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A Unified Approach to the Daucane and Sphenolobane Bicyclo[5.3.0]decane Core: Enantioselective Total Syntheses of Daucene, Daucenal, Epoxydaucenal B, and 14-*para*-Anisoyloxydauc-4,8-diene

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Abstract: Access to the bicyclo[5.3.0]decane core found in the daucane and sphenolobane terpenoids via a key enone intermediate enables the enantioselective total syntheses of daucene, daucenal, epoxydaucenal B, and 14-*para*-anisoyloxydauc-4,8-diene. Central aspects include a catalytic asymmetric alkylation followed by a ring contraction and ring-closing metathesis to generate the five- and seven-membered rings, respectively.

Keywords: allylic alkylation · asymmetric catalysis · natural products · terpenoids · total synthesis

Introduction

The daucane (carotane) sesquiterpenes[1] and sphenolobane (tormesane) diterpenes are two structurally related families of natural products that share a bicyclo[5.3.0]decane core (Figure 1 A). These terpenoids feature varied degrees of oxidation with diverse peripheral functionality and, as a group, exhibit a wide range of biological activities (Figure 1 B).[2] As such, the synthetic community has reported several studies[3] and total syntheses[2i,4] of a number of these natural products. Central to our interest in these molecules is the cyclopentane motif, which we envisioned accessing from a γ-quaternary acylcyclopentene (**1**) generated by a combination of the palladium-catalyzed asymmetric enolate alkylation[5,6,7] and ring-contraction chemistry that we originally reported in 2011 (Figure 1 A).[8] As part of our ongoing efforts to apply this methodology,[9] we have developed a route to the sesquiterpene and diterpene bicycles, explored functionalization of the hydroazulene skeleton to form oxidized compounds including epoxydaucenal B (**3b**), and completed the first total syntheses of 14-*para*-anisoyloxydauc-4,8-diene (**5**) and daucenal (**4**) via the archetypal daucane (**2**).

Our initial target, 14-*para*-anisoyloxydauc-4,8-diene (**5**), was first isolated by Miski et al.[10] in 1986 from the roots of *Ferula tingitana*. Viola and co-workers[2a] later isolated ester **5** from *Ferula communis* and found that this molecule displays antiproliferative activity against HL-60, Jurkat, K562, RS 4;11, and SEM human tumor cells with IC_{50} values comparable or superior to many of the more oxygenated and complex daucane sesquiterpenes screened. Interestingly, the related 14-(4′-hydroxybenzoyloxy)dauc-4,8-diene (**6**), which was isolated from *Ferula hermonis*, displays antibacterial and antifungal activity.[2b] Despite the earliest isolation occurring over twenty-five years ago and this bioactivity, to our knowledge, no total syntheses have been reported for any of these C(14)-oxidized sesquiterpenes.

Results and Discussion

Retrosynthetically, we envisioned preparing 14-*para*-anisoyloxydauc-4,8-diene (**5**) through an allylic oxidation at the C(14) position of daucene (**2**, Scheme 1). This bicyclic natural product, one of the structurally simplest of the daucane sesquiterpenes, has been isolated from several sources[11] and may be the biosynthetic precursor to more functionalized derivatives.[11a,12] Several groups have completed total syntheses of daucene;[12,13] however, they have either generated the racemic product or relied on enantioenriched, naturally occurring starting materials. In contrast, we sought to access daucene by implementation of enantioselective catalysis.

