In a convergent approach to the marine natural product (+)-norrisolide (1) the two bicyclic ring systems are coupled through the C9–C10 bond to assemble the carbon framework in a late stage of the synthesis. Other highlights of the synthetic strategy include the formation of the unusual fused \(\gamma\)-lactone–\(\gamma\)-lactol motif of 1 through a sequence of oxidation reactions.

T. P. Brady, S. H. Kim, K. Wen, E. A. Theodorakis

**Keywords:** alkylation - Diels–Alder reaction - natural products - synthetic methods - total synthesis

2004 – 43/6
Stereoselective Total Synthesis of (+)-Norrisolide**

Thomas P. Brady, Sun Hee Kim, Ke Wen, and Emmanuel A. Theodorakis*

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 products share a common structural motif characterized by a fused tetrahydrofuran–γ-lactone ring system that 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 hyridnane 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 (95% ee after a single recrystallization).6 Selective reduction of the more reactive C9 carbonyl group, followed by protection of the resulting alcohol, afforded the silyl ether 5 in 83% yield (from 4). 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 12 (2.5:1) after a single recrystallization.7 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 12 (2.5:1) after a single recrystallization.

* Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/anie.200352868
© 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
These compounds were separated after conversion into the which underwent oxidation and elimination to give the alkene with respect to C14) was then converted into the selenide.

PCC oxidation provided the ketone 13 in 91% yield. 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.

Finally, treatment of 14 with 1/Et3N led to the formation of the desired vinyl iodide 5 (62% yield).

The construction of aldehyde 6 is highlighted in Scheme 4. The C11 and C12 centers were connected by a Diels–Alder junction of the bicycle. 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 SOCl₂ in the presence of pyridine.

This manipulation produced the aldehyde 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 3). The silyl ether at C21 was cleaved (99% yield), and the resulting alcohol was then oxidized to the aldehyde 24 and subsequently converted into the ketone 25 (MeMgBr, then Dess–Martin oxidation, 68% yield). Treatment of 24 with CrO₃ in aqueous acetic acid produced the lactone 25 in 80% yield. Finally, Baeyer–Villiger oxidation of 25 (MCPBA, NaHCO₃, 60% yield) led to insertion of the oxygen atom as desired between the C19 and C21 centers with complete retention of structure was confirmed unambiguously by X-ray crystallographic analysis.

The remaining steps in the synthesis of 1 are illustrated in Scheme 4. Reagents and conditions: a) AlCl₃ (0.33 equiv), CH₂Cl₂, 60°C, 6 days, 85%; b) DiBAL-H (1.2 equiv), CH₂Cl₂, –78°C, 0.5 h, 98%; c) OsO₄ (0.01 equiv), NMO (1.1 equiv), pyridine (3 drops), acetone/H₂O (1:1), 25°C, 8 h; d) Pb(OAc)₄ (1.2 equiv), amylene 15, molecular sieves (3 Å), Et₂O, 25°C, 10 h, 77% (18a/18b 1:1); e) NaBH₄ (1.5 equiv), MeOH, 25°C, 0.5 h; f) iridazol (2.2 equiv), PPh₃ (1.1 equiv), L₄ (1.2 equiv), THF, 25°C, 0.5 h, 93% (over two steps); g) (PhSe)₂ (0.55 equiv), NaBH₄ (1.5 equiv), EtOH, 25°C, 0.5 h, 92%; h) NaI (1.6 equiv), MeOH/H₂O (3:2), 25°C, 1 h, then Et₃N/PhH (1:1), reflux, 0.5 h, 90%; i) OsO₄ (0.05 equiv), NMO (1.1 equiv), pyridine (3 drops), acetone/H₂O (1:1), 25°C, 10 h; k) Pb(OAc)₄ (1.2 equiv), CH₂Cl₂, 0°C, 0.5 h, 94% (over two steps). DiBAL-H = disobutylaluminum hydride, NMO = 4-methylmorpholine N-oxide.
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.

Received: September 15, 2003  [ZS2868]

Keywords: alkylation - Diels–Alder reaction - natural products - synthetic methods - total synthesis


[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.


[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 CB2 1EZ, UK; fax: (+ 44) 1223-336-033; or deposit@ccdc.cam.ac.uk).


[19] In principle, both C14 isomers can be used for the synthesis of I. 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).


