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Total Syntheses of Scaparvins B, C, and D Enabled by a Key C−H Functionalization

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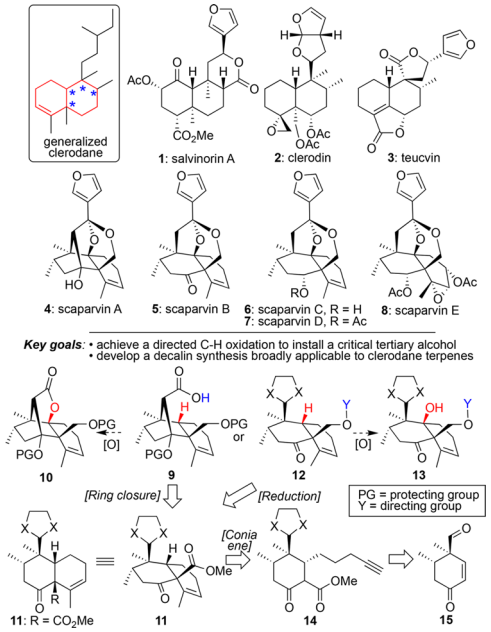
Supporting Information

ABSTRACT: The clerodane diterpene family possesses an impressive range of bioactivities and high synthetic challenge due to their unique amalgamation of rings, stereocenters, and oxygenation. Herein, we disclose the first total syntheses of three members, scaparvins B, C, and D, through a route fueled by several chemoselective and carefully orchestrated steps. One such operation is a tailored late-stage C−H functionalization converting a carboxylic acid into a lactone through the oxidation of a tertiary C−H bond under conditions that minimize epoxidation of an alkene. This step, among others, afforded critical functionality to complete the targets. In addition, use of an appropriate chiral catalyst with a Rawal diene renders the sequence enantioselective.

Over the past half century, over 1000 clerodane diterpenoids have been isolated from various sources and shown to possess a range of bioactivities, including antifeedant, antitumor, antifungal, and antibiotic properties.[1] As indicated by the framework in Scheme 1, they are unified structurally by the presence of four contiguous stereogenic centers, two of which are quaternary, on a decalin skeleton. Salvinorin A,[2] clerodin,[3] and teucvin[4] (**1**−**3**) are representative, with differing degrees of oxidation and exocyclic connectivities, as well as the *cis*- or *trans*-fusion of their decalin cores, distinguishing them; some of these drawn targets,[5,6] among others,[1f,7] have been synthesized.

As part of programs interested in strategies for the synthesis of unique terpenes,[8] coupled with a desire to identify family level solutions,[9] we were drawn to the unique connectivities of the scaparvins (**4**−**8**).[10] These molecules were isolated from the epilithic liverwort *Scapania parva* Steph. and were assigned through a combination of NMR, CD, and HRMS techniques. The lead structure, scaparvin A (**4**) possesses a distinct cage, including an intramolecular ketal, along with seven contiguous stereocenters; its cousins (**5**−**8**) have similar elements, minus one bridging C−C bond. Arguably, their greatest synthetic challenge resides in the three proximal oxygenated carbons in the core, functionality that could render selective functional group manipulation difficult within such a congested space. As detailed herein, we developed the means to access these frameworks through a number of chemoselective operations, including a tailored late-stage C−H oxidation;[11] these efforts afforded scaparvins B, C, and D (**5**−**7**) and access to most of the carbogenic framework of scaparvin A (**4**). The means to render the sequence asymmetric is also defined.

Scheme 1. Structures of Several Members of the Clerodane Family of Natural Products and an Approach To Access the Scaparvins through a Directed C−H Functionalization



Our general retrosynthetic plan (bottom half of Scheme 1) was predicated on utilizing a C−H functionalization[12] to install a tertiary alcohol late in the sequence; that decision was based on the idea other oxygen groups, either in the form of a carboxylic acid or an alcohol derivative (i.e., **9** or **12**), might serve to direct such a process and thus overcome the challenges inherent in manipulating multiple functional groups in proximity. In turn, **9** and **12** were envisaged to be accessible from *cis*-decalin **11**, either through an appropriate ring-closure event or reduction, respectively. We then anticipated that **11** might arise via a Conia ene cyclization[13] of alkyne **14**, assuming that an appropriate promoter could be found to effect the key C−C bond forming reaction as well as isomerization of the resultant exocyclic alkene into the endocyclic, trisubstituted olefin of **11**; of

