**Abstract:** The total synthesis of sculponeatin N, a bioactive polycyclic diterpene isolated from Isodon sculponeatus, is reported. Key features of the synthesis include diastereoselective Nazarov and ring-closing metathesis reactions, and a highly efficient formation of the bicyclo[3.2.1]octane ring system by a reductive radical cyclization.

Plants of the Isodon genus have found widespread use in traditional Chinese and Japanese medicine, with extracts from several species being used for the treatment of numerous ailments as far back as ancient times.[1] Among the many natural products isolated from these extracts to date, the wide variety of bioactive polycyclic 6,7-secoterpene species being used for the treatment of numerous ailments as far back as ancient times.[1] Among the many natural products isolated from these extracts to date, the wide variety of bioactive polycyclic 6,7-secoterpene skeletons that have been reported[2] has stimulated significant interest in their biosynthesis[3] and made them attractive targets for total synthesis (Figure 1).[4, 5]

Biosynthetically, the 6,7-secoterpene skeletons are derived from the parent enantiomeric (1) carboskeleton by oxidative scission of the C6–C7 bond, with additional oxidations and skeletal rearrangements leading to further structural diversification.[2, 3] Many family members, such as sculponeatin N (2) for example, maintain the bicyclo[3.2.1]octane ring system present within enantiomeric (1).[6] In maoecrystal V (3), the bicyclo[3.2.1]octane core has rearranged to a congested bicyclo[2.2.2]octane system, whereas within maoecrystal Z (4), fragmentation of the C8–C15 bond and formation of a new C6–C8 bond generates a fluorene-type ring system reminiscent of the gibberellins.[7] The structural presence of enones within these compounds correlates strongly with cytotoxicity. For example, sculponeatin N (2), possesses activity against K562 and HepG2 cell lines ($IC_{50} = 0.21$ and 0.29 µm, respectively), whereas derivatives lacking the exocyclic enone function are significantly less active.[6]

Previously, we demonstrated the feasibility of forging the C10 quaternary stereocenter and lactone within 6,7-secoterpene skeletons by a stereoselective Nazarov cyclization and subsequent oxidative ring expansion of the thus formed cyclohexanone.[8] Although our initial efforts were directed towards maoecrystal V (3), we also wished to apply these reactions to the synthesis of other 6,7-secoterpene skeletons with the long-term goal of establishing a general approach. Herein, we report the successful total synthesis of sculponeatin N (2), which establishes a blueprint for future studies into this class of natural products.[9]

Our retrosynthetic analysis of sculponeatin N (2) is shown in Scheme 1. We envisioned late-stage installation of both the lactone and C15 ketone through successive oxidative transformations of ketone 5. Disconnection of the C13–C16 bond within 5 led to cis hydrindane 6 as a suitable subtarget for further simplification. Compound 6 contains the full retinol for the Diels–Alder reaction, and logically led to cyclopentanone 7, which in turn keyed the application of a Nazarov cyclization transform to afford dienone 8. An important design element within this approach would be the stereocenter imparted by the protected C5 hydroxymethyl substituent, which due to its size should dictate the facial selectivity of both the Nazarov cyclization and Diels–Alder reaction.

Our investigations began with the known methyl cuprate conjugate addition/formaldehyde aldol reaction of 3-methyl-
The failure of the cycloaddition approach necessitated exploration of an alternative route to produce the desired cis hydrindane. We speculated that tris(allyl) intermediate 17 might enable construction of the desired ring system through a diastereoselective ring-closing metathesis reaction to diene 19. We hypothesized that the less strained cis hydrindane would be favored over the higher energy trans hydrindane. Accordingly, we set about preparing 17 from cyclopentenone 13. Attempts to conduct the direct 1,4-addition of an allyl group to 13 using a variety of methods were met only with formation of the undesired 1,2-addition product. We therefore made recourse to the higher order cuprate derived from halide 16, which underwent 1,4-addition only in the presence of excess BF₃·OEt (78% yield). Removal of both TBS ethers followed by subsequent double Grieco elimination and ketone allylation yielded tris(allyl) intermediate 17, which we had hoped, exposure of 17 to Grubbs II catalyst led to the formation of cis hydrindane 19. We did not observe any evidence of the trans hydrindane. Diene 19 was converted into enol triflate 21 by Wacker oxidation of the terminal olefin to form methyl ketone 20, which underwent selective triflation upon exposure to potassium hexamethyldisilazane (KHMDS) and the Comins reagent (48% yield, 2 steps).

With a route to enol triflate 21 secured, we began investigating its transformation into the desired bicyclo[3.2.1]octane species 22 (Table 1). As expected, under non-reducing conditions, the regular Heck product 23 was the major product (Table 1, entry 1). Exploration of conditions for the reductive Heck cyclization were met with limited success (Table 1, entry 2). Although synthetically useful ratios of 22/23 could be obtained, we noted a significant amount of alkene 24 in the reaction mixture. The formation of 24, however, opened the possibility of conducting a radical-based reductive cyclization to 22. Elimination of the trflate group from 21 was most efficiently carried out using TBAF to provide an 87% yield of alkene 24. Using conditions originally reported by Stork and co-workers 24 was then smoothly converted into the desired bicyclo[3.2.1]octane system upon treatment with Bu₂SnH and AIBN in 82% yield (71% over 2 steps from 21; Table 1, entry 3).

Completion of the synthesis would entail conversion of the cyclopentanone within 22 into the requisite lactone, and installation of the C15 ketone group (Scheme 3).

