Natural Products Synthesis

Stereoselective Total Synthesis of (+)-Norrisolide**

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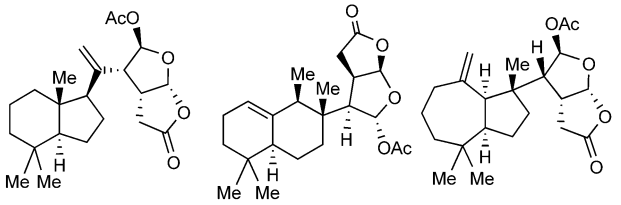
In memory of David J. Faulkner

Nudibranch molluscs are known to harvest a variety of chemical metabolites from sponges and use them for their own defense.[1,2] In an effort to understand this behavior from a chemical perspective, Faulkner and co-workers isolated a novel diterpene named norrisolide (**1**) from the skin extracts of the dorid nudibranch *Chromodoris norrisi*.[3] Further studies led to the isolation of **1** from different species of sponges that support the feeding patterns of these molluscs.[4]

From a structural standpoint, norrisolide belongs to a family of marine diterpenes that also includes macfarlandin C (**2**) and dendrillolide A (**3**; Scheme 1).[5] These natural



Scheme 1. Representative natural products with a fused tetrahydrofuran–γ-lactone ring system

products share a common structural motif characterized by a fused γ-lactone–γ-lactol ring system attached to a hydrophobic bicyclic core. The unusual pattern of functionalities encountered in this highly oxygenated system confers to these molecules a high degree of chemical reactivity, the biological significance of which remains largely unexplored.[6] Herein we describe a stereoselective synthesis of (+)-norrisolide (**1**). Not only have our studies led to the first synthesis of any member of this family of diterpenes, but they have also established the absolute configuration of **1** to be that shown in Scheme 1.[7,8]

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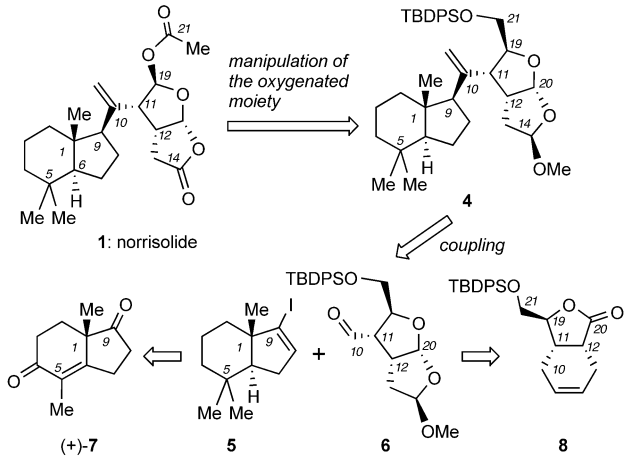
Our retrosynthetic strategy towards norrisolide (**1**) is illustrated in Scheme 2. As we were concerned about the potential reactivity of the fused γ-lactone–γ-lactol motif



Scheme 2. Strategic bond disconnections of **1**. TBDPS = *tert*-butyldiphenylsilyl.

towards nucleophilic attack, we attempted the synthesis of **1** via the less-oxygenated and more-stable precursor **4**.[9] In the forward direction, we envisaged that **4** could be converted into the natural product through oxidation at C14 and subsequent insertion of an oxygen atom between the C19 and C21 centers. The latter manipulation would be possible, in principle, by a Baeyer–Villiger oxidation, which was expected to proceed in a regio- and stereoselective manner.[10] Disconnection at the C9–C10 bond in **4** unveils components **5** and **6**, which could be connected in the desired manner by a nucleophilic reaction at the aldehyde in **6**. It was planned to construct the bicyclic framework of **6** from the lactone **8**, which contains the desired *cis* stereochemistry at the C11 and C12 centers. The *trans*-fused hydrindane motif of **5** could be formed from the enantiomerically enriched enone (+)-**7**. Our efforts to bring this plan to fruition are highlighted in the schemes that follow.