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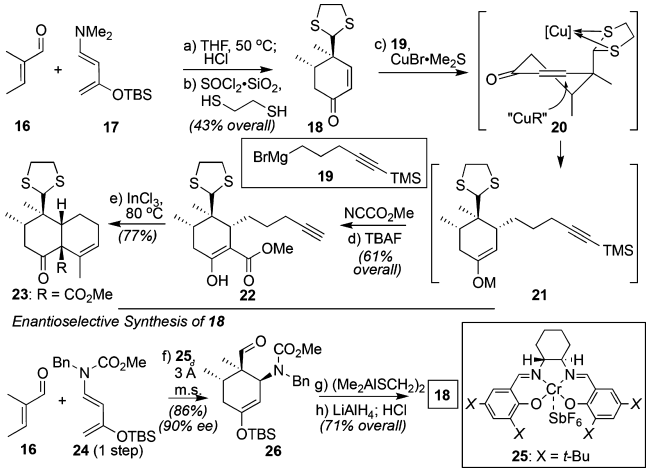
relevance, the Lee group had also used a Conia ene reaction as part of their synthesis of (−)-teucvidin,[14] though not to generate this final alkene patterning. Finally, intermediate **14** was anticipated as arising from a vicinal difunctionalization of enone **15**, a compound we hoped could be prepared in enantioenriched form, with the resident chirality directing the incorporation of all the remaining stereocenters.

Our explorations began as shown in Scheme 2 by probing the Conia ene sequence envisioned to access a *cis*-decalin of type **11** (cf. Scheme 1) as a racemate. As indicated, a Diels−Alder reaction between tiglic aldehyde (**16**) and Rawal diene **17**[15,16] in THF at 50 °C for 16 h, followed by treatment with aq. HCl, smoothly afforded the desired enone. Subsequent dithiolane protection of the pendant aldehyde then completed the synthesis of **18** in 54% yield overall, with the use of $SOCl_2{\cdot}SiO_2$[17] being critical in preventing competitive thia-Michael addition of 1,2-ethanedithiol to the enone. While alternate modes of aldehyde protection could have been envisioned, based on precedent from Ley,[18] such protection was essential to the stereocontrolled introduction of the cuprate reagent derived from Grignard **19**[19] in the following step, where copper coordination with the dithiolane is postulated to generate sufficient steric blocking to enforce addition from the desired α-face to deliver **21**; with a standard oxygen-containing acetal, the other diastereomer was predominant (~5:1 d.r., commensurate yield). Trapping of this intermediate with methylcyanoformate, followed by filtration through Celite and *in situ* treatment with TBAF, then completed a stereocontrolled synthesis of **22** in 61% yield, setting the stage for the planned Conia ene cyclization to complete the *cis*-decalin framework. Although that key process failed under the action of a number of Au promoters,[20] it could be affected using a full equivalent of $InCl_3$ in refluxing 1,2-dichloroethane, with the desired alkene isomerization occurring *in situ* to deliver **23** in 77% yield. Overall, this five-step sequence proved readily scalable, with over 10 g of **23** generated to date.

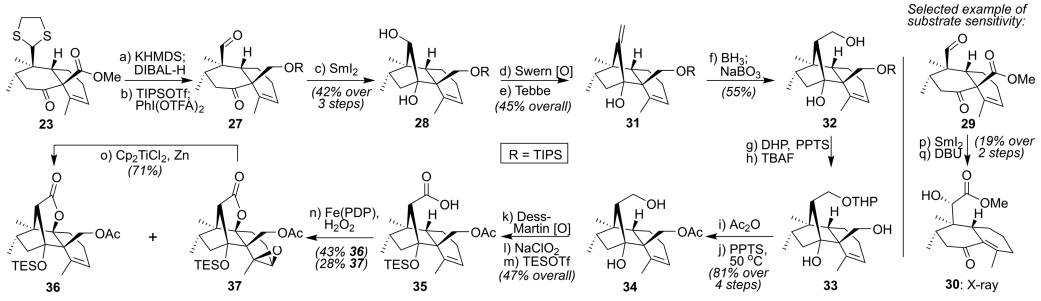
Though this material was used to evaluate the remaining sequence toward the scaparvins, an enantioenriched preparation of **18** could also be achieved. Although Hsung, Cole, and co-workers already documented[16] tiglic aldehyde (**16**) could merge with **24** with high enantiocontrol using Cr(III)-salen promoters of type **25**[21] possessing a BF_4 counterion, we found good selectivity (90% e.e.) and material throughput could result using 5 mol % of **25** with an SbF_6 counterion[15b,c] in the presence of 3 Å molecular sieves in CH_2Cl_2.[22] This process, when conducted at 23 °C for 2 d, afforded **26** in 86% yield on near decagram scale. The synthesis of **18** was then completed in two steps, where the most challenging was dithiolane protection of the aldehyde in the presence of the readily hydrolyzed silyl enol ether, a reaction that proved necessary prior to carbamate manipulation. Pleasingly,

