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Concise Synthesis of the *neo*-Clerodane Skeleton of Teucrolivin A Using a Pericyclic Reaction Cascade

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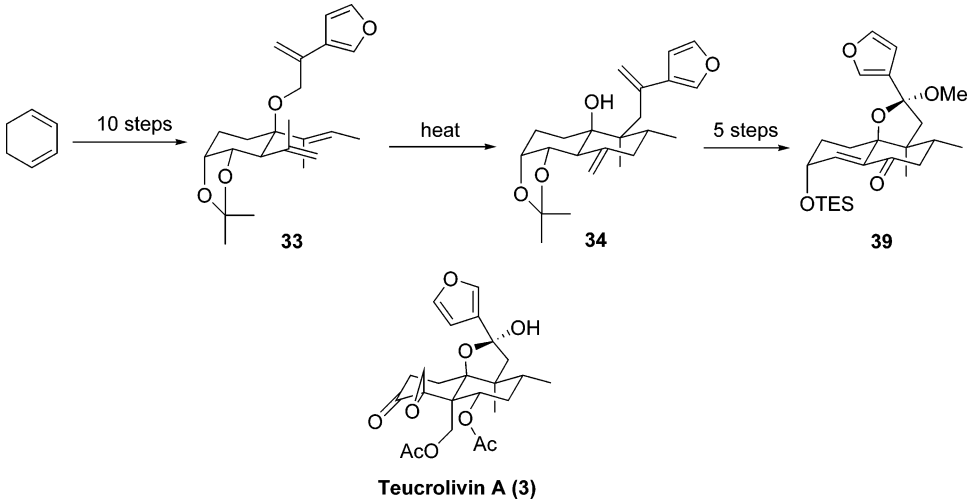

Teucrolivin A (3)

Herein, we describe the synthesis of advanced intermediate **39** on the path towards the total synthesis of teucrolivin A (**3**) in 16 steps from commercially available 1,3-cyclohexadiene. We have constructed the *trans*-decalin core of the natural product **3** as a single diastereomer using a tandem oxy-Cope/Claisen/ene cascade and in doing so have incorporated sufficient functionality to allow completion of the total synthesis.

neo-Clerodane diterpenoids[1] are a large family of natural products which are isolated from a variety of natural sources, in particular from plants of the genus *Teucrium*.[2] This group of compounds has attracted considerable interest from the natural products community as they often exhibit specific and pronounced biological activity as insect antifeedants,[3] antifungal, antimicrobial, and antitumor agents[4] and even as hallucinogens.[5] Several examples include plectrornatin A (**1**),[4] which shows moderate antimicrobial and strong antibacterial activity against Gram-positive and Gram-negative bacteria, and salvinorin C (**2**),[5] one of the most potent naturally occurring hallucinogens thus far identified and the only known diterpene which induces hallucinations in humans (Figure 1).

Another *neo*-clerodane diterpenoid, teucrolivin A (**3**), is isolated from the aerial parts of *Teucrium oliverianum*, a plant native to Saudi Arabia which finds use as a folk medicine for the treatment of diabetes (Figure 2).[6] Rodriguez and co-workers assigned its structure and relative stereochemistry in 1990 through extensive spectroscopic measurements and X-ray diffraction analysis, and to date, there has been no determination of its absolute configuration. Although the biological activity is undetermined, this complex natural product is an attractive synthetic target because of several challenging structural motifs

(1) Although more correctly described as *ent*-clerodanes, the term *neo*-clerodane is preferred by most, as proposed by Rogers et al. (Rogers, D.; Unal, A. A.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Commun*. **1979**, 97.), and is commonly used to describe all structures with this framework.

(2) Bruno, M.; Bondi, M. L.; Rosselli, S.; Maggio, A.; Piozzi, F.; Arnols, N. A. *J. Nat. Prod.* **2002**, *65*, 142 and references therein.

(3) Simmonds, M. S. J.; Blaney, W. M.; Ley, S. V.; Bruno, M.; Savona, G. *Phytochemistry* **1989**, *28*, 1069.

(4) Rijo, P.; Gaspar-Marques, C.; Simoes, M. S.; Duarte, A.; Apreda-Rojas, M. del-C.; Cano, F. H.; Rodriguez, B. *J. Nat. Prod*. **2002**, *65*, 1387.

(5) Valdez, L. J., III; Chang, H.-M.; Visger, D. C.; Koreeda, M. *Org. Lett.* **2001**, *3*, 3935.

(6) Bruno, M.; Omar, A. A.; Perales, A.; Piozzi, F.; Rodriguez, B.; Savona, G.; de la Torre, M. C. *Phytochemistry* **1991**, *30*, 275.