To this end, we treated the enolate of ketone 22 with MoO₃-Py-HMPA under Vedejs conditions to provide what we
Table 1: Reaction development. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Product(s)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh3)2 (50 mol%), K2CO3, 4 Å MS, MeCN, RT</td>
<td>23</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2 (10 mol%), TBACl (3.0 equiv) HCO2Na (2.5 equiv), 4 Å MS, DMF, RT</td>
<td>22, 23, 24</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>1) TBAF (2.5 equiv), THF, RT 2) Bu3SnH (4.0 equiv), AIBN (0.1 equiv), toluene, reflux; silica gel</td>
<td>22</td>
<td>71%</td>
</tr>
</tbody>
</table>

[a] Yield of isolated product after silica gel chromatography. [b] Determined by 1H NMR spectroscopic analysis. [c] Combined yield of mixture.

Initially thought was a 1:1 mixture of diastereomeric α-hydroxyketones (i.e., 25). Exposure of this mixture to aqueous H3IO6 gave mixed results; it appeared that only one of the α-hydroxyketones underwent oxidative cleavage, a situation we thought may be due to steric congestion from the large TBDPS group hampering the cleavage of one isomer. Indeed, removal the TBDPS ether prior to oxidative cleavage resulted in consumption of both α-hydroxy ketones, but much to our frustration two different isomer lactones were produced (i.e., 26 and 27), whose structures were confirmed by X-ray crystallographic analysis. Whereas the structure of 26 was easily reconciled with α-hydroxy ketone 25, the isomeric species 27 indicated a possible α-ketol shift had occurred. Owing to differences in their NMR spectra, we suspect that the two α-hydroxy ketones formed by the hydroxylation of ketone 22 are not stereoisomers, but rather regioisomers, thereby establishing a pathway to lactone 27.

As an alternative to oxidative cleavage of an α-hydroxyketone derived from 22, we next investigated the ozonolysis of the corresponding enol ether. A potential pitfall with this option was the likelihood of competitive cleavage of the C16–C17 exo-methylene group. Therefore, in order to attenuate the reactivity of this alken, we first conducted an allylic oxidation of 22 using SeO2/BuOOH, and converted the resultant alcohol into bis-silylated species 28. We anticipated that the inductive electron-withdrawing effect of the allylic C15-oxygen substituent would provide a bias for chemoselective ozonolysis of the more electron-rich π-bond. In the event, careful exposure of 28 to ozone in the presence of pyridine cleanly provided lactol 29, following reductive workup with dimethylsulfide (49% yield, 3 steps). Attempts to directly reduce the intermediate secondary ozonide to lactone 30 using NaBH4 for the reductive workup instead of dimethylsulfoxide produced only lactol 29. In sharp contrast to seemingly related examples in the literature, conversion of 29 into lactone 30 proved significantly difficult. Ultimately, we found that exposure of 29 to a solution of LiBH4 in diglyme at 50°C generated the desired product. Completion of the synthesis was then readily achieved by concomitant removal of both silyl protecting groups and selective oxidation of the allylic alcohol using MnO2 (36%, 2 steps). The synthetic sculponeatin N (2) thus obtained displayed identical spectral properties (1H NMR, 13C NMR) to those reported in the literature for the natural product.

In summary, the synthesis of sculponeatin N (2) has been achieved in 23 steps from 3-methylcyclohex-2-enone (9) by a route featuring several key diastereoselective transformations. Of particular note are the Nazarov and metathesis reactions that installed the critical C8 and C10 quaternary stereocenters with complete diasterecontrol, and the reductive radical cyclization that forged the bicyclo[3.2.1]octane ring system. The approach delineated herein should be applicable to the synthesis of other members of this fascinating class of natural products and allow further exploration of their biological properties.

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Keywords: isodon terpenes · natural products · reductive cyclization · ring-closing metathesis


[6] Compound 2 was isolated from Isodon scalpulaeae (vanriot) Kudo by Sun and co-workers in 2010, and given the name scalpulane N; see: X. Li, J.-X. Pu, Z.-Y. Weng, Y. Zhao, W.-L. Xiao, H.-D. Sun, Chem. Biotechnology 2010, 7, 2888 – 2896. Prior to this report, Liu and co-workers had given the name scalpulane N to a different compound isolated from Isodon scalpulaeae (vanriot) Haras. For: F. Wang, X.-M. Li, J.-K. Liu, Chem. Pharm. Bull. 2009, 57, 525 – 537; For simplicity, in this manuscript we refer to scalpulane N as structure 2, but suggest that a renaming of the scalpulane is take place in the future.


[12] Enolate 10 was formed as a 3:1 ratio of isomers that could be separated after conversion into the corresponding Weinreb amide. Both isomers could be carried forward to the Nazarov cyclization. See the Supporting Information for full details.


[16] Calculations (Avogadro MMFF94) indicated that the cis hydrindane 19 was approximately 6 kcal mol−1 more stable than the corresponding trans isomer and 1.7 kcal mol−1 more stable than spirocycle 18. A methyl ether was used in place of the TBDDS ether for these calculations.


[20] Some O-allylated product formed during this alkylation (16%). This material could be converted into ketone 17 in quantitative yield by a thermal Claisen rearrangement. See the Supporting Information for details.


[27] CCDC 970246 (26) and 970247 (27) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


[31] For examples, see: S. K. Leitch, P. S. Blake, L. N. Mander, ARKIVOC 2003, 145 – 160 and ref. [5h].

[32] We observed some retro-aldol products during the final deptection step that led to diminished yields of the desired diol.