Scheme 2. Synthesis of Key Building Block 23 as a Racemate and an Enantioselective Preparation of 18[a]



[a]Reagents and conditions: (a) **17** (1.2 equiv), THF, 50 °C, 16 h; aq. HCl, 23 °C, 5 h, 74%; (b) $SOCl_2{\cdot}SiO_2$ (0.78 equiv), 1,2-ethanedithiol (1.0 equiv), benzene, 0 → 23 °C, 16 h, 73%; (c) **19** (2.5 equiv), CuBr·Me_2S (1.2 equiv), Et_2O, −78 → −60 °C, 1 h; **18**, −78 → 23 °C, 10 h; $NCCO_2Me$ (3.0 equiv), HMPA, −78 → 23 °C, 16 h; (d) TBAF (3.6 equiv), MeOH, 23 °C, 10 h, 61% over two steps; (e) $InCl_3$ (1 equiv), 1,2-dichloroethane, 80 °C, 16 h, 77%; (f) **24** (1.5 equiv), **25** (5 mol %), 3 Å m.s., CH_2Cl_2, 10 → 23 °C, 2 d, 86%, 90% e.e. (determined once converted to **18**); (g) $Me_2AlSCH_2CH_2SAlMe_2$ (3.0 equiv), 1,2-dichloroethane, 60 °C, 6 h; (h) $LiAlH_4$ (1.0 equiv), THF, 0 °C, 3 h; aq. HCl, 23 °C, 5 h, 71% over two steps. For abbreviations, see SI.

Scheme 3. A Directed C−H Functionalization to Fashion the Core Architecture of the Scaparvin Family of Natural Products[a]



[a]Reagents and conditions: (a) KHMDS (2.0 equiv), THF, −78 → 0 °C, 30 min; DIBAL-H (3.2 equiv), 0 → 23 °C, 12 h; (b) 2,6-lutidine (4.0 equiv), TIPSOTf (2.0 equiv), CH_2Cl_2, 0 → 23 °C, 3 h; $PhI(OTFA)_2$ (2.2 equiv), MeOH, 23 °C, 4 h; aq. HCl, 23 °C, 10 h; (c) SmI_2 (2.5 equiv), THF, 0 → 23 °C, 2 h, 42% over three steps; (d) oxalyl chloride (1.5 equiv), DMSO (5.0 equiv), CH_2Cl_2, −78 °C, 30 min; **28**, −78 °C, 1 h; Et_3N (10 equiv), −78 → 23 °C, 2 h, 94%; (e) pyridine (10 equiv), Tebbe reagent (5.0 equiv), THF, 0 → 50 °C, 24 h, 48%; (f) BH_3·THF (2.5 equiv), THF, 0 → 35 °C, 1.5 h; $NaBO_3{\cdot}H_2O$ (2.0 equiv), H_2O, 23 °C, 6 h, 55%; (g) DHP (10 equiv), PPTS (0.1 equiv), CH_2Cl_2, 23 °C, 1 h; (h) TBAF (1.2 equiv), THF, 0 → 23 °C, 6 h; (i) DMAP (2.0 equiv), Ac_2O (1.5 equiv), CH_2Cl_2, 23 °C, 2 h; (j) PPTS (0.2 equiv), EtOH, 50 °C, 4 h ; (k) DMP (1.2 equiv), CH_2Cl_2, 23 °C, 30 min; (l) $NaClO_2$ (30 equiv), $NaH_2PO_4{\cdot}2H_2O$ (20 equiv), *t*-BuOH, 2-methyl-2-butene, H_2O, 0 → 23 °C, 9 h, 66% over two steps; (m) 2,6-lutidine (3.0 equiv), TESOTf (2.0 equiv), CH_2Cl_2, 0 → 23 °C, 6 h; AcOH, MeOH, 23 °C, 2 h, 76%; (n) Fe(PDP) (2 mol %), H_2O_2 (1.2 equiv), CH_3CN, 10 °C, 45 min, 43% for **36**, 28% for **37**; (j) Zn (10 equiv), Cp_2TiCl_2 (3.0 equiv), THF, 10 °C, 15 min, 71%; (p) SmI_2 (5.0 equiv), THF, 0 → 23 °C, 4 h; aq. Rochelle's salt, aq. K_2CO_3, 23 °C, 1.5 h; (q) DBU, DCE, 23 °C, 18 h, 19% over two steps. For abbreviations, see SI.