Toward daucene, we planned a late-stage installation of the C(13) methyl group through olefination and hydrogenation of enone **11** (Scheme 1). This key intermediate possesses the [7–5] bicyclic core and could potentially allow entry to either terpenoid series through incorporation of the appropriate sesquiterpene or diterpene chain at the C(11) position. We also anticipated that enone **11** may be converted to more oxidized members of the daucane family. Retrosynthetically, the cycloheptenyl portion of enone **11** would be formed through ring-closing metathesis of acylcyclopentene **1a**, which could be generated by employing our retro-aldol/aldol ring-contraction sequence[8] after Grignard addition to

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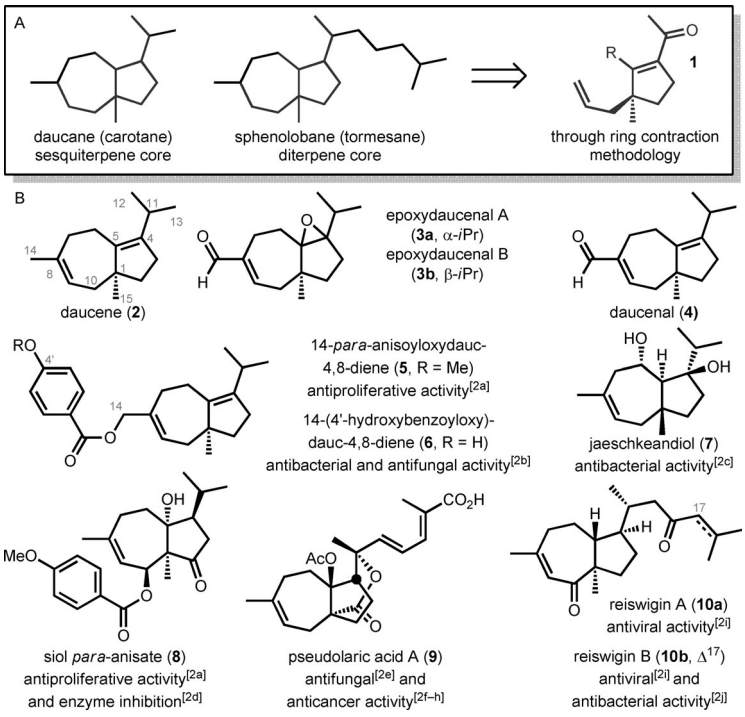
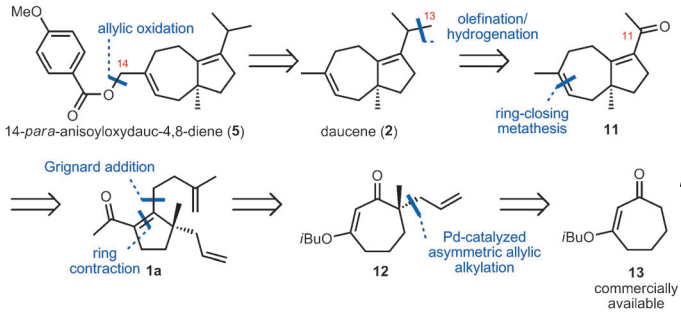


Figure 1. a) Daucane and sphenolobane carbon skeletons related to acylcyclopentene **1** and b) daucene (**2**), epoxydaucenals A and B (**3a** and **b**), daucenal (**4**), and several bioactive [7–5] bicyclic terpenoids.

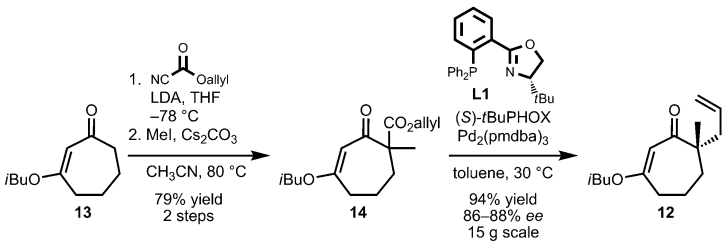


Scheme 1. Retrosynthetic analysis.

