Natural Product Synthesis

DOI: 10.1002/ange.201310060

Total Synthesis of the *Isodon* Diterpene Sculponeatin N**

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Dedicated to Professor Lewis N. Mander

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-*seco*-terpenes 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-*seco*-terpenes are derived from the parent *ent*-kaurene (**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 *ent*-kaurene (**1**).[6] In maoecrystal V (**3**), the

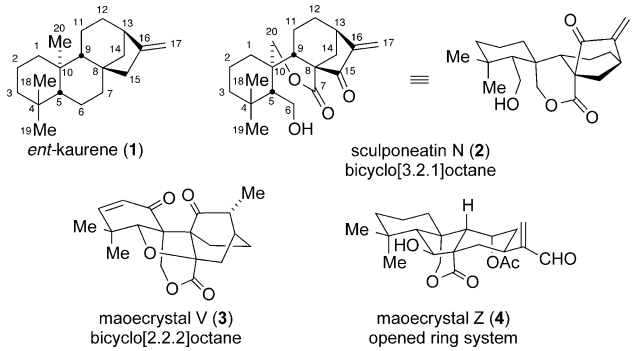

Figure 1. Selected *Isodon*-derived diterpenes.

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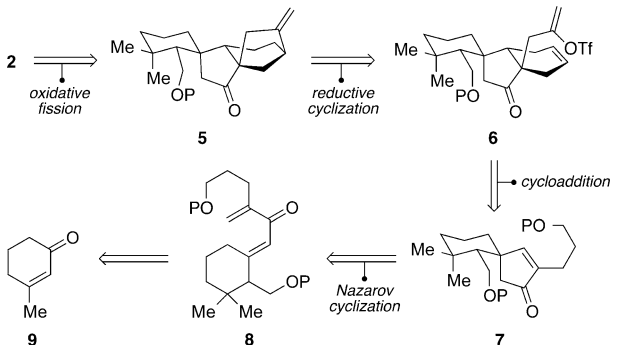
[**] We acknowledge support from Northwestern University and the American Cancer Society by way of an Illinois Division Research Scholar Award (RSG-12-253-01-CDD) to R.J.T. and an institutional grant (ACS-IRG 93-037-15) to the Robert H. Lurie Comprehensive Cancer Center at NU. We thank Reed Larson for assistance with X-ray crystallography.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201310060.



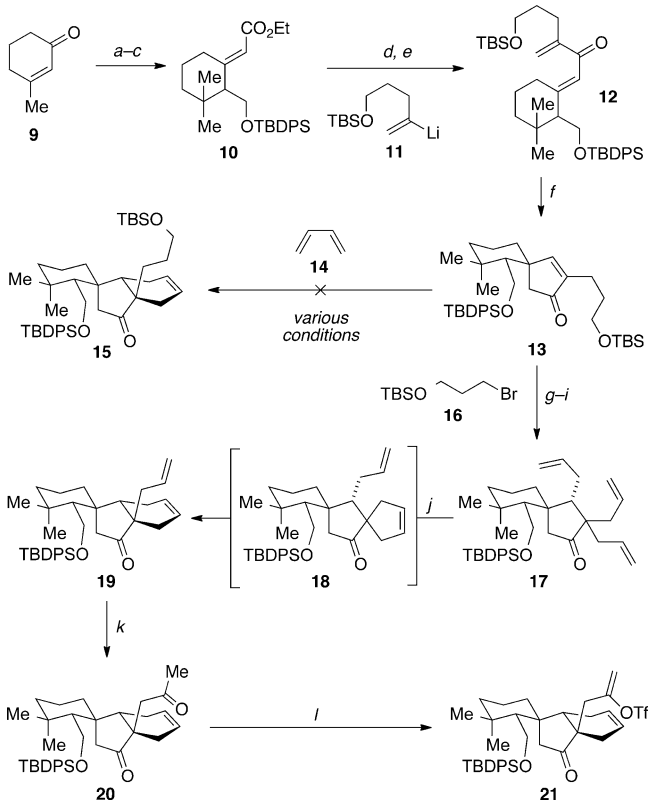
Scheme 1. Retrosynthetic analysis of sculponeatin N.

bicyclo[3.2.1]octane core has rearranged to a congested bicyclo[2.2.2]octane system,[7] 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.[8] 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-*seco*-terpenes by a stereoselective Nazarov cyclization and subsequent oxidative ring expansion of the thus formed cyclopentanone.[5h] Although our initial efforts were directed towards maoecrystal V (**3**), we also wished to apply these reactions to the synthesis of other 6,7-*seco*-terpenes 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 retron for the Diels–Alder reaction, and logically led to cyclopentenone **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 stereocontrol imparted by the protected C5 hydroxylmethyl 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-



