SHORT COMMUNICATION

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Concise Synthesis of Norrisolide

Krista Granger[a] and Marc L. Snapper*[a]

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The marine natural product norrisolide has been synthesized in a convergent manner with a longest linear sequence of 14 steps. The hydrindane portion of the molecules is prepared through conjugate addition of a functionalized allyl group into cyclopentenone, followed by stereoselective trapping of the enolate generated from the resulting enol silyl ether with an allyl electrophile. Ring-closing metathesis then establishes the 6–5 ring system. Likewise, selective preparation of the side chain features an enantioselective cyclopropanation of furan-2-one, followed by rearrangement and hydrogenation. Coupling of the two major fragments through a Shapiro reaction, followed by reduction and olefination then completes the carbon framework of the natural product. The final steps of the synthesis involve adjustments to the oxidation state of the side chain. New strategies to generate both the hydrindane core and the oxidized side chain has allowed for the more concise and efficient preparation of the natural product.

Introduction

Norrisolide is a marine natural product that was first isolated from the nudibranch mollusc *Chromodoris norrisi* in 1983 (Figure 1).[1] Norrisolide has also been found in minor amounts in sponges from the same area. It has been suggested that the molluscs acquire the precursor to norrisolide and related compounds through feeding on the sponges.[2]

As shown in Figure 1, there are several natural products that share some of norrisolide's structural features. For example, macfarlandin C,[3] spongionellin,[4] and dendrillolides A and E[5] all possess the same oxygenated side chain. Likewise, chelonoplysin, norrlandin, and cheviolenes C and E have norrisolide's hydrophobic hydrindane ring system.[6] Chromodorolides A[7] and B[8] can be found in the same aplysillid sponge as the cheviolenes. The chromodorolides have shown significant cytotoxicity against the P388 mouse leukemia cell line. In addition, chromodorolide A possesses antimicrobial and nematocidal activity. To the best of our knowledge, no total synthesis of any of these structurally related natural products, other than norrisolide, has been reported.

Biological activities reported for norrisolide include secretary phospholipase A_2 ($SPLA_2$) inhibition,[9] ichthyotoxicity,[10] and cytotoxicity.[11] Given our work with ilimaquinone,[12] we were particularly interested in Theodorakis and co-workers' disclosure concerning norrisolide's irreversible influence on the structure of the Golgi apparatus.[13] To better understand norrisolide's biological activities, the Theodorakis group described the first total synthesis of the natural product in 2004.[14] A second-generation approach shortened their longest linear sequence to norrisolide from

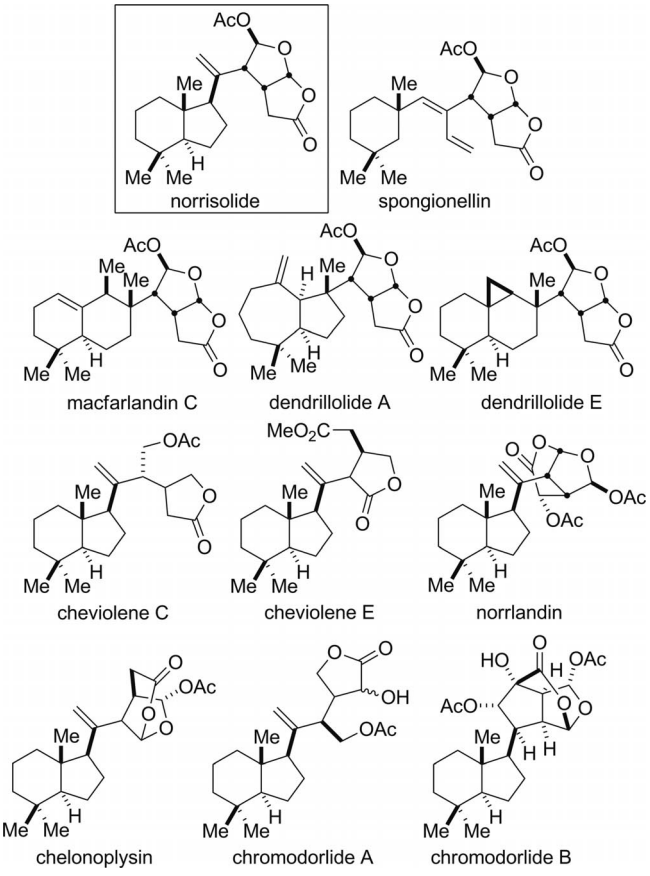

Figure 1. Norrisolide and structurally related natural products.

