely, 50%) of a virtually 1:1 mixture of **9** and **10**. It seems very likely that initial iodination occurs at the β-dicarbonyl locus (C7). This reaction is, in turn, followed by "iodonium"-induced attack with either carbon or oxygen atoms competing as the nucleophilic arms of the cyclization. In the latter variant, ring closure occurs through competitive 6-*endo* or 5-*exo* modes (**9** and **10**, respectively).




***Scheme 2.*** Synthesis of **8**. Reagents and conditions: a) AllylOH, $Pd(OAc)_2$, $PPh_3$, $Ti(OiPr)_4$, MS (4 Å), 50 °C, 50%; b) Grubbs' 2nd generation cat., 2-methyl-2-butene/$CH_2Cl_2$, 40 °C, 79%; c) LiI, 2,4,6-collidine, 140 °C, 82%; d) $I_2$, KI, $KHCO_3$, THF/$H_2O$, RT, 32% for **8**, 29% for **9**, 24% for **10**; e) Zn, THF/$H_2O$, 65 °C. MS = molecular sieves.

Fortunately, though not surprisingly, both **9** and **10** could be reconverted into **7** in very high yield by the action of zinc in aqueous THF. Thus, the existence of seriously competing cyclization modes was a significant complication at the process level, rather than a crippling blow to the synthesis. We note that the problem of competitive O cyclization in establishing the bicyclo[3.3.1] matrix did not surface in the initiating total synthesis of garsubellin A.[1] Perhaps the tetrahydrofurano moiety serves to tilt the conformation of its neighboring reverse prenyl group to favor iodinative cyclization through strict C–C bond formation (see hypothetical reaction conformers (i) and (ii) in Scheme 2).

Returning to the nemorosone and clusianone total syntheses, compound **8** was converted into the novel bridgehead-fused cyclopropane **11** by reductive elimination (Scheme 3). Following our earlier precedent, the latter suffered nucleophilic ring opening through the agency of TMSI to afford **12**. Following implementation of the highly

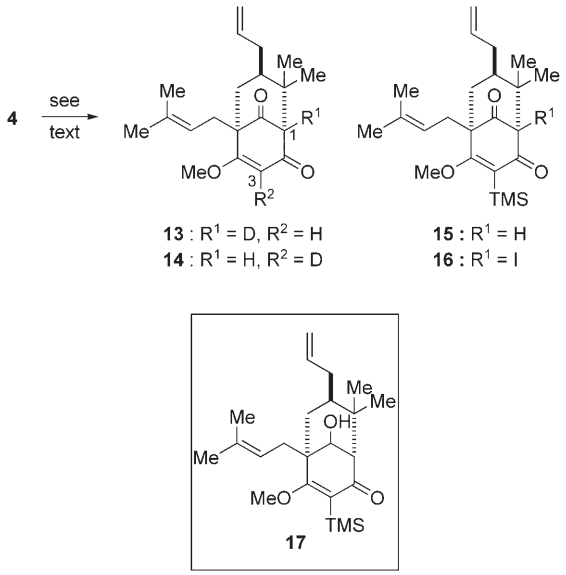


***Scheme 3.*** Synthesis of intermediate **4**. Reagents and conditions: a) *i*PrMgCl, $Et_2O$/THF, −78 °C, 93%; b) TMSI, $CH_2Cl_2$, 0 °C, 98%; c) Allyl$SnBu_3$, AIBN, benzene, 80 °C, 84%. TMS = trimethylsilyl, AIBN = azobisisobutyronitrile.

elegant allylation protocol of Keck and Yates,[11,12] compound **4**, the intermediate we had envisioned en route to either nemorosone (**1**) or clusianone (**2**), was in hand. Indeed, **4** had been reached in a mere six steps from **5**.