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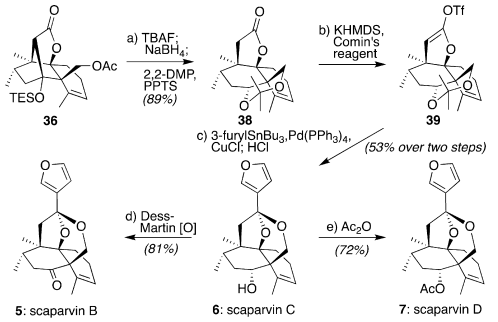
the reagent formed by combining 1,2-ethanedithiol with 2 equiv of Me_3Al as developed by Corey was uniquely successful.[23] Of note, enantioenriched **18** could be recrystallized from Et_2O/hexanes to afford material with >98% e.e.; the absolute configuration drawn is by analogy to prior studies.[15b]

With the decalin framework established, we attempted various C−H functionalizations to complete the oxygenated core of the targets. Initial efforts attempted to utilize various primary alcohol derivatives of type **12**, formed by selectively reducing the ester within redrawn **23** (Scheme 3) by ketone enolization and subsequent treatment with DIBAL-H. However, despite numerous attempts using Hofmann−Löffler−Freytag-type radical methods,[24] success was never realized. Rationalizing that these results might reflect too much conformational flexibility within **23** and its reduced variants, we sought next to constrain the system further by forging the bridging C−C bond found in the core of scaparvin A to test intermediates of type **9**.

As shown in Scheme 3, that bridge was generated from aldehyde **27** [formed following silyl protection of the primary alcohol derived from **23** and *in situ* dithiolane cleavage as effected by $PhI(OTFA)_2$] through a SmI_2-promoted pinacol coupling.[25] Critical to its success was the initial reduction of the ester within **23**, as its presence in compounds such as **29** led to alternate cyclizations/fragmentations, such as the formation of decalin **30**. From here, Swern oxidation[26] of the bridgehead secondary alcohol followed by treatment with the Tebbe reagent[27] afforded **32** in 45% overall yield.[28] Subsequent hydroboration/oxidation afforded alcohol **32** with complete stereocontrol in 55% yield; the bulky TIPS protecting group was crucial for the regio- and facial-selectivity of this step, as substrates with smaller protecting groups (including a TBS group) typically afforded complex product mixtures. Unfortunately, that TIPS group was too large for effective C−H functionalization once **32** was converted into its carboxylic acid congener (structure not shown). Following extensive explorations, we found the ideal array of protected groups was that expressed in **35**, formed from **32** in 7 standard synthetic operations. Although lengthy, this sequence could deliver **35** in good overall yield, noting several of its steps did not require chromatographic separations; either crude material or compound quickly filtered through silica gel was sufficient.[29,30]

With this material in hand, we were pleased to find initial scouting of the conditions developed by the White group[31] by adding 15 mol % of racemic Fe(PDP) and 3 equiv of H_2O_2 in 3 equal portions to a solution of **35** in MeCN over 45 min gave **37** in ∼30% yield wherein both the desired C−H oxidation[32] as well as epoxidation of the trisubstituted double bond had occurred; trace amounts of **36** were observed. While that unwanted epoxidation could be erased through subsequent treatment of **37** with Cp_2TiCl_2 and Zn[33] to afford lactone **36** in 71% yield, more useful would be a chemoselective C−H oxidation to selectively deliver **36** in one step, not only for this substrate but for others where reactive olefins might also be present. Ultimately, such optimization proved possible, both by lowering the equivalents of each of the two main reagents [2 mol % of Fe(PDP) and 1.2 equiv of H_2O_2],[34] as well as affecting slow addition of these components to substrate **35** over 45 min (rather than in 3 batches)[35] in an effort to minimize the amount of free catalyst available to effect epoxidation. Though we could not fully eliminate formation of **37**, we obtained **36** as the predominant product in 43% yield along with a 28% yield of **37**, which, as indicated, could be separately converted into **36**. Of note, efforts to use other catalytic systems that have been used to oxidize tertiary C−H bonds as directed by acids,[11] such as $Cu(OAc)_2$/H_2O_2 and (*R*)-Fe[(mepp)$(MeCN)_2$][SbF_6]$_2$ with H_2O_2 or *t*-BuOOH, led only to recovered starting material.[36]