Our synthetic approach began with the optically pure enone **7**, which was available through an L-phenylalanine-mediated asymmetric Robinson annulation (55–65% yield, >95% *ee* after a single recrystallization).[11] Selective reduction at the more reactive C9 carbonyl group, followed by protection of the resulting alcohol, afforded the silyl ether **9** in 76% yield over the two steps (Scheme 3).[12] Methylation of the extended enolate of **9** at the C5 center produced ketone **10** (66% yield), the reduction and radical deoxygenation of which led to the alkene **11** in 83% yield (from **10**). Several methods were examined for the conversion of the alkene **11** into the *trans*-fused bicycle **12**.[13] The best results were obtained by hydroxylation of the double bond (ratio at C6: *trans*/*cis* 2.5:1) and subsequent reduction of the resulting alcohol (52% yield from **11**). The use of the bulky TBDPS group to protect the C9 hydroxy group was found to be crucial in terms of the diastereomeric outcome of the hydroxylation reaction.[11d] Fluoride-induced desilylation of **12** followed by

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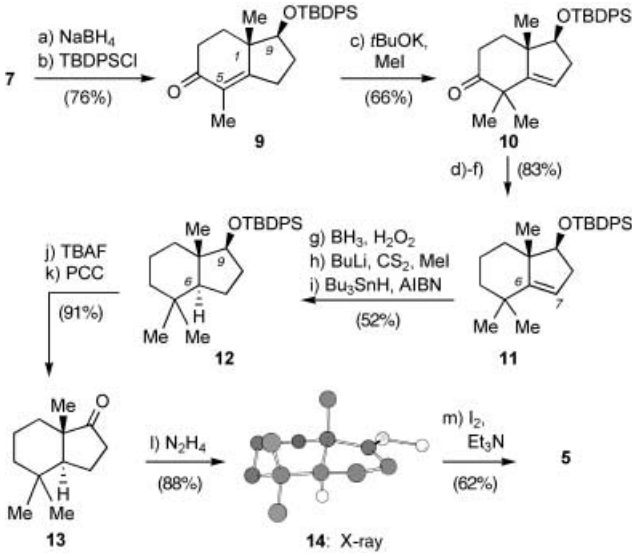
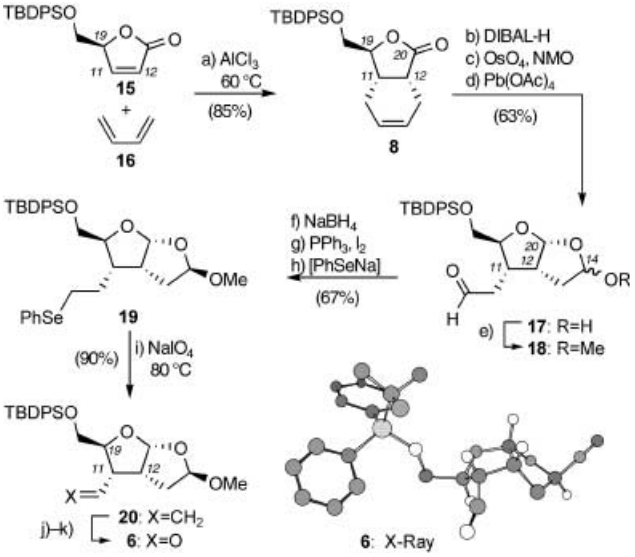