We began to explore compound **4** with respect to its susceptibility to lithiation at either its C1 or C3 sites. An orienting experiment in this regard arose through treatment of **4** with lithium diisopropylamide (LDA). In the first experiment, we employed approximately 1.05 equivalents of base. Upon quenching with deuterated methanol, we obtained approximately 30% deuteration at each position (**13** and **14**; Scheme 4). When a large excess of base was used,



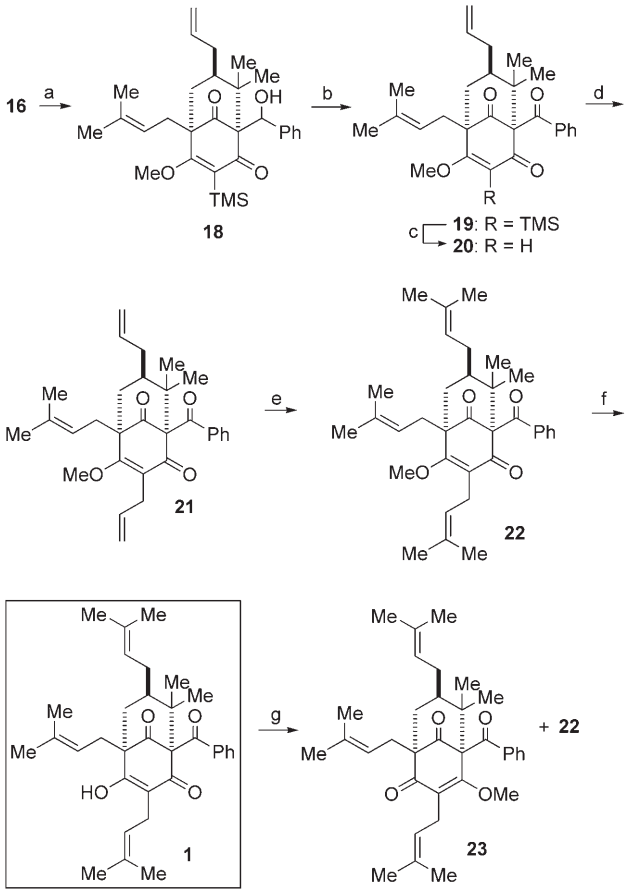

***Scheme 4.*** Functionalization of intermediate **4**.

and this treatment was followed by quenching with MeOD, an approximately 70–75% yield of the monodeuterated products **13** and **14** was realized.[13] We surmised that the C1 and C3 sites had been lithiated to approximately equal extents. Although these findings did not necessarily go to the question of relative rates of lithiation, they tended to suggest that a site-specific deprotonation could not be conducted cleanly and adequately with only a single equivalent of ionizing base. The novel lithiations (bridgehead enolate at C1 and the sp enolate at C3)[14] could be accomplished, but would be sluggish. Hence, an excess of base would be needed to achieve required levels of deprotonation at either C1 or C3 or both. That being the case, we hoped to exploit differential quenching reactions as a means of distinguishing the two lithio derivatives. In practice, the deprotonation phase of the experiment was conducted with approximately five equivalents of LDA in the presence of trimethylsilyl chloride (TMSCl). We were pleased to obtain a 74% yield of compound **15**.[15] Thus, if C1 had actually undergone deprotonation, exposure to TMSCl had not resulted in a detectable, let alone isolable, product.

We then turned to the functionalization of **15** at C1. Toward this end, **15** was treated with LDA, and the presumed enolate was quenched with iodine. Unfortunately, a rather low yield of **16** was obtained. By contrast, when **15** was exposed to the active excess LDA in the presence of TMSCl,[15] and the reaction mixture quenched with iodine, a 45% yield of **16** was obtained.

