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Synthetic Studies on Norrisolide: Enantioselective Synthesis of the Norrisane Side Chain

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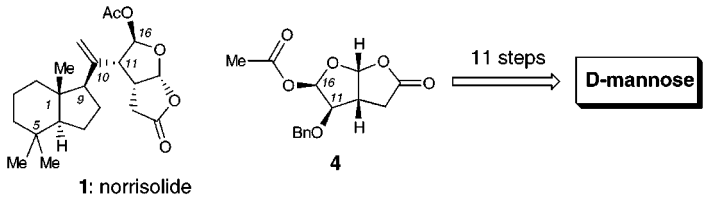
ABSTRACT



Norrisolide (1) belongs to a family of marine diterpenes that are characterized by the assembly of a bicyclic core with a unique and highly oxygenated side chain (norrisane side chain). As a prelude to the synthesis of 1, we present herein a short, efficient, and enantioselective synthesis of the norrisane side chain 4. The synthetic route toward 4 departs from D-mannose and is short (11 steps), efficient, and enantioselective.

Norrisolide (**1**) is a marine natural product, initially isolated by Faulkner and co-workers from the nudibranch *Chromodoris norrisi*, collected in the Gulf of California.[1] The structure and relative stereochemistry of **1** were established by extensive spectroscopic and crystallographic studies, which revealed a unique assembly of a perhydroindane core to a side chain containing a fused γ-lactone−γ-lactol ring system. This peculiar side chain was subsequently identified as a structural motif of other members of the norrisane family, which currently include macfarlandin C (**2**) and dendrillolide A (**3**) (Figure 1).[2]

The surprising lack of any synthetic studies toward norrisolide and related compounds may be attributed to their initially reported poor antimicrobial activity.[2b] Recent studies, however, have indicated that norrisolide (**1**) interferes with the structure and promotes the vesiculation of the Golgi apparatus in vivo.[3] Among the few natural products known to affect the Golgi organization, **1** distinguishes itself as being the only compound known to induce an irreversible effect.[4] The observed inability of the treated cells to recover may imply that norrisolide forms a covalent interaction with its biological receptor and points to the side chain of **1** as the

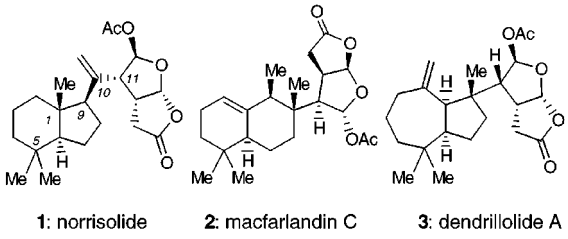


Figure 1. Marine natural products of the norrisane family.

(1) Hochlowski, J.; Faulkner, D. J.; Matsumoto, G.; Clardy, J. *J. Org. Chem.* **1983**, *48*, 1141−1142.

(2) (a) Sullivan, B. J.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3204−3209. (b) Molinski, T. F.; Faulkner, D. J.; He, C.-h.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4564−4567. (c) Rudi, A.; Kashman, Y. *Tetrahedron* **1990**, *46*,4019−4022.

(3) Malhotra, V.; Faulkner, D. J. Personal communication, 1999.

(4) (a) Takizawa, P. A.; Yucel, J. K.; Veit, B.; Faulkner, D. J.; Deerinck, T.; Soto, G.; Ellisman, M.; Malhotra, V. *Cell.* **1993**, *73*, 1079−90. (b) Lippincott-Schwartz, J.; Yuan, L. C.; Bonifacino, J. S.; Klausner, R. D. *Cell.* **1989**, *56*, 801−813.