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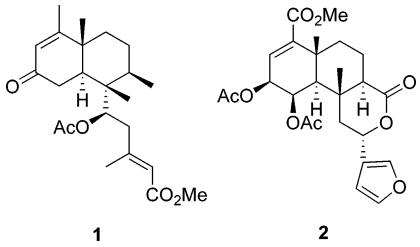
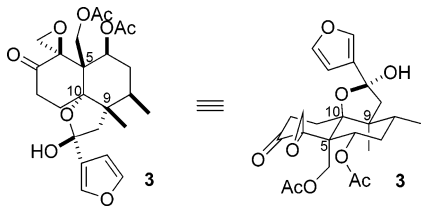


1 **2**

FIGURE 1. Some representative *neo*-clerodane diterpenoids.



3 **3**

FIGURE 2. Structure of teucrolivin A (**3**).

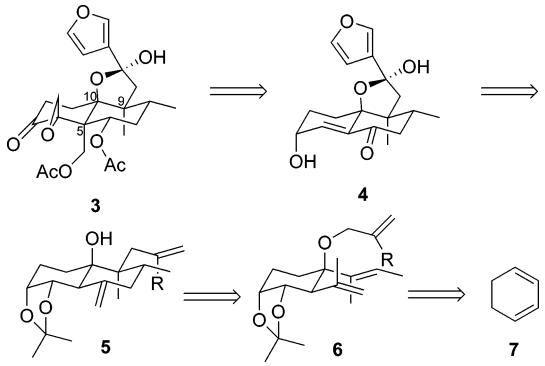
including its compact, highly oxygenated *trans*-decalin core, six contiguous stereogenic centers including all-carbon quaternary centers[7] at C5 and C9, and an unusual 3-furanyl-substituted hemiacetal functionality. There are no other ongoing synthetic pursuits.

Recently, our laboratory reported a cascading oxy-Cope/Claisen/ene reaction[8] sequence that rapidly accesses highly functionalized *trans*-decalin systems with a quaternary carbon at C9 and a tertiary alcohol at C10 that map perfectly onto the core structure of teucrolivin A (**3**). Cascading reaction sequences are powerful tools by which significant molecular complexity can be established in a single transformation.[9] Hence, it is to be expected that these types of transformations see wide use in synthesis. Such reactions are made more attractive if they can be used to construct functionality or structural elements that are difficult to establish using more conventional methods.

We envisaged that teucrolivin A (**3**) could ultimately be obtained via a 1,4-addition/enolate trapping sequence or a 2,3-Wittig rearrangement protocol performed on intermediates derived from compound **4**. This advanced intermediate could be obtained from *trans*-decalin **5** by oxidative cleavage of the olefins, oxidation of the resulting lactol, and alkylation using 3-lithiofuran (Scheme 1). These *trans*-decalin systems are accessed via the oxy-Cope/Claisen/ene reaction, revealing allyl ether **6** as a key intermediate on the path to (±)-teucrolivin A (**3**). The precursor of the tandem reaction could be synthesized from commercially available 1,3-cyclohexadiene.

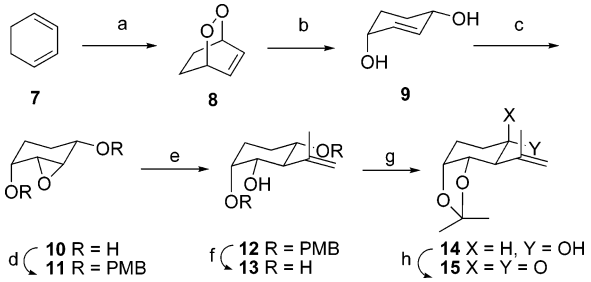
In this paper, we describe our efforts to construct the carbon framework of the core of teucrolivin A (**3**) using the aforementioned oxy-Cope/Claisen/ene sequence. We then elaborate the core to an intermediate with appropriate functionality to construct the quaternary carbon at C5.

SCHEME 1. Retrosynthesis



3 **4** **5** **6** **7**

SCHEME 2 [a]



7 **8** **9**

d **10** R = H, **11** R = PMB; f **12** R = PMB, **13** R = H; h **14** X = H, Y = OH, **15** X = Y = O

[a] (a) O_2, TPP, hν, CH_2Cl_2. (b) Thiourea, MeOH, 83% over two steps. (c) *m*CPBA, Et_2O/EtOAc (1:1), 0 °C to room temperature, 50%. (d) PMBCl, NaH, NaI, DMF, 90%. (e) $CH_2{=}C(CH_3)MgBr$, CuI, THF/Et_2O (1:1), −10 °C, 100%. (f) I_2, MeOH, reflux, 85%. (g) 2,2-Dimethoxypropane, PTSA, acetone, 0 °C, 72%. (h) Dess−Martin periodinane, CH_2Cl_2, 87%.