Scheme 4. Completion of Scaparvins B, C, and D[a]



[a]Reagents and conditions: (a) TBAF (1.5 equiv), THF, 0 °C, 1 h; $NaBH_4$ (5.0 equiv), MeOH, 0 to 23 °C, 11 h; *p*-TsOH·H_2O (20 equiv), 2,2-dimethoxypropane, 23 °C, 2 h, 89%; (b) KHMDS (3.0 equiv), Comins' reagent (4.0 equiv), THF, 1 h; (c) tributyl(furan-3-yl)stannane (1.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuCl (2.0 equiv), K_2CO_3 (2.0 equiv), THF, 23 °C, 2 h; HCl, MeOH, 23 °C, 10 h, 53% over two steps; (d) Dess-Martin periodinane (2.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 0 °C, 1 h, 81%; (e) 4-DMAP (5.0 equiv), Ac_2O (3.0 equiv), THF, 0 °C, 1 h, 72%.

With the critical oxygenation pattern of the core installed, the main challenge remaining was installation of the furan unit. Extensive efforts to add 3-furyllithium[37] under various conditions to lactone **36** (Scheme 4), as well as to the less constrained lactone **38** generated following TBAF-mediated retro-aldol C−C bond cleavage, stereoselective ketone reduction, and diol protection, consistently afforded no conversion at low temperature (<−20 °C) and occasionally the formation of several uncharacterizable byproducts at higher temperature (>23 °C), with or without Lewis acid promoters in various solvents. In contrast, once we formed vinyl triflate **39** from **38** through the action of KHMDS and Comins' reagent,[38] a smooth coupling with 3-furylSnBu$_3$ in the presence of $Pd(PPh_3)_4$ and CuCl could be achieved, with HCl workup cleaving the acetonide and promoting ketal formation to deliver scaparvin C (**6**) in 53% yield from **38**. Its spectral properties fully matched the natural isolate.[10] In turn, we converted this material into scaparvins B and D (**5** and **7**) through oxidation and acetylation of its alcohol, respectively. In total, 22 operations were needed to access scaparvin C (**6**) as a racemate from commercial Rawal diene **17**; 24 steps would afford a formal asymmetric synthesis.

In conclusion, we have accomplished the first total syntheses of scaparvins B, C, and D. The overall route required several carefully orchestrated steps and specific protecting group arrays to accomplish key operations within such a constrained framework, with a critical discovery being an optimized protocol to effect a C−H functionalization using the White−Chen system[31] that preferentially oxidized a tertiary C−H bond over a trisubstituted alkene. We postulate that this, as well as several other operations, will be of further synthetic value.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06185.

Detailed experimental procedures, copies of all spectral data (PDF)

cif file for compound **30** (CIF)

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Notes

The authors declare no competing financial interest.

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(28) Use of Wittig reagents led to slow decomposition.

(29) A three-step alternative to convert **31** into **34** was also developed, but was not always consistent; thus, the longer route is defined here.

(30) Tertiary alcohol protected was required to prevent retro-aldol opening of the key C−C bridge needed to rigidify the framework.

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(32) For a review of Fe-catalyzed C−H oxidation reactions, see: Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

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(34) Substoichiometric H_2O_2 (0.8 equiv) led to minimal conversion. A few test experiments on very small scale (2−3 mg) have shown that *t*-BuOOH could also be used as the oxidant, with excess quantity (6.0 equiv) not affording significant epoxide formation; an effort at scale-up under these conditions, however, afforded a low yield of **36**.

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(36) Only one enantiomer of the mepp ligand is available through chemical synthesis; as our material was racemic, throughput might be reduced because of matched/mismatched chirality.

(37) For the use of this nucleophile for a clerodane, see: Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 757.

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