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potential site where such an interaction can occur. Our interest in these aspects of this class of compounds led us to envision a convergent synthesis of norrisolide (**1**). As a prelude to this effort, we report herein the construction of the norrisane side chain **4**. Our strategy also represents the first synthetic entry to this type of fused bicyclic γ-lactone−γ-lactol ring system.[5]

Respectful of the inherent reactivity of the bicyclic array of **4** toward nucleophilic attack or acid treatment (oxonium ion formation), we sought to design its synthesis starting from the less oxygenated and more stable lactone **5**. Installation of the C16 acetoxy group was then envisioned to occur at the last step of the synthesis by oxidizing ketone **5** under Baeyer−Villiger conditions (Figure 2).[6] This oxidation was

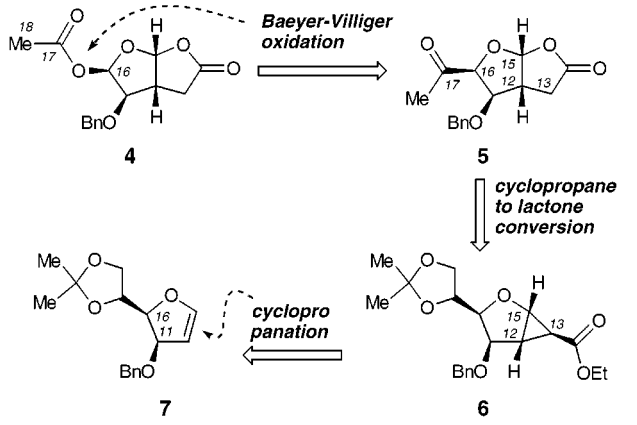
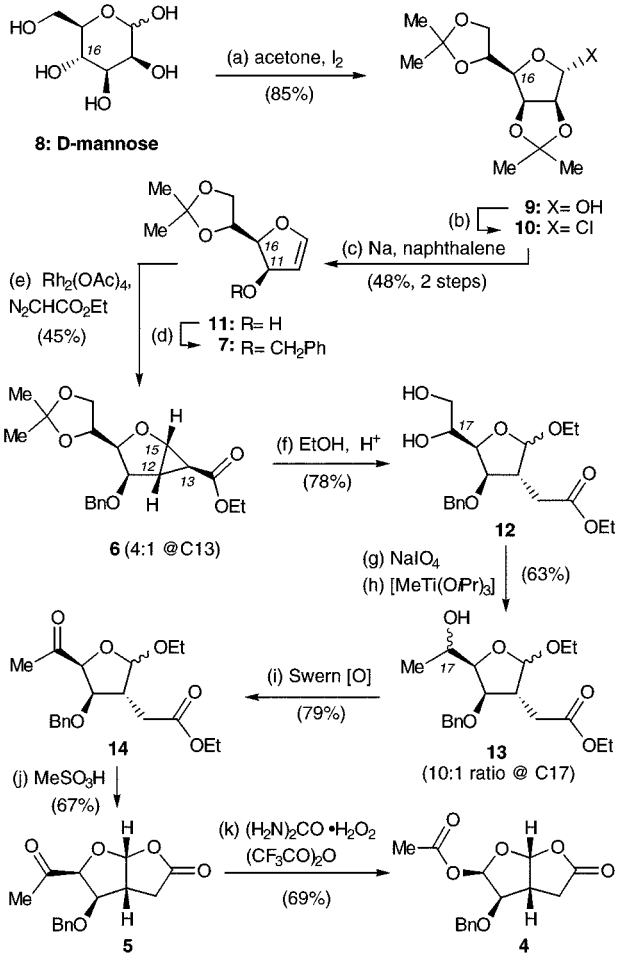


Figure 2. Retrosynthesis of fragment **4** (norrisane side chain).

advantageous since it proceeds under mild conditions and is regio- and stereoselective.[7] The fused bicyclic system **5** was expected to be formed from ester **6** via a sequence of reactions involving cyclopropane opening followed by lactone formation. Further disassembly of the cyclopropyl ester at the C12 and C15 centers suggested the mannose-derived glycal **7** as a putative starting material. Taking advantage of the facial differentiation of **7**, a substrate-controlled cyclopropanation could introduce the desired chirality at C12 center, ultimately dictating the stereochemical outcome at the C15 center. Moreover, the chirality inherited from the structure of D-mannose at the C16 center could be translated to the desired stereochemistry of the acetoxy group of **4** during the Baeyer−Villiger oxidation. Our efforts to bring this strategy to fruition are shown in Scheme 1.