Scheme 2. a) MeMgBr (1.2 equiv), CuI (5 mol%), LiCl (10 mol%); then CH_2O, 88%; b) TBDPSCl (1.1 equiv), Im (2.1 equiv), 98%); c) $TMSCH_2CO_2Et$ (2.0 equiv), LDA (2.0 equiv), 57% (87% brsm); d) Me(OMe)NH·HCl (2.0 equiv), *i*PrMgCl (4.0 equiv), 85%; e) **11** (1.2 equiv), 95%; f) 1) $AlCl_3$ (2.0 equiv); 2) TBSCl (1.1 equiv), Im (2.1 equiv), 80%; g) **16** (4.0 equiv), *t*BuLi (8.0 equiv), (2-thiophene)-Cu(CN)Li (4.0 equiv), $BF_3{\cdot}Et_2O$ (4.0 equiv), 78%; h) 1) 10% HF, acetonitrile; 2) the Grieco reagent (2.5 equiv), Bu_3P (3.0 equiv); then H_2O_2 (50 equiv), 71%; i) 1) TMSOTf (6.0 equiv), NEt_3 (8.0 equiv); 2) MeLi (1.2 equiv), allyl iodide (5.0 equiv) 57%; j) Grubbs II (5 mol%), 91%; k) $PdCl_2$ (25 mol%), CuCl (1.5 equiv), O_2; l) KHMDS (1.5 equiv), Comins reagent (4.0 equiv), 48% from **19**. TBDPS = *tert*-butyldiphenylsilyl, Im = imidazole, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, KHMDS = potassium hexamethylsilazide.

cyclohex-2-enone (**9**; Scheme 2).[10] Protection of the formed primary alcohol, followed by Peterson olefination[11] delivered enoate **10** in 49% yield over the three steps.[12] Generation of dienone **12** proceeded from ester **10** through its Weinreb amide,[13] which underwent smooth reaction with organolithium **11**. Despite extensive investigation of various reaction conditions, the Nazarov cyclization of dienone **12** was best achieved using $AlCl_3$, which also resulted in some cleavage of the TBS protecting group.[14] Nevertheless, cyclopentenone **13** could be generated as a single stereoisomer in 80% yield following reprotection. At this juncture, we were poised to investigate the reaction of **13** with butadiene (**14**) to construct the desired *cis* hydrindane **15**. Under a variety of thermal conditions, both with and without Lewis acid additives, no desired cycloadduct was detected; the starting material was recovered unchanged in most cases. Exploration of more reactive dienes, such as the Danishefsky diene or furan, was met with similarly disappointing results. The lack of reactivity is most probably a consequence of steric hindrance due to the spirocyclic quaternary center and the strain associated with forming an additional quaternary stereocenter in the developing transition state to the product. This lack of reactivity was further highlighted by several failed attempts to induce cycloaddition in a high-pressure reactor at 15 kbar.[15]

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**.[16] We hypothesized that the less strained *cis* hydrindane would be favored over the higher energy *trans* hydrindane.[17] 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[18] derived from halide **16**, which underwent 1,4-addition only in the presence of excess $BF_3{\cdot}Et_2O$ (78% yield). Removal of both TBS ethers followed by subsequent double Grieco elimination[19] and ketone allylation yielded tris(allyl) intermediate **17**.[20] As we had hoped, exposure of **17** to Grubbs II catalyst (5 mol%)[21] provided the desired *cis* hydrindane **19** in excellent yield (91%). We noted during the course of the reaction that **17** initially converted into two species, one that corresponded to product **19** and another that slowly converted into **19** as the reaction progressed. Premature termination of the reaction allowed us to confirm that this other species was spirocycle **18**, and that treatment of **18** with 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**,[22] which underwent selective triflation upon exposure to potassium hexamethyldisilazane (KHMDS) and the Comins reagent (48% yield, 2 steps).[23]

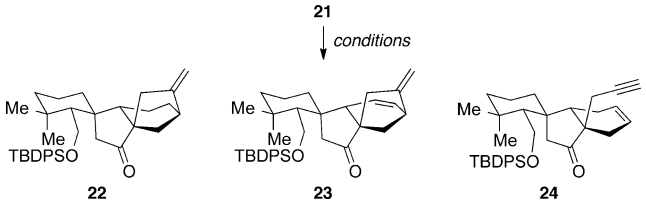
With a route to enol triflate **21** secured, we began investigating its transformation into the desired bicyclo-[3.2.1]octane species **22** (Table 1).