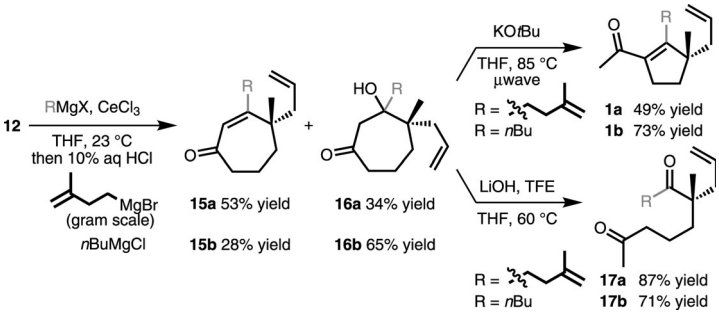
vinylogous ester **12**. We have previously reported the enantioselective preparation of vinylogous ester **12**[8a] from commercially available vinylogous ester **13** by using our palladium-catalyzed alkylation methodology (Scheme 2).[5]

As we pursued this route, we encountered two challenges. First, addition of (3-methylbut-3-en-1-yl)magnesium bromide to vinylogous ester **12** results in poor selectivity for the desired β-hydroxyketone (**16a**), favoring formation of cycloheptenone **15a** (Scheme 3). This product distribution contrasts with our prior work with *n*-butylmagnesium chloride,[8] and ultimately limits our synthetic route by directing considerable material to a less productive compound (see below). Second, our previously optimized microwave-assisted ring-contraction conditions generate acylcyclopentene **1a** in a diminished yield compared to the *n*-butyl analogue (**1b**). Alternatively, treatment of β-hydroxyketone **16a** with lithium hydroxide and TFE provides an excellent yield of acyclic dione **17a**, from which we envisioned installing the necessary cyclopentene ring in a later aldol reaction (see below). With an acceptable solution for the second issue, we turned our attention to resolving the first.

A series of workup parameters were screened in attempts to alter the Grignard addition product ratio, but unfortunately all of the acidic quenching conditions investigated formed the cycloheptenone in significant quantities.[14] As varying the workup parameters appeared ineffective at resolving this issue, we decided to redesign our electrophile and began examining alternative vinylogous systems. Previous research indicated that a sodium phosphate buffer quench transiently provides enol ether **18b** en route to cycloheptenone **15b** (Scheme 4).[15] We hypothesized that a more labile vinylogous group in a related system could be orthogonally removed after Grignard addition to afford β-hydroxyketone **16a** preferentially. Kuwajima and co-workers have reported that the addition of lithium and cerium nucleophiles to five- and six-membered ring siloxyenones temporarily generates an α-hydroxy silyl enol ether that eliminates to form β-substituted enones upon exposure to silica gel.[16] We envisioned that this silyl enol ether (**20**) could be

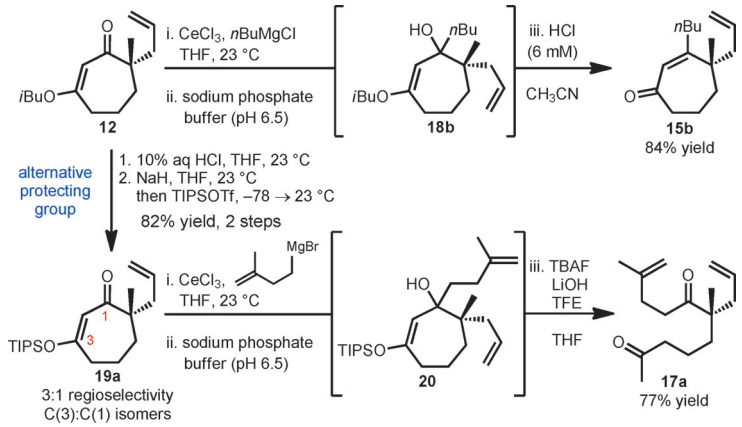


Scheme 2. Synthesis of vinylogous ester **12** (LDA = lithium diisopropylamide, PHOX = phosphinooxazoline, pmdba = *para*-methoxydibenzylideneacetone).