Scheme 1.[a] Synthesis of Norrisane Side Chain **4**



[a]Reagents and conditions: (a) 0.1 M D-mannose in acetone, 0.2 equiv. I_2, 25 °C, 2 h, 85%; (b) 0.6 equiv DMAP, 1.2 equiv TsCl, 1.0 equiv Et_3N, CH_2Cl_2, 25 °C, 2 h, 60%; (c) 3.0 equiv naphthalene,10 equiv Na, THF, 0 °C to 25 °C, 10 min, 80%; (d) 1.2 equiv BnBr, 1.2 equiv NaH, 0.5 equiv $nBu_4N^+I^-$, 0 °C to 25 °C, 2 h, 90%; (e) 0.01 equiv $Rh_2(OAc)_4$, 1.1 equiv N_2CHCO_2Et (0.1 M in CH_2Cl_2, syringe pump addition), CH_2Cl_2, 25 °C, 14 h, 45%; (f) EtOH, 0.8 M H_2SO_4, 25 °C, 48 h, 78%; (g) 3.0 equiv $NaIO_4$, THF/H_2O: 1/1, 20 min, 25 °C; (h) 1.0 equiv $TiCl_4$, 3.0 equiv. $Ti(OiPr)_4$, THF, 0 °C; 4.0 equiv MeLi, 1 h, 0 °C, 25 °C, 1 h, 63% (2 steps); (i) 4.0 equiv $(COCl)_2$, 5.0 equiv DMSO, −78 °C, 0.5 h, CH_2Cl_2; Et_3N, −40 °C, 10 min, 79%; (j) 6.0 equiv $MeSO_3H$ in CH_2Cl_2, −5 to 0 °C, 12 h, 67%; (k) Urea-hydrogen peroxide, trifluoroacetic anhydride, 40 min, 0 °C, CH_2Cl_2, 25 °C, 2 h, 69%.

Our synthetic venture departed with transformation of D-mannose (**8**) to the known bisacetonide **9** (Scheme 1).[8] Superior results were obtained using iodine as a catalyst (as compared to H_2SO_4 treatment) and delivered **9** in 85% yield

(5) For a catalytic asymmetric Diels−Alder approach to a related tricyclic γ-lactone−γ-lactol ring system, see: Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616−9617.

(6) For an impressive demonstration of the Baeyer−Villiger reaction in total synthesis, see: Corey, E. J.; Trybulski, E. J.; Melvin, L. S., Jr.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falk, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618−4620. Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falk, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620−4622.

(7) (a) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990; pp 186−195. (b) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533−535. (c) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318−2322. For a discussion on the migratory aptitude involved in Baeyer−Villiger oxidations, see: (d) Goodman, R. M.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392−9393.

(8) Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415−3416.