We then asked the question as to whether one could interface the TMSCl-mediated deprotonation and the iodination in the context of a single reaction. Toward this end, **4** was treated with excess LDA in the presence of excess TMSCl. This step was followed by oxidative quenching with iodine. Happily, a 51% yield of **16** was obtained directly from **4**.[15] In addition to recovered **15**, the reaction mixture also contained variable amounts of the formal reduction product **17**. The reduction of difficult-to-deprotonate ketones by metalated secondary amines is not without precedent.[16]

The stage was now set for introduction of the benzoyl group at C1. Toward this end, the trimethylsilyl group would serve the purpose of protecting C3. Reductive de-iodination of **16** under the agency of isopropylmagnesium chloride as shown, was followed by quenching the presumed metalated intermediate with benzaldehyde. The aldol-like reaction was conducted from −78 °C to 0 °C. Work-up afforded a benzaldehyde adduct, presumably **18**, since upon oxidation under the conditions shown, the C1-anchored benzoyl group was in place (**19**). Upon cleavage of the C3-vinylsilane linkage, compound **20** was in hand (Scheme 5).




***Scheme 5.*** Synthesis of nemorosone (**1**). Reagents and conditions: a) *i*PrMgCl, −78 °C, THF then PhCHO, −78 to 0 °C; b) Dess–Martin periodinane, $CH_2Cl_2$, RT; c) TBAF, THF, RT, 61% (3 steps); d) LDA, THF, −78 °C, then lithium 2-thienylcyanocuprate, then allyl bromide, 88%; e) Grubbs' 2nd generation cat., 2-methylpropene, 40 °C, 91%; f) LiI, 2,4,6-collidine, 140 °C, 31%; g) diazomethane, ether, 0 °C, 60% for **23** and 7% for **22**. TBAF = tetrabutylammonium fluoride.

The next goal en route to nemorosone was the functionalization of C3. We proceeded with circumspection. The first stage involved deprotonation at this C3 center. We were well-mindful that the β,β′-carbonyl system, already present in **20**, might prove to be quite susceptible to nucleophilic cleavage. However, in practice, it was possible to accomplish functional deprotonation. The presumed C3 lithium intermediate was

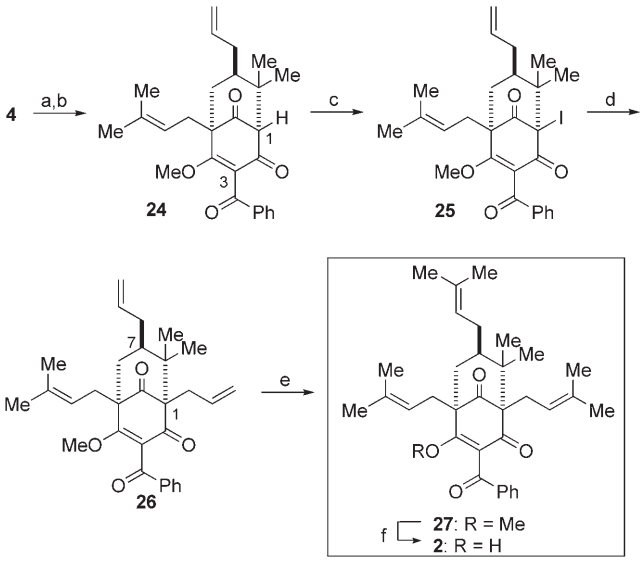
  

then transformed into the corresponding higher order thienyl cyano cuprate.[17] With the cuprate presumed to have been generated, the system was allylated by allyl bromide. There was thus obtained an 88% yield of the bis-allyl compound **21**. The stage was now well set for a second twofold cross-metathesis reaction.[7] Indeed, this transformation could be accomplished, under the conditions shown, in the presence of 2-methylpropene, to afford a 91% yield of **22**. There now remained only the cleavage of the methyl ether to reach nemorosone (**1**). It was in this end-game that we discovered some serious vulnerabilities of nemorosone itself. As a result of its lability, attempted cleavage of the methyl ether linkage of **22** with a hydroxylic nucleophile was unsuccessful. However, the methyl ether function could be cleaved by nucleophilic de-alkylation.[8–10]

Given the instability of free nemorosone,[18] it was perhaps not surprising that the yield in the isolation of the natural product was rather modest (31%). The NMR spectrum obtained on fully synthetic, albeit racemic, nemorosone, which is actually a mixture of enol tautomers, was somewhat variable and did not correspond exactly to that reported for the number of natural **1** tautomers. An early concern had been the variability of the NMR spectrum of the synthetic nemorosone. However, the spectrum could be stabilized and rendered identical with that reported for natural nemorosone by the inclusion of ammonium formate in the solvent system.[19] Finally, with regard to nemorosone, remethylation of the enol mixture with diazomethane restored the separable mixture (approximately 8:1 of the previously encountered **22**) and iso-nemorosone methyl ether **23**.