[a] Department of Chemistry,
Merkert Chemistry Center, Boston College,
Chestnut Hill, MA 02467 USA
Fax: +1-617-552-1442
E-mail: marc.snapper@bc.edu

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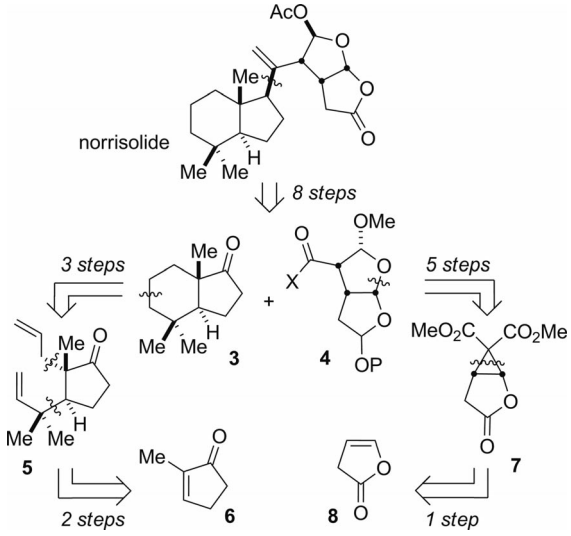
28 to 23 steps.[15] In addition to preparing the natural product, their routes also provided access to structural analogs designed to probe norrisolide's biological activities.[16]

Results and Discussion

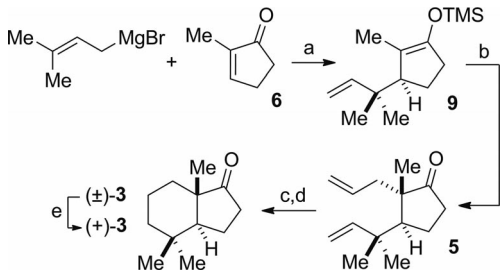
Our approach to norrisolide features some significant differences in the preparation of the key fragments. As summarized in Scheme 1, construction of hydrindane fragment **3** was envisioned through ring-closing metathesis/reduction of appropriately functionalized cyclopentanone **5**, which in turn could be prepared by selective conjugate addition/allylation of methylcyclopentenone **6**. Oxidized side chain **4** could be prepared through the thermal rearrangement/reduction of cyclopropane **7**, which is generated through asymmetric cyclopropanation of lactone **8**. The overall plan allowed for a concise preparation of the natural product with a longest linear sequence of 14 steps.



Scheme 1. Retrosynthetic analysis of norrisolide.

At the start of the project, the state of the art for the preparation of the hydrindane portion of norrisolide (i.e., **3**) was a 12-step route developed by the Paquette group for their synthesis of *ent*-grindelic acid.[17] In light of the work by Lipshutz and co-workers demonstrating a selective conjugate addition of various allyl groups to cyclic enones,[18] we envisioned combining this transformation with an allylation and ring-closing metathesis to provide a more rapid access to the desired hydrindane fragment (i.e., **6** → **5** → **3**).[19]

Along these lines, enone **6** can be alkylated with the cuprate of isoprenyl Grignard in the presence of HMPA[20] to generate corresponding silyl enol ether **9** (Scheme 2). Because attempts to allylate the enolate directly were unsuccessful, treatment of TMS enol ether **9** with methyllithium and allyl bromide provided diene **5** in 60% yield over two steps as a single diastereomer. With the diene in hand, ring-closing metathesis with Grubbs second generation catalyst **10** (0.5 mol-%) gave the ring-closed product in 80% yield, thus constructing the carbon framework for the hydrindane portion of the molecule in only three steps. Hydrogenation of the olefin with Pd/C gave (±)-**3** quantitatively without the need for further purification.