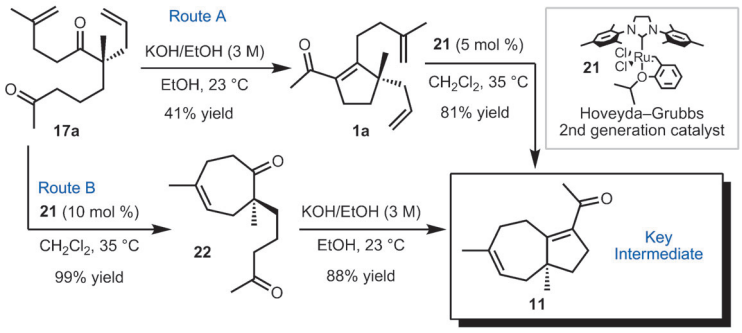


Scheme 3. Challenges with the early steps (TFE = trifluoroethanol).

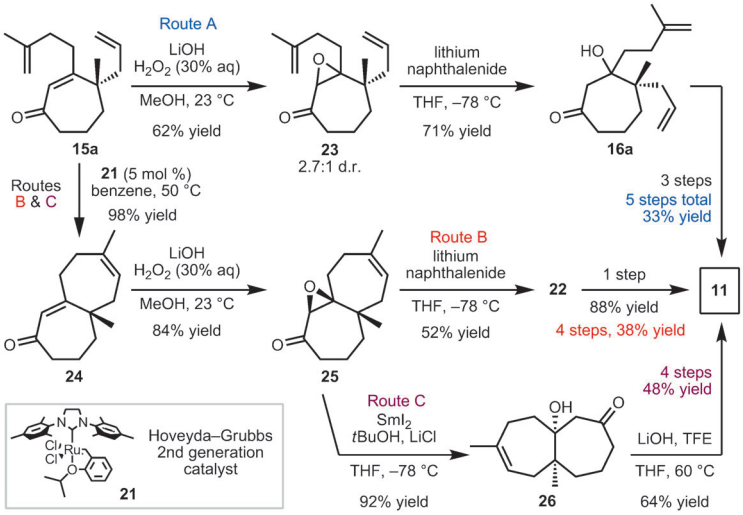
cleaved prior to chromatography with a fluoride source, prompting us to pursue siloxyenones as an alternative approach.



Scheme 4. Siloxyenone inspiration, preparation, and Grignard addition results (TIPS = triisopropylsilyl, TBAF = tetra-*n*-butylammonium fluoride).



Scheme 5. Two paths to [7–5] enone **11**.



Scheme 6. Routes to reincorporate cycloheptenone **15a** into our synthetic efforts.

Toward this motif, vinylogous ester **12** was hydrolyzed and the resulting dione was treated with sodium hydride and triisopropylsilyl triflate[17] to produce siloxyenone **19a** in good yield with 3:1 regioselectivity (Scheme 4).[18] To test our hypothesis, siloxyenone **19a** was exposed to conditions for a Grignard reaction with a buffer and fluoride quench. We were pleased to find that no cycloheptenone **15a** is observed and the reaction also incorporates the ring-opening step by directly producing acyclic dione **17a**.[19] This new approach resolves the issues with the selectivity of the Grignard addition and provides the first example of interrupting the standard Stork–Danheiser ketone-transposition process by use of a siloxyenone.

With dione **17a** in hand, we pursued preparation of our key intermediate, enone **11** (Scheme 5). Although this molecule can be synthesized from dione **17a** via acylcyclopentene **1a** (route A), the sequence proceeds in higher yield when the ring-closing metathesis is performed first (route B). Racemic dione **22** has previously been prepared from nerolidol by Urones and co-workers by several synthetic routes in 7–10 steps (5–33% overall yield).[20] By comparison, our route proceeding through enantioselective catalysis affords dione **22** in 7 steps and 40% overall yield. Applying Urones' potassium hydroxide aldol conditions generates enone **11** from dione **22** as reported.[20]