Scheme 3. Reagents and conditions: a) $NaBH_4$ (0.33 equiv), EtOH, −25 °C, 0.5 h, 99%; b) imidazole (2.5 equiv), TBDPSCl (2.0 equiv), DMAP (0.1 equiv), DMF, 25 °C, 4 h, 77%; c) *t*BuOK, MeI, DMF, 25 °C, 1 h, 66%; d) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 1 h, 100%; e) *n*BuLi (1.2 equiv), 0 °C, 0.5 h, CS_2 (10 equiv), 2 h, then MeI (3.0 equiv), THF, 0.5 h, 95%; f) nBu_3SnH (2.5 equiv), AIBN (0.1 equiv), toluene, 120 °C, 0.25 h, 87%; g) BH_3·THF (3.0 equiv), THF, 0 °C, 12 h, then aqueous NaOH (3 M, 20 equiv), H_2O_2 (20 equiv), 25 °C, 12 h, 80% (56% *trans*, 24% *cis*); h) *n*BuLi (1.2 equiv), 0 °C, 0.5 h, CS_2 (10 equiv), 2 h, then MeI (3.0 equiv), THF, 0 °C, 0.5 h; i) nBu_3SnH (2.5 equiv), AIBN (0.1 equiv), toluene, 120 °C, 0.25 h, 92% (over two steps); j) TBAF (3.0 equiv), THF, 60 °C, 8 h, 99%; k) PCC (4.5 equiv), celite, CH_2Cl_2, 25 °C, 1 h, 92%; l) N_2H_4·H_2O (30 equiv), Et_3N (4.0 equiv), EtOH, reflux, 5 h, 88%; m) I_2 (until N_2 evolution has ceased), Et_3N (10 equiv), THF, 25 °C, 0.25 h, 62%. AIBN = azobisisobutyronitrile, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, PCC = pyridinium chlorochromate TBAF = tetrabutylammonium fluoride.



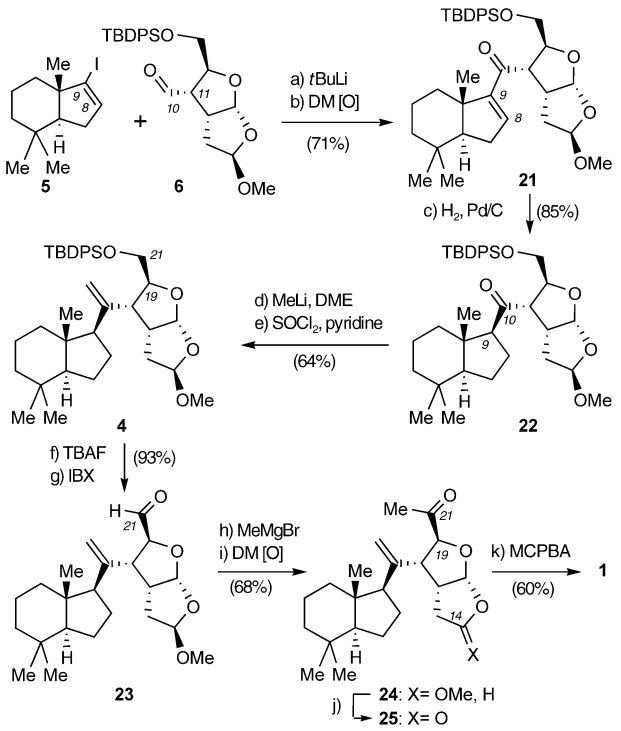
Scheme 4. Reagents and conditions: a) $AlCl_3$ (0.33 equiv), CH_2Cl_2, 60 °C, 6 days, 85%; b) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, 0.5 h, 98%; c) OsO_4 (0.01 equiv), NMO (1.1 equiv), pyridine (3 drops), acetone/H_2O (10:1), 25 °C, 8 h; d) $Pb(OAc)_4$ (1.2 equiv), CH_2Cl_2, 0 °C, 0.5 h, 64% (over two steps); e) MeOH (1.2 equiv), amberlyst 15, molecular sieves (3 Å), Et_2O, 25 °C, 10 h, 77% (**18**α/**18**β 1:1); f) $NaBH_4$ (1.5 equiv), MeOH, 25 °C, 0.5 h; g) imidazole (2.2 equiv), PPh_3 (1.1 equiv), I_2 (1.2 equiv), THF, 25 °C, 0.5 h, 93% (over two steps); h) $(PhSe)_2$ (0.55 equiv), $NaBH_4$ (1.5 equiv), EtOH, 25 °C, 0.5 h, 92%; i) $NaIO_4$ (1.6 equiv), MeOH/H_2O (5:2), 25 °C, 1 h, then Et_3N/PhH (1:1), reflux, 0.5 h, 90%; j) OsO_4 (0.05 equiv), NMO (1.1 equiv), pyridine (3 drops), acetone/H_2O (10:1), 25 °C, 10 h; k) $Pb(OAc)_4$ (1.2 equiv), CH_2Cl_2, 0 °C, 0.5 h, 94% (over two steps). DIBAL-H = diisobutylaluminum hydride, NMO = 4-methylmorpholine *N*-oxide.