after a simple filtration and crystallization. Treatment of **9** with *p*-toluenesulfonyl chloride and triethylamine afforded the desired glycosyl chloride **10**,[9] which upon slow addition to a stirring mixture of sodium naphthalenide in THF gave rise to glycal **11** in 48% overall yield.[10] Compound **11** proved to be labile upon standing (presumably due to self-oligomerization) and was immediately benzylated (BnBr, NaH, *n*-Bu_4I) to produce vinyl ether **7** in 90% yield. We anticipated that the bulky acetonide group at C16 in conjuction with the benzyl ether group at C11 would shield the top face of vinyl ether **7** and direct the sterically cumbersome rhodium acetate carbenoid from the β-face of the molecule. Indeed, this cyclopropanation furnished ester **6** with the desired configuration at C12 center, albeit in only 45% yield.[11,12] To improve upon the yield of this reaction, we altered the temperature (0 °C to 80 °C in refluxing benzene), rate of addition, and concentration of reagents. An increase in temperature had no observable effect in product formation; however, the reagent concentration appeared to be crucial, since under dilute conditions an increased amount of byproducts arising from dimerization of the ethyl diazoacetate was observed. Best results were obtained upon syringe pump addition of ethyl diazoacetate (0.1 M in CH_2Cl_2) into a concentrated mixture of **7** (2 M in CH_2Cl_2) and rhodium(II) acetate at 25 °C. The only diastereomers acquired during this reaction were produced at the C13 center (4:1 ratio in favor of the *exo* adduct) and both were taken forward.

Exposure of **6** to a dilute ethanolic solution of sulfuric acid induced acetonide deprotection followed by concomitant opening of the cyclopropane ring afforded compound **12** in 78% overall yield.[13,14] After oxidative cleavage of diol **12** ($NaIO_4$), the resulting aldehyde was methylated upon treatment with MeTi(*i*-OPr)$_3$ (formed in situ by mixing $TiCl_4$, Ti(*i*OPr)$_4$, and MeLi)[15] to produce **13** in 63% combined yield. This addition proceeded with excellent chemoselectivity (no interference with the ester functionality) and diastereoselectivity (about 10:1 mixture of diastereomers at the C17 center, presumably arising from a chelation-controlled addition). Oxidation of **13** under Swern conditions gave rise to ketone **14** (79% yield). A series of Brönsted acids or Lewis acids ($TiCl_4$, $BF_3{\cdot}Et_2O$, $AlCl_3$, H_2SO_4, $MeSO_3H$) were evaluated for the conversion of **14** to **5**. Although all these acids effected the desired transformation in variable yields, best yields were obtained using methanesulfonic acid, which at 0 °C produced bicycle **5** as a single isomer in 67% yield.[16]

The stage was now set for the crucial Baeyer−Villiger oxidation. Several peracids were tested, such as *m*-CPBA and H_2O_2 (30% aqueous), but these proved to be ineffective. The conversion of **5** to **4** was ultimately achieved using urea−hydrogen peroxide and trifluoroacetic anhydride and gave rise to the desired material in 69% yield.[17] As predicted, a single isomer was obtained during this oxidation, the structure of which was established by COSY and NOE experiments.[18]

In conclusion, we have presented herein a concise, enantioselective approach to the C11−C18 fragment of norrisolide **1**. Our approach departs from commercially available D-mannose (**8**) and delivers the fused γ-lactone−γ-lactol ring system **4** in 11 steps and good overall yield. The synthetic route takes advantage of the inherent chirality of D-mannose and is highlighted by a rhodium-catalyzed substrate-controlled cyclopropanation, followed by an acid-catalyzed conversion of a cyclopropane ester to a five-membered lactone and subsequent Baeyer−Villiger oxidation of a methyl ketone. Extension of the above strategy to the synthesis of norrisolide (**1**) and related compounds is currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data (including copies of ^1H and ^{13}C NMR spectra) for compounds **4**−**7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For asymmetric versions of cyclopropanation, see: (a) Evans, D. A.; Woerpel, K. M.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (b) Müller, D.; Umbright, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (c) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 430−432. (d) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373−7376. (e) Davies, H. M. L.; Kong, N.; Churchill, M. R. *J. Org. Chem.* **1998**, *63*, 6586−6589. (f) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133−4136.

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(17) Interestingly, no reaction was observed when the above oxidation was performed under buffered conditions (Na_2HPO_4) (see ref 7b).

(18) All new compounds exhibited satisfactory spectroscopic and analytical data (see Supporting Information). Yields refer to spectroscopically and chromatographically homogeneous materials.