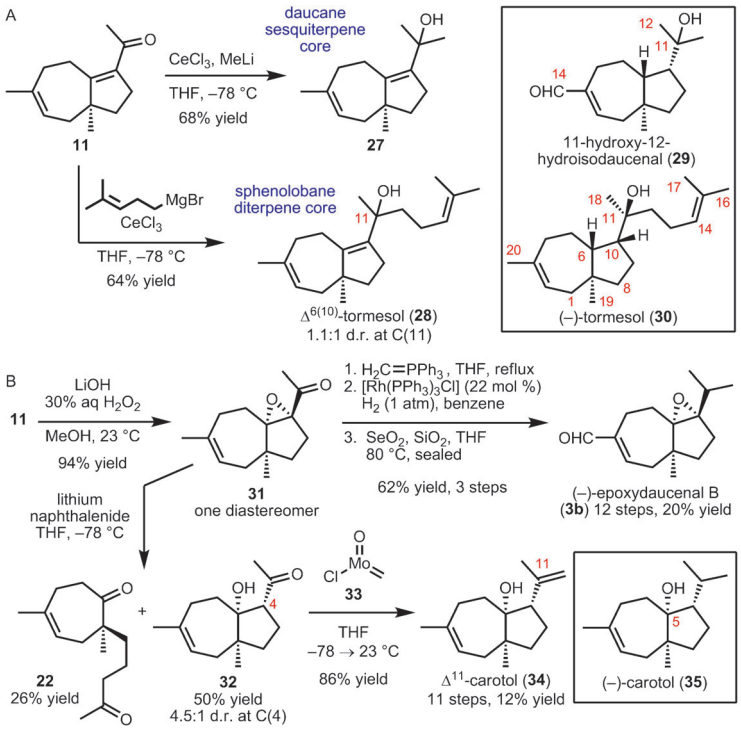
As our early research on the addition of (3-methylbut-3-en-1-yl)magnesium bromide to vinylogous ester **12** had generated a significant quantity of cycloheptenone **15a** (Scheme 3), we also investigated means to direct this material to enone **11**. To this end, oxidation of cycloheptenone **15a** with lithium hydroxide and hydrogen peroxide generates epoxide **23** as an inconsequential 2.7:1 mixture of diastereomers (route A, Scheme 6). Subsequent lithium naphthalenide reduction affords β-hydroxyketone **16a**, which may be converted into enone **11** in 3 steps, as discussed previously. Unfortunately, the epoxidation step proceeds moderately, prompting us to examine alternative routes.

We consequently pursued two other approaches through bicyclic enone **24** (routes B and C), which can be formed from cycloheptenone **15a** through a nearly quantitative ring-closing metathesis.[15] Gratifyingly, oxidation of enone **24** under the same hydrogen peroxide conditions as used in route A furnishes epoxide **25** in 84% yield. Interestingly, reduction of epoxide **25** with lithium naphthalenide also promotes an in situ retro-aldol reaction that produces dione **22**, albeit in low yield (route B). Dione **22** may be converted to enone **11** following the Urones precedent (see above). Alternatively, reduction of epoxide **25** under milder samarium diiodide conditions with lithium chloride as an additive gives β-hydroxyketone **26** in 92% yield.[21] Use of our standard ring-contraction parameters (LiOH, TFE, THF, 65 °C) initiates both retro-aldol fragmentation of β-hydroxyketone **26** and the ensuing aldol condensation to form enone **11**. Overall, route C provides enone **11** from cycloheptenone **15a** in the shortest sequence with the greatest overall yield.[22]