Our synthesis commenced by converting 1,3-cyclohexadiene into ketone **15** using a modification of a procedure recently reported by our laboratory.[10] A [4+2] cycloaddition of singlet oxygen generated by irradiation with a tungsten lamp in the presence of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP)[11] produced endoperoxide **8** which was immediately reduced using methanolic thiourea[12] to give the 1,4-diol **9** in 83% yield over two steps (Scheme 2). Directed epoxidation was achieved using *m*CPBA to give **10** in 50% yield (dr > 25:1). The diol was protected as a PMB ether using PMBCl to afford **11** in 90% yield.

Opening of the epoxide moiety in **11** was achieved with isopropenylmagnesium bromide and copper(I) iodide to afford **12** in quantitative yield. Subsequent deprotection of the bis-PMB-protected diol **12** proceeded smoothly using a refluxing 1% w/v solution of iodine in methanol,[13] providing the corresponding 1,2-diol **13** in 85% yield. The latter was protected by employing 2,2-dimethoxypropane and catalytic PTSA to give acetonide **14** in 72% yield, and oxidation of the secondary alcohol using Dess−Martin periodinane led to ketone **15** in 87% yield.[14]

(7) For examples of the stereoselective formation of quaternary carbons using the tandem pericyclic reaction, see: (a) Barriault, L.; Denissova, I. *Org. Lett*. **2002**, *4*, 1371. (b) Barriault, L.; Farand, J. A.; Denissova, I. *Heterocycles* **2004**, *62*, 735. For reviews on the synthesis of quaternary carbon centers, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *59*, 10105. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1688. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed*. **2001**, *40*, 4591. (e) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed*. **1998**, *110*, 42. (f) Fuji, K. *Chem. Rev*. **1993**, *93*, 2037. (g) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(8) Barriault, L.; Sauer, E. L. O. *J. Am. Chem. Soc*. **2004**, *126*, 8569.

(9) (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Ziegler, F. *Comprehensive Organic Synthesis, Combining C−C á Bonds*; Paquette, L. A., Ed.; Permagon Press: Oxford, 1991; Vol. 5, Chapter 7.3. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed*. **1993**, *32*, 131.

(10) (a) Morency, L.; Barriault, L. *Tetrahedron Lett*. **2004**, *45*, 6105. (b) Hutchings, M.; Moffat, D.; Simpkins, N. S. *Synlett* **2001**, 661.

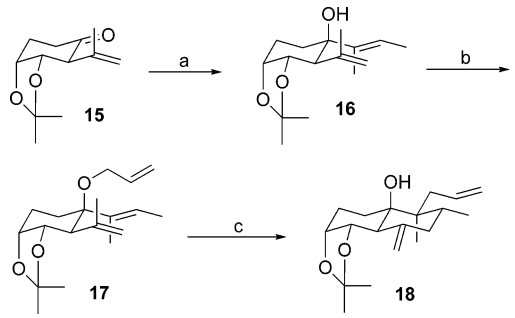
(11) Tsuji, T.; Okuyama, M.; Ohkita, M.; Kawai, H.; Suzuki, T. *J. Am. Chem. Soc*. **2003**, *125*, 951.

(12) Yunus, K.; Balci, M. *Tetrahedron* **2003**, *59*, 2063.

(13) Vaino, A. R.; Szarek, W. A. *Synlett* **1995**, 1157.

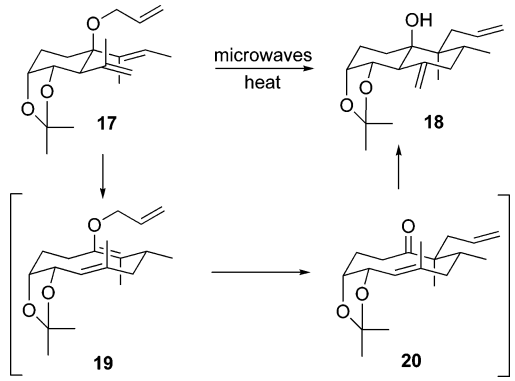
(14) (a) Dess, D. B.; Martin J. C. *J. Am. Chem. Soc.* **1991**, *113*, 2350. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

SCHEME 3 [a]



[a] (a) *E*-2-Bromo-2-butene, *t*-BuLi, Et_2O, −78 °C, 35%. (b) Allyl bromide, KH, NaI, DME, 0 °C to room temperature, 82%. (c) Toluene, microwaves, 220 °C, 82%.