PCC oxidation provided the ketone **13** in 91% yield.[14] The treatment of **13** with hydrazine then produced the hydrazone **14**. Single-crystal X-ray diffraction analysis of **14** showed the *trans* junction of the bicycle unambiguously.[15] Finally, treatment of **14** with I_2/Et_3N led to the formation of the desired vinyl iodide **5** (62% yield).[16]

The construction of aldehyde **6** is highlighted in Scheme 4. The C11 and C12 centers were connected by a Diels–Alder reaction between the butenolide **15**[17] and butadiene (**16**). Under Lewis acid catalysis this cycloaddition proceeded exclusively from the opposite face to that with the bulky TBDPS group to afford **8** as a single isomer (85% yield).[18] Reduction of the lactone unit at C20, followed by oxidative cleavage of the alkene in the other ring, produced the fused lactol **17** in 63% yield as a 1:1 mixture of isomers at C14. These compounds were separated[19] after conversion into the corresponding methyl ether **18**.[20] The aldehyde **18** (β isomer with respect to C14) was then converted into the selenide **19**, which underwent oxidation and elimination to give the alkene **20** (61% from **18**).[21] Osmylation of **20**, followed by oxidative cleavage of the resulting diol, furnished the aldehyde **6** (two steps, 94% yield). The aldehyde **6** was crystalline and its structure was confirmed unambiguously by X-ray crystallographic analysis.[15]

The remaining steps in the synthesis of **1** are illustrated in Scheme 5. Lithiation of the vinyl iodide **5**, followed by addition of the aldehyde **6** and oxidation of the resulting alcohol, afforded the enone **21** in 71% yield. Hydrogenation of the C8–C9 double bond proceeded exclusively from the more accessible α face of the bicyclic core to form the ketone **22** in 75% yield. Standard olefination procedures (Wittig, Peterson) failed to convert **22** into **4**, presumably as a result of the steric hindrance at the C10 carbonyl group. This obstacle was circumvented by implementing a two-step procedure that included methylation of the ketone **22** (MeLi, DME) and treatment of the resulting alcohol with $SOCl_2$ in the presence of pyridine.[22] This manipulation produced the alkene **4** in 64% yield from **22**.

With substrate **4** in hand the stage was now set for the final functionalization of the oxygenated bicycle (Scheme 5). The silyl ether at C21 was cleaved (99% yield), and the resulting alcohol was then oxidized to the aldehyde **23**[23] and subsequently converted into the ketone **24** (MeMgBr, then Dess–Martin oxidation, 68% yield). Treatment of **24** with CrO_3 in aqueous acetic acid produced the lactone **25** in 80% yield.[24] Finally, Baeyer–Villiger oxidation of **25** (MCPBA, $NaHCO_3$, 60% yield) led to insertion of the oxygen atom as desired between the C19 and C21 centers with complete retention of