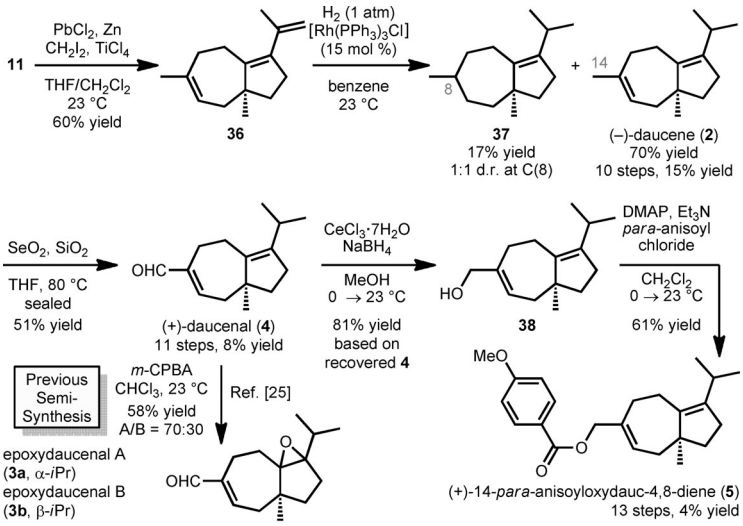
Having developed several routes to our key intermediate, we converted enone **11** into both terpenoid scaffolds and other oxygenated daucane molecules. Treatment of enone **11** with methyllithium or (4-methylpent-3-en-1-yl)magnesium bromide results in the formation of alcohols **27** and **28**, which contain the daucane and sphenolobane carbocyclic cores, respectively (Scheme 7A). This C(10) tertiary alcohol motif is present in natural products in both the daucane[23] and sphenolobane series, and alcohol **28** is the $\Delta^{6(10)}$-analogue of the natural product (−)-tormesol (**30**).[24] Enone **11** can also be selectively epoxidized with lithium hydroxide and hydrogen peroxide to provide epoxyketone **31** in excellent yield as a single diastereomer (Scheme 7B). Several daucane sesquiterpenes incorporate an epoxide at this position, and of these, we decided to pursue the synthesis of epoxydaucenal B (**3b**), which was isolated in 1991 by Hashidoko from the leaves of *Rosa rugosa*.[23] Toward this target, Wittig olefination of epoxyketone **31** furnishes a diene that can be selectively hydrogenated at the terminal alkene with the Wilkinson catalyst. The resulting isopropyl-accessorized epoxide was heated in a sealed vessel with selenium dioxide[25] to generate epoxydaucenal B (**3b**) in twelve steps and 20% overall yield from vinylogous ester **13** (the longest linear sequence).[26]

Having completed this natural product, we turned our attention to the carotol series, which contains a tertiary alcohol at C(5) (Scheme 7B). We first explored samarium diiodide reduction of ketoepoxide **31** based on the previous success with epoxide **25** (Scheme 6), but surprisingly isolated enone **11** in 96% yield. The preference for elimination in the cyclopentyl, but not the cycloheptyl system corresponds with the unique reactivity of seven-membered-ring compounds that we have observed in many other cases.[8,15] Alternatively, lithium naphthalenide reduction opens ketoepoxide **31** to furnish tertiary alcohol **32** in 50% yield, favoring the desired C(4) isomer in 4.5:1 diastereoselectivity.[27] When considering olefination conditions for the installation of the C(13) carbon atom,[28] we were drawn to the work of Kauffmann and co-workers,[29] who observed that methylene(oxo)molybdenum(V) chloride (**33**)[30] preferentially methylenates α- and β-hydroxyketones.[29c] Surprisingly, only the reports by Kauffmann and co-workers on this molybdenum alkylidene exist and no synthetic applications with this system have been reported. Treatment of sterically hindered β-hydroxyketone **32a** (α-Ac at C(4)) with complex **33** proceeds in good yield to generate Δ^{11}-carotol (**34**), the dehydro analogue of (−)-carotol (**35**).[31]

In addition to these transformations, we investigated the conversion of enone **11** into daucene (**2**) and related C(14)-oxidized natural products (Scheme 8). Following our retrosynthetic plan, we attempted to olefinate enone **11** with the standard Wittig ylide, but unfortunately recovered the starting material and observed poor conversion. Alternatively, methylenation under the Lombardo conditions[32] generates triene **36** in moderate yield in conjunction with a number of more polar products. With triene **36** in hand, we explored hydrogena-



Scheme 7. Derivatization of enone **11** to form sesquiterpene/diterpene cores and conversion to (−)-epoxydaucenal B (**3b**) and Δ^{11}-carotol (**34**).