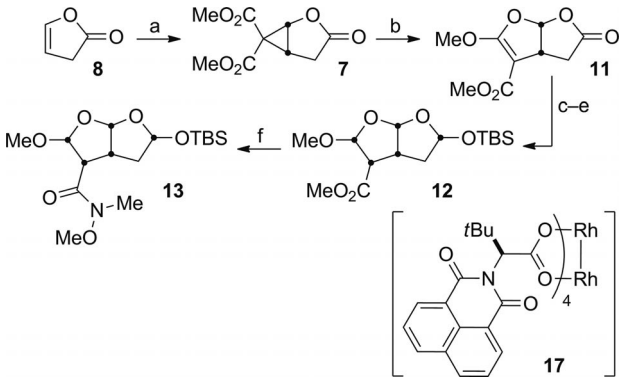


Scheme 2. Synthesis of hydrindane **3**. Conditions: (a) CuBr·DMS, TMSCl, HMPA, THF, –78 °C; Et_3N, hexanes, –78 °C. (b) MeLi, HMPA, THF, –15 °C to r.t.; allyl bromide, THF, –78 °C to r.t., 12 h (60% yield, 2 steps). (c) Grubbs 2nd gen. cat. **10**, CH_2Cl_2, r.t., 12 h, (80% yield). (d) H_2 (10 atm), Pd/C (5 mol-%), EtOAc, r.t., 12 h (99% yield). (e) (*S*)-(–)-2-Methyl-CBS-oxazaborolidine (10 mol-%), BH_3·DMS, THF, 0 °C, 90 s (36% yield recovered **3**, >95%*ee*).

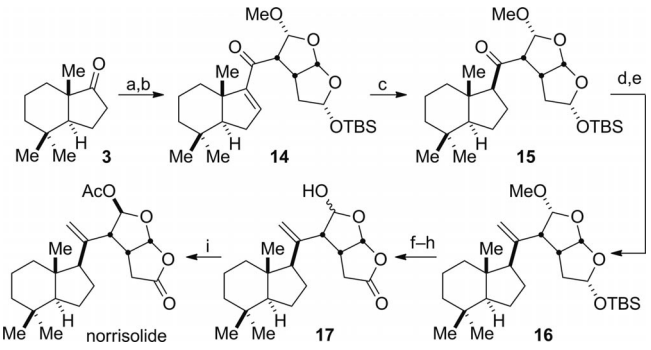
To access enantiomerically enriched **3**, it was necessary to perform a kinetic resolution. A Corey–Bakshi–Shibata (CBS) reduction of (±)-**3** was used to selectively reduce the undesired enantiomer while leaving the desired enantiomer at the ketone oxidation state. Specifically, treatment of (±)-**3** with (*S*)-(–)-2-methyl-CBS-oxazaborolidine (10 mol-%) and BH_3·DMS (0.5 equiv.) yielded a 36% recovery of (+)-**3**. The enantiomeric excess of the product typically ranged from 95 to 98%*ee*, indicating an *S* value of approximately 12 (±3).[21] This five-step sequence can be used to provide the hydrindane portion of norrisolide in an enantiomerically enriched fashion on a multigram scale.

The concise preparation of norrisolide's tetrahydrofurofuranone side chain should be possible through a formal 1,3-dipolar cycloaddition between a diazo diester compound and the appropriate furanyl derivative, as demonstrated by Pirrung and co-workers.[22] In this regard, furan-2(3*H*)-one **8** was cyclopropanated with dimethyl 2-diazomalonate to generate cycloadduct **7** (Scheme 3).[23] Unlike earlier examples, this intermediate did not rearrange in situ to the desired ring system. We surmised that the electron-withdrawing nature of the lactone (relative to furan) hindered the cleavage of the cyclopropane, suppressing the usually observed rearrangement. Fortunately, thermolysis of **7** in benzene at 185 °C provided adduct **11**. Using this strategy, the framework of the norrisane side chain was prepared in just two steps.

Access to the enantiomerically enriched norrisane side chain is possible by carrying out the cyclopropanation with Müller's catalyst **17**.[24] Using slow addition of the diazo compound, cycloadduct **7** was obtained with 85:15 *er*. Interestingly, relative to other catalysts tested, complex **17** displayed an increase in the rate of the reaction, reducing the



Scheme 3. Preparation of the norrisane side chain. Conditions: (a) Müller's catalyst **17**, dimethyl 2-diazomalonate, PhF (70% yield, 60–70% *ee*). (b) Benzene, 185 °C (82% yield). (c) H_2 (60 atm), Pd/C (5 mol-%), EtOAc, r.t., 72 h (65% yield). (d) DIBAL-H, THF, –65 to –50 °C. (e) TBSCl, imid., DMF (50%, 2 steps). (f) MeN(OMe)·HCl, *i*PrMgCl, THF, –15 °C, 4 h (65% yield).