Scheme 5. Reagents and conditions: a) **5** (1.5 equiv), *t*BuLi (3.0 equiv), THF, −78→−40°C, 0.5 h, then **6**, THF, −78°C, 1 h, 75%; b) Dess–Martin periodinane (8.0 equiv), CH_2Cl_2, 25°C, 10 h, 95%; c) 10% Pd/C, H_2, MeOH, 25°C, 10 h, 85%; d) MeLi (5.0 equiv), THF/DME (1:3), 0°C, 0.5 h, 75%; e) $SOCl_2$ (10.0 equiv), pyridine (20.0 equiv), CH_2Cl_2, 0°C, 0.5 h, 85%; f) TBAF (2.0 equiv), THF, 25°C, 8 h, 99%; g) IBX (3.0 equiv), MeCN, 80°C, 2 h, 96%; h) MeMgBr (10.0 equiv), THF, 0°C, 0.5 h, 72%; i) Dess–Martin periodinane (2.5 equiv), CH_2Cl_2, 25°C, 6 h, 94%; j) CrO_3 (10 equiv), $AcOH/H_2O$ (2:1), 25°C, 6 h, 80%; k) MCPBA (2.5 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2, 0°C, 4 h, 60%. DME = dimethoxyethane, DM[O] = Dess–Martin oxidation, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, MCPBA = *m*-chloroperbenzoic acid.

configuration[10] to produce norrisolide (**1**). Synthetic **1** was spectroscopically and analytically identical to natural norrisolide (**1**).

In conclusion, we have presented herein a synthesis of (+)-norrisolide (**1**) that also establishes its absolute stereochemistry. Our strategy is highlighted by the union of fragments **5** and **6** to produce the natural product after manipulations of the oxygenated bicyclic moiety. The synthetic approach paves the way for the preparation of analogues of **1** and will be helpful for the evaluation of the biological potential of norrisolide and related metabolites.

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[1] For selected reviews, see: a) D. J. Faulkner in *Biomedical Importance of Marine Organisms, Vol. 13* (Ed.: D. G. Fautin), Memoirs California Academy of Sciences, San Francisco, CA, **1988**, pp. 29–36; b) P. Karuso in *Bioorganic Marine Chemistry* (Ed.: P. J. Scheuer), Springer, Berlin, **1987**, pp. 31–60; c) D. J. Faulkner, *Nat. Prod. Rep.* **1984**, *1*, 251–280; d) T. E. Thompson, *J. Mar. Biol. Assoc. U. K.* **1960**, *39*, 115–122.

[2] For selected natural products isolated from nudibranchs, see: a) B. J. Burreson, P. J. Scheuer, J. Finer, J. Clardy, *J. Am. Chem. Soc.* **1975**, *97*, 4763–4764; b) E. J. Dumbei, E. D. de Silva, R. J. Andersen, M. I. Choudhary, J. Clardy, *J. Am. Chem. Soc.* **1989**, *111*, 2712–2713; c) B. Carte, D. J. Faulkner, *J. Chem. Ecol.* **1986**, *12*, 795–804; d) G. Cimino, S. De Rosa, S. De Stefano, G. Sodano, G. Villani, *Science* **1983**, *219*, 1237–1238; e) M. Tischler, R. J. Andersen, *Tetrahedron Lett.* **1989**, *30*, 5717–5720.

[3] J. E. Hochlowski, D. J. Faulkner, G. K. Matsumoto, J. Clardy, *J. Org. Chem.* **1983**, *48*, 1141–1142.

[4] a) B. Sullivan, D. J. Faulkner, *J. Org. Chem.* **1984**, *49*, 3204–3206; b) A. Rudi, Y. Kashman, *Tetrahedron* **1990**, *46*, 4019–4022.

[5] a) S. C. Bobzin, D. J. Faulkner, *J. Org. Chem.* **1989**, *54*, 5727–5731; b) T. F. Molinski, D. J. Faulkner, *J. Org. Chem.* **1986**, *51*, 4564–4567.

[6] For recent biological data on related metabolites, see: M. Arno, L. Betancur-Galvis, M. A. Gonzalez, J. Sierra, R. J. Zaragoza, *Bioorg. Med. Chem.* **2003**, *11*, 3171–3177.

[7] For synthetic studies toward **1**, see: a) C. Kim, R. Hoang, E. A. Theodorakis, *Org. Lett.* **1999**, *1*, 1295–1297; b) R. L. Casaubon, M. L. Snapper, *224th ACS Natl. Meeting*, Boston, USA, **2002**.