Scheme 8. The end game for the total syntheses of (−)-daucene (**2**), (+)-daucenal (**4**), and (+)-14-*para*-anisoyloxydauc-4,8-diene (**5**) and the formal syntheses of epoxydaucenals A and B (**3a** and **b**).

tion conditions and found that the Wilkinson catalyst again reduces the terminal olefin to afford (−)-daucene (**2**) in ten steps (from **13**) and 15% overall yield.[26] Over hydrogenation to alkene **37** is also observed, especially with extended exposure to H_2.

We next examined allylic oxidation of daucene to access C(14)-functionalized sesquiterpenes. Gratifyingly, the selenium dioxide conditions employed previously proved effective in the oxidation of daucene to generate (+)-daucenal (**4**) in 8% overall yield over eleven steps (from **13**).[26] Hashidoko and co-workers also isolated this aldehyde from *Rosa rugosa* in conjunction with epoxydaucenals A and B (**3a** and **b**) and found that oxidation of daucenal with *meta*-chloroperoxybenzoic acid (*m*-CPBA) provides a 70:30 mixture of the epoxidized molecules in 58% yield.[23] By comparison to our previous route, this formal synthesis of epoxydaucenal B (**3b**) also produces the natural product in twelve steps, albeit in much lower overall yield (1%). Continuing toward our initial goal, Luche reduction of daucenal (**4**) provides allylic alcohol **38**, which can be treated with base and *para*-anisoyl chloride to afford (+)-14-*para*-anisoyloxydauc-4,8-diene (**5**) in 13 steps (from **13**) with 4% overall yield.[26] Given the bioactivity observed for esters **5** and **6**, we envision that exploration of other unnatural ester derivatives prepared from alcohol **38** may prove promising in structure–activity-relationship studies and enable the subsequent preparation of more potent analogues.

Conclusion

We have completed the first catalytic enantioselective total syntheses of epoxydaucenal B (**3b**), daucene (**2**), daucenal (**4**), and 14-*para*-anisoyloxydauc-4,8-diene (**5**) in 10–13 steps with 20, 15, 8, and 4% overall yield, respectively. Our route overcomes the challenge of accessing β-substituted acylcyclopentene **1a** by employing a siloxyenone to effect the Grignard addition and ring opening in a single step. Subsequent ring-closing metathesis and aldol reactions form the bicyclo[5.3.0]decane core. Derivatization of the key intermediate, enone **11**, allows access to the daucane sesquiterpene or the sphenobolane diterpene carbon skeletons, as well as other oxygenated scaffolds. Our efforts feature several olefination methods to install the C(13) carbon atom, including the underutilized molybdenum alkylidene developed by Kauffmann and co-workers. Biological evaluation of the molecules reported herein and application of the developed synthetic strategy to other daucane sesquiterpenes and sphenolobane diterpenes are underway and will be reported in due course.

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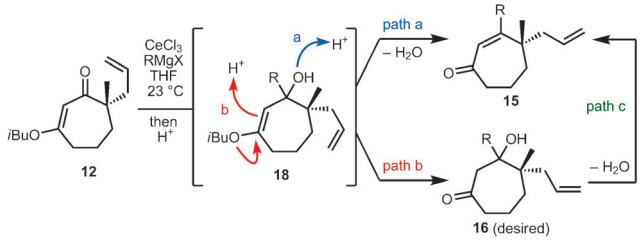
[14] The propensity for elimination under acidic workup conditions is likely due to the stability of the carbocation generated by hydrolysis of tertiary alcohol **18** or **16** (i.e., paths a/c favored over path b).



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[18] TIPS-substituted siloxyenones were selected due to their stability to silica gel chromatography, which allows for separation of isomeric siloxyenones **19a** and **19b**. The undesired siloxyenone (**19b**) is quantitatively recycled to the precursor dione with TBAF. See the Supporting Information.