SCHEME 4. Tandem Reaction Mechanism

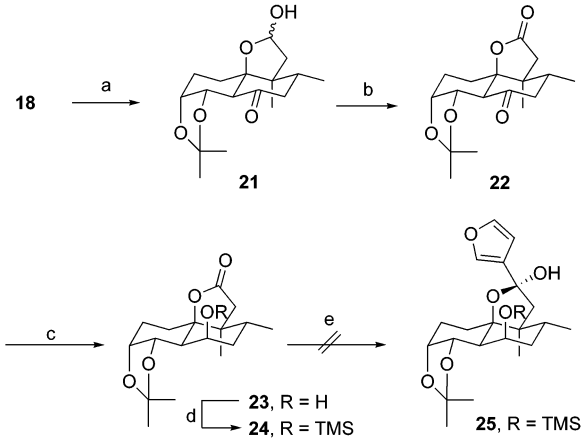


With ketone **15** in hand, we were prepared to synthesize the precursor of the tandem oxy-Cope/Claisen/ene reaction. Alkylation of **15** by lithium−halogen exchange of *E*-2-bromo-2-butene afforded **16** as a single diastereomer, albeit in a modest yield of 35% (Scheme 3).[15] Treatment of **16** with KH and allyl bromide in DME produced allyl ether **17** in 82% yield, and subjecting this compound to microwave irradiation[16] induced the tandem oxy-Cope/Claisen/ene reaction, ultimately giving **18** in 78% yield as the only detectable diastereomer.

The cascading sequence is initiated by an oxy-Cope rearrangement that gives the ten-membered macrocycle **19** (Scheme 4). This intermediate immediately undergoes a [3,3] Claisen shift which generates a second macrocyclic intermediate **20**. The latter is poised to react in a transannular carbonyl ene reaction which results in the formation of the final *trans*-decalin product **18** in the tandem process. It has been shown by previous work in our laboratory that the diastereoselectivity in this reaction cascade is a direct result of the preferred conformations of the intermediate macrocycles at the transition states of the latter two pericyclic reactions.[8]

Ozonolysis of the olefins in **18** followed by workup with dimethyl sulfide afforded lactol **21**, which was immediately oxidized with catalytic TPAP[17] in the presence of NMO to give

SCHEME 5 [a]



[a] (a) O_3, CH_2Cl_2, −78 °C then DMS. (b) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 97%, two steps. (c) $NaBH_4$, MeOH, 90%. (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96%. (e) 3-Bromofuran, *t*-BuLi, various conditions.

lactone **22** in 97% yield over two steps (Scheme 5). Selective reduction of the ketone moiety in **22** using $NaBH_4$ afforded the axial secondary alcohol **23** (dr > 25:1) as the sole product in 90% yield, and protection of this alcohol as the TMS ether was achieved by treatment with TMSOTf to provide **24** in 96% yield. Attack of the reducing reagent on the top face of **22** was not observed, as the five-membered lactone blocks this face from attack by an incoming nucleophile.

The stage was then set to install the 3-furanyl hemiketal moiety that is seen in teucrolivin A (**3**). Unfortunately, all attempts at alkylation of lactone **24** were met with failure, and all conditions employed simply resulted in the return of the starting material. We suspected a competing enolization of the lactone that effectively quenches the nucleophile.

Having encountered a potentially fatal roadblock in the completion of the synthesis using the aforementioned approach, we found that it was necessary to devise another method to install the 3-substituted furan functionality. We postulated that if we could synthesize an appropriately substituted allyl ether such as **6**, where R = 3-furan, we might be able to perform a tandem reaction analogous to the transformation of **17** to **18**, as displayed in Scheme 4. Simple oxidative cleavage of the olefin would then result in the formation of the hemiacetal seen in **3**.[18]

The preparation of the desired allyl bromide **32** from commercially available methyl glycolate **26** is illustrated in Scheme 6. Protection of the primary alcohol as the TBS ether **27** proceeded smoothly in 94% yield by treatment with TBDMSCl in the presence of imidazole. Conversion to the Weinreb amide[19] **28** and subsequent alkylation to **29** via lithium−halogen exchange of 3-bromofuran[20] were achieved in 80 and 85% yields, respectively. Wittig olefination of **29** to **30** was achieved in 93% yield, and deprotection of the primary alcohol using TBAF in THF smoothly generated **31** in 76%

(15) Any and all attempts at improving the efficiency of this transformation unfortunately did not result in any improvements in yield.