With a novel and highly convergent total synthesis of nemorosone accomplished, we returned to **4**, which, as described above, was perceived as a common intermediate en route to both targets **1** and **2**. We now attempted to reach clusianone (**2**) by treatment of **4** with LDA and benzaldehyde, followed by oxidation, to introduce the benzoyl group at C3 (**24**, Scheme 6). The earlier experiments in this study were indicators that functional deprotonation at C1 in **4** could be accomplished. However, the only agent which we have successfully introduced at the presumed C1 bridgehead carbanion arising from deprotonation at C1 in reasonable yield was the iodo group (**16**) or a deuterium atom from MeOD (**13**). Direct introduction of other electrophiles, such as benzaldehyde at C1 in compound **4** following deprotonation, occurred in poor yield. To complete the total synthesis of clusianone (**2**), we faced the challenge of incorporation of a prenyl function at the corresponding C1 site in **24**.

Fortunately, a successful two-step protocol to deal with the end-game of the clusianone synthesis could be developed. Thus, **24** was converted into its C1-iodo derivative, **25**, by the TMSCl-mediated process[15] (Scheme 6). The iodo group of **25** was transformed to an allyl function using allyl tributylstannane and triethyl boron in the presence of air.[20] Thus was obtained compound **26**. The stage was now set for concurrent cross-olefin metathesis at C1 and C7.[7] This double cross-metathesis was accomplished (**27**). Once again, it proved possible to cleave the methyl ether group. This conversion was much simpler than the case of nemorosone and could be accomplished with aqueous sodium hydroxide, thus affording




***Scheme 6.*** Synthesis of clusianone (**2**). Reagents and conditions: a) LDA, THF, −78 °C, then PhCHO; b) Dess–Martin periodinane, $CH_2Cl_2$, RT, 57% (two steps); c) LDA, TMSCl, THF, −78 to 0 °C then $I_2$, 48%; d) Allyl$SnBu_3$, $Et_3B$, air, benzene, RT, 71%; e) Grubbs' 2nd generation cat., 2-methylpropene, 40 °C, 94%; f) 10% aq NaOH, 1,4-dioxane, 90 °C, 64%.

fully synthetic clusianone as a tautomeric mixture of enols.[7b] We note that the mixture of free enol tautomers of clusianone (**2**) is rather more stable than the corresponding enolic form of nemorosone (**1**).[18] Presumably, this reflects the stabilizing effect of the benzoyl group in the β-dicarbonyl network. The total synthesis of clusianone had thus been accomplished.

In summary, the total syntheses of both **1** and **2** have been accomplished. These routes are quite direct. The key skeleton-building stages were allylative de-aromatization (see **5**) and iodinative cyclization (see **8**). While yield issues remain, we were able to generate and exploit nonconventional anions ("anti-Bredt bridgehead" at C1; and "sp enolate" at C3)[14] arising from the common intermediate **4**. Progress in understanding these uncommon "carbanion" types and in establishing structure–activity patterns in the acylphloroglucinals is ongoing.

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[18] With nemorosone in hand, we found that it was both light-sensitive and air-sensitive. When nemorosone was dissolved in chloroform, a solution of fully synthetic nemorosone and chloroform had decomposed after a few days at room temperature. In fact, a solution of nemorosone in chloroform at −20 °C is also significantly decomposed after a few days. We resorted to the use of ammonium formate because the original isolation was such that ammonium formate would have been present in the methanol solvent wherein the NMR spectrum of nemorosone was measured. Through this device, a stable spectrum was obtained.
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