Scheme 4. Completion of norrisolide. Conditions: (a) 2,4,6-Triisopropylphenylsulfonyl hydrazide, HBF_4, CH_3CN, r.t., 12 h (72% yield). (b) *n*BuLi, THF, 2 h, –78 to 0 °C; **13**, THF, –78 to –30 °C, 12 h, (92% yield). (c) H_2 (10 atm), Rh/Al_2O_3 (10 mol-%), EtOAc, r.t., 12 h (65% yield). (d) $TMSCH_2MgCl$, Et_2O, r.t. (99% yield). (e) KHMDS, THF, r.t.; Tf_2O, pyr. THF, r.t. (60% yield) (f) TBAF, AcOH, THF, r.t. (g) PCC, NaOAc, CH_2Cl_2, 4 Å MS, (70% yield, 2 steps) (h) TFA/H_2O (3.3:1). (i) Ac_2O, DMAP, Et_3N, CH_2Cl_2, r.t. (40% yield, 2 steps).

cyclopropanation time from 12 h for the racemic reaction with $Rh_2(OAc)_4$ to 2 h. This rate enhancement also allowed for a reduction in the number of equivalents of **8**, which tended to isomerize into conjugation during the course of the reaction. After cyclopropanation, catalyst **17** can be precipitated from acetonitrile with 85% recovery and used one more time for the cyclopropanation with the same efficiency.

Further elaboration of the side chain was continued by diastereoselective hydrogenation of intermediate **11** by using Pd/C under 60 atm H_2 with triethylamine (1 equiv., Scheme 3). The resulting lactone was then reduced with DIBAL-H and protected as the TBS lactol to provide compound **12** with a *syn* relationship between all stereogenic ring system hydrogen atoms, establishing the cup-shaped ring system present in norrisolide. Finally, the methyl ester of intermediate **12** was transformed into Weinreb amide **13**,[25] which was found to be a suitable electrophile for the fragment coupling step.

The completion of the synthesis is shown in Scheme 4. A Shapiro reaction was used to join the indane fragment to the oxidized side chain. Condensation of ketone **3** with 2,4,6-triisopropylphenylsulfonyl hydrazide followed by treatment of the resulting hydrazone with *n*BuLi (2 equiv.) gave a vinyl anion, which was treated with Weinreb amide **13**. This sequence provided enone **14** as a mixture of diastereomers stemming from the minor enantiomer from the cyclopropanation. At this stage, the diastereomers were not readily separable and were taken on as a mixture. Hydrogenation of **14** by using rhodium on alumina in ethyl acetate provided ketone **15** along with the minor diastereomer, which at this point could be separated.

The next step was to olefinate the relatively hindered carbonyl group in **15**, which proved to be more difficult than initially expected.[26] Unfortunately, direct methenylations of this ketone were unsuccessful.[27] For example, Takai olefination[28] and methenylations with the use of the Nysted reagent[29] failed to give the desired product. Theodorakis used a two-step approach to access the 1,1-disubstituted olefin, through addition of methyl Grignard and then elimination with thionyl chloride. In our case, methyl Grignard added cleanly to the ketone; however, attempts to eliminate water to form the 1,1-disubstituted olefin were unproductive. After significant optimization, promising results were identified by using a stepwise Peterson olefination procedure.[30] Addition of $TMSCH_2MgCl$ into ketone **15** occurred in quantitative yield. Unfortunately, direct elimination with the use of either basic or acidic conditions, with and without additives (e.g., HMPA, TMEDA, etc.) failed to generate desired methenylated product **16**. Fortunately, activation of the tertiary hydroxy group with triflic anhydride and the use of an excess amount of pyridine cleanly generated desired 1,1-disubstituted olefin **16** as the only product.

With **16** in hand, we were able to complete the synthesis, with the remaining steps consisting of deprotection of the lactol and oxidation to the lactone and manipulation of the methyl acetal by epimerization and acetylation. The TBS acetal of **16** was deprotected with acetic acid buffered TBAF. The resulting lactol was not purified, but oxidized directly with PCC in 70% yield for the two steps. After TFA hydrolysis, intermediate **17** was obtained as a 1:1 mixture of lactol epimers. Upon acetylation, only the desired diastereomer, which had spectroscopic data that matched that of natural norrisolide, was isolated in 40% yield over the two steps.

Conclusions

In summary, the total synthesis of norrisolide was completed with a longest linear sequence of 14 steps in an overall yield of 1.7%. This synthesis is concise and offers asymmetric entry to the hydrindane core and the catalytic asymmetric preparation of the oxidized norrisane side chain, advancements that can facilitate the preparation of additional members of this class of marine natural products.

Supporting Information (see footnote on the first page of this article): Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final products.

Acknowledgments

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