[19] TLC analysis indicates the initial formation of both acyclic dione **17a** and β-hydroxyketone **16a**, which is converted to the dione over time. Addition of LiOH and TFE expedites this process. A screen of other fluoride sources revealed that a tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) quench only produces β-hydroxyketone **16a** even after extended exposure (determined by TLC analysis), whereas a cesium fluoride and LiOH workup also generates dione **17a**, albeit in a lower (70%) yield. See the Supporting Information.

[20] Dione (±)-**22** and enone (±)-**11** are key intermediates in the efforts of Urones and co-workers toward a total synthesis of racemic tormesol (**30**), which resulted in the preparation of the non-natural C(10) diastereomer, (±)-10-epi-tormesol. See: a) I. S. Marcos, I. M. Oliva, R. F. Moro, D. Díez, J. G. Urones, *Tetrahedron* **1994**, *50*, 12655–12672; b) I. S. Marcos, I. M. Oliva, D. Díez, P. Basabe, A. M. Lithgow, R. F. Moro, N. M. Garrido, J. G. Urones, *Tetrahedron* **1995**, *51*, 12403–12416.

[21] The samarium diiodide conditions we examined are based on a report by Wood and co-workers. See: J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Ovaska, J. L. Wood, *Angew. Chem.* **2004**, *116*, 1290–1292; *Angew. Chem. Int. Ed.* **2004**, *43*, 1270–1272.

[22] As cycloheptenone **15a** may alternatively be prepared from vinylogous ester **12** in 82% yield by a buffer quench (see Refs. [8b] and [15]), we also considered the relative merit of pursuing our daucane targets via this cycloheptyl molecule. Along this approach, the key intermediate enone **11** is produced in 8 steps from vinylogous ester **12** with 29% overall yield. By comparison, our siloxyenone route also proceeds to enone **11** in 8 steps, but with a higher (35%) overall yield.

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[26] Attempts to obtain authentic samples of the natural products prepared herein have been unsuccessful.

[27] The reduction also produces dione **22**, likely through an in situ retro-aldol process, but this material can be recycled through our route.

[28] Olefination of β-hydroxyketone **32** under Wittig or Lombardo conditions failed to provide the desired alkene product **34**.

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[30] Methylene(oxo)molybdenum(V) chloride (**33**) is generated by dropwise addition of methyllithium to oxotrischlorobis(tetrahydrofuran)-molybdenum(V). For the preparation of the later molybdenum complex, see: C. A. McUliffe, A. Hosseiny, F. P. McCullough, *Inorg. Chim. Acta* **1979**, *33*, 5–10.

[31] Unfortunately, hydrogenation of allylic alcohol **34** with the Wilkinson catalyst generated a complex product mixture and failed to provide carotol (**35**).

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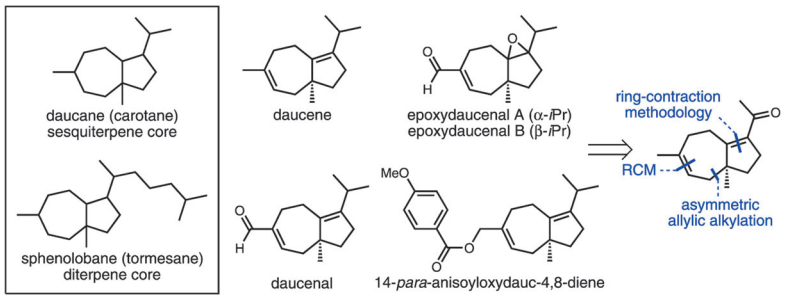

United front! A route to the bicyclo-[5.3.0]decane core of the daucane and sphenolobane terpenoids via a key enone intermediate is described that enables the enantioselective total syntheses of several members of this family of natural products (see scheme).

Natural Product Synthesis

*N. B. Bennett, B. M. Stoltz** ▮▮▮▮–▮▮▮▮

A Unified Approach to the Daucane and Sphenolobane Bicyclo-[5.3.0]decane Core: Enantioselective Total Syntheses of Daucene, Daucenal, Epoxydaucenal B, and 14-*para*-Anisoyloxydauc-4,8-diene