[8] For selected syntheses of related metabolites, see: a) A. D. Lebsack, L. E. Overman, R. J. Valentekovich, *J. Am. Chem. Soc.* **2001**, *123*, 4851–4852; b) A. Abad, M. Arno, M. L. Marin, R. J. Zaragoza, *J. Org. Chem.* **1992**, *57*, 6861–6864; c) M. Arno, M. A. Gonzalez, R. J. Zaragoza, *J. Org. Chem.* **2003**, *68*, 1242–1251.

[9] For a catalytic asymmetric Diels–Alder approach to a related tricyclic γ-lactone–γ-lactol ring system, see: E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617.

[10] For selected reports on the Baeyer–Villiger reaction, see: a) M. Hudlicky in *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 186–195; b) K. Mislow, J. Brenner, *J. Am. Chem. Soc.* **1953**, *75*, 2318–2322; c) R. M. Goodman, Y. Kishi, *J. Am. Chem. Soc.* **1998**, *120*, 9392–9393.

[11] a) U. Eder, G. Sauer, R. Wiechert, **1971**, *83*, 492–493; b) Z. G. Hajos, D. R. Parrish, (Hoffmann-La Roche, Inc.), US 70–96597, **1976** [*Chem. Abstr.* **1977**, 86, 89274]; c) H. Hagiwara, J. Uda, *J. Org. Chem.* **1988**, *53*, 2308–2311; d) H. Hagiwara, H. Sakai, T. Uchiyama, Y. Ito, N. Morita, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc. Perkin Trans. 1* **2002**, 583–591.

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

[13] All hydrogenation conditions produced a mixture of *cis* (major product) and *trans* bicycles, which were difficult to separate by using standard chromatographic techniques.

[14] For an alternative synthetic route to **13**, see: a) L. Paquette, H.-L. Wang, *Tetrahedron Lett.* **1995**, *36*, 6005–6008; b) L. Paquette, H.-L. Wang, *J. Org. Chem.* **1996**, *61*, 5352–5357.

[15] CCDC-216393 (**14**) and CCDC-216394 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[16] a) D. H. R. Barton, R. E. O'Brien, S. Sternhill, *J. Chem. Soc. Perkin Trans. 1* **1962**, 470–476. b) A. Fernandez-Mateos, G. P. Coca, R. R. Gonzalez, C. T. Hernandez, *Tetrahedron* **1996**, *52*, 4817–4828.

[17] Compound **15** is readily available from D-mannitol by the procedures reported in the following publications: a) C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Shantz, N. L. Sear, C. S. Vianco, *J. Org. Chem.*

1991, *56*, 4056 – 4058; b) J. Mann, A. Weymouth-Wilson, *Carbohydr. Res.* **1991**, *216*, 511 – 515; c) F. Fazio, M. P. Scheider, *Tetrahedron: Asymmetry* **2000**, *11*, 1869 – 1876**.**

[18] M. G. B. Drew, J. Mann, A. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1986**, 2279 – 2285.

[19] In principle, both C14 isomers can be used for the synthesis of **1**. Nonetheless, to facilitate the spectroscopic characterization of the synthetic intermediates the strategy was evaluated with the β isomer (with respect to the substituent at C14).

[20] F. Petit, R. Furstoss, *Synthesis* **1995**, 1517 – 1520.

[21] P. J. Kocienski, P. Raubo, C. Smith, F. T. Boyle, *Synthesis* **1999**, 2087 – 2095.

[22] E. J. Corey, M. Ohno, R. B. Mitra, P. A. Vatakencherry, *J. Am. Chem. Soc.* **1964**, *86*, 478 – 485.

[23] J. D. Moore, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001 – 3003.

[24] Y. Lin, Y. Kuo, Y. Chen, *Chem. Pharm. Bull.* **1989**, *37*, 2191 – 2193.