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).[24] Although synthetically useful ratios of **22**/**23** could be obtained, we noted a significant amount of alkyne **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 triflate group from **21** was most efficiently carried out using TBAF to provide an 87% yield of alkyne **24**. Using conditions originally reported by Stork and co-workers,[25] **24** was then smoothly converted into the desired bicyclo[3.2.1]octane system upon treatment with Bu_3SnH 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 $MoO_5{\cdot}Py{\cdot}HMPA$ under Vedejs conditions to provide what we

Table 1: Reaction development.[a]



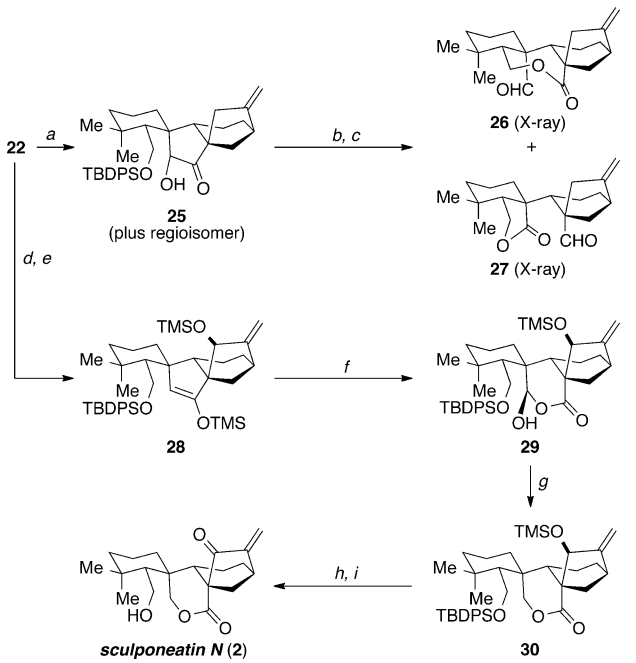
Entry	Reaction conditions	Product(s)	Yield
1	$Pd(PPh_3)_4$ (50 mol%), K_2CO_3, 4 Å MS, MeCN, RT	**23**	43
2	$Pd(OAc)_2$ (10 mol%), TBACl (3.0 equiv) HCO_2Na (2.5 equiv), 4 Å MS, DMF, RT	**22**:**23**:**24** (3:1:6)[b]	68[c]
3	1) TBAF (2.5 equiv), THF, RT 2) Bu_3SnH (4.0 equiv), AIBN (0.1 equiv), toluene, reflux; silica gel	**22**	71

[a] Yield of isolated product after silica gel chromatography. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Combined yield of mixture. AIBN = azobisisobutyronitrile, DMF = dimethyl formamide, MS = molecular sieves, TBACl = tetrabutylammonium chloride, TBAF = tetrabutylammonium fluoride.

initially thought was a 1:1 mixture of diastereomeric α-hydroxyketones (i.e., **25**).[26] Exposure of this mixture to aqueous H_5IO_6 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 isomeric lactones were produced (i.e., **26** and **27**), whose structures were confirmed by X-ray crystallographic analysis.[27] 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.[28] 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 alkene, we first conducted an allylic oxidation of **22** using SeO_2/*t*BuOOH,[29] 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.[30] 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 $NaBH_4$ for the reductive workup instead of dimethylsulfide produced only lactol **29**. In sharp contrast to seemingly related examples in the literature,[31] conversion of **29** into lactone **30** proved significantly difficult. Ultimately, we found that exposure of **29** to a solution of $LiBH_4$ 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 MnO_2 (36%, 2 steps).[32] The synthetic sculponeatin N (**2**) thus obtained displayed identical spectral properties (^{1}H NMR, ^{13}C NMR) to those reported in the literature for the natural product.[6]

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 diastereocontrol, 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.



Scheme 3. a) 1) TMSOTf (15 equiv), NEt_3 (20 equiv); 2) MeLi (3.0 equiv) MoO_5·Py·HMPA (5.0 equiv), 67%; b) TBAF (10 equiv), 80%; c) H_5IO_6 (3.0 equiv), 42% (**26**), 29% (**27**); d) SeO_2 (2.0 equiv), *t*BuOOH (1.2 equiv); e) TMSOTf (15 equiv), NEt_3 (20 equiv); f) O_3, Py, methanol, chloroform 49% over 3 steps from **22**; g) $LiBH_4$ (5.0 equiv), 50 °C, 47%; h) TBAF (5.0 equiv), 38%; i) MnO_2 (5 equiv by mass), 95%. HMPA = hexamethylphosphoric triamide, LDA = lithium diisopropylamide, Py = pyridine, TBAF = tetrabutylammonium fluoride, TMSOTf = trimethylsilyl triflate.

Received: November 20, 2013
Published online: February 12, 2014

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

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