(16) For a review on microwaves in organic synthesis, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Lidström, P.; Tierny, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199. (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (e) Majetich, G.; Hichs, R. J. *J. Microwave Power Electromagn. Energy* **1995**, *30*, 27.

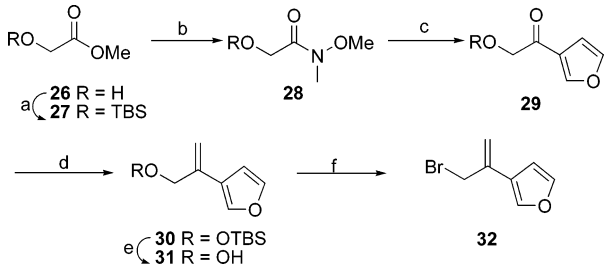
(17) Ley, S. V.; Griffith, W. P. *Aldrichimica Acta* **1990**, *23*, 1.

(18) Assuming that the stereochemistry of the anomeric center in the natural product is the thermodynamic isomer, we should observe the stereochemistry upon oxidative cleavage and subsequent cyclization should be equivalent to that seen in **3**.

(19) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

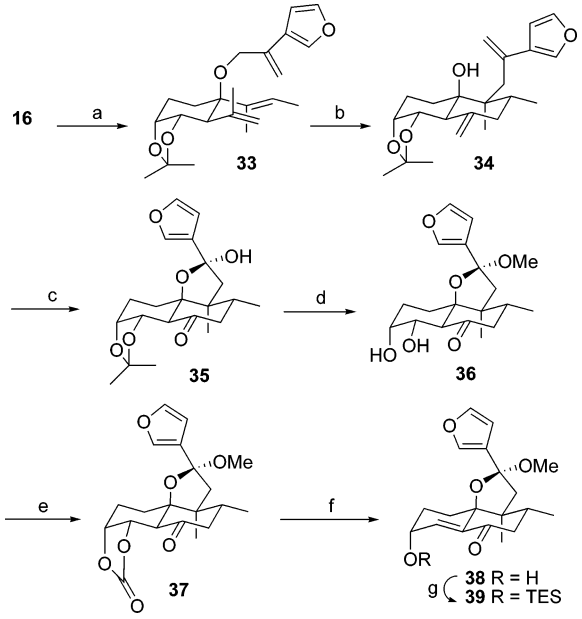
(20) Politis, J. K.; Nemes, J. C.; Curtis, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 2537.

SCHEME 6 [a]



[a] (a) TBDMSCl, imidazole, THF, 95%. (b) HN(OMe)Me·HCl, $AlMe_3$, CH_2Cl_2, 0 °C, 80%. (c) 3-Bromofuran, *t*-BuLi, THF, −78 °C, 83%. (d) $IPPh_3CH_3$, KHMDS, THF, 0 °C, 93%. (e) TBAF, THF, 76%. (f) CBr_4, PPh_3, CH_2Cl_2, 69%.

SCHEME 7 [a]



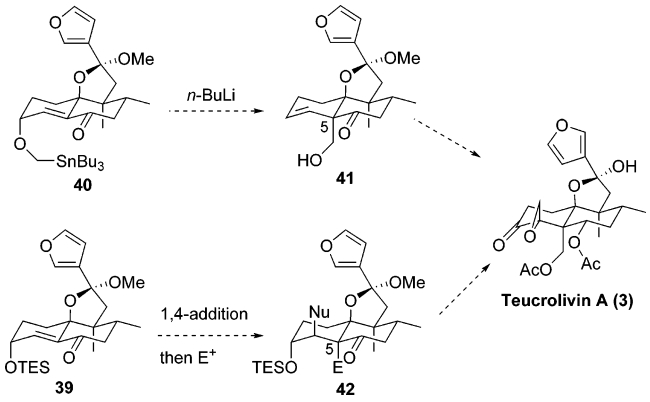
[a] (a) **32**, KH, NaI, DME, 0 °C to room temperature, 47%. (b) Toluene, microwaves, 220 °C, 59%. (c) OsO_4, NMO, THF/H_2O (5:1), 72%. (d) MeOH, PTSA, 95%. (e) Triphosgene, pyridine, CH_2Cl_2, 0 °C, 100%. (f) DBU, benzene, 98%. (g) TESCl, Et_3N, DMAP, THF, 97%.

yield. Finally, light-sensitive allyl bromide **32** was obtained in 69% yield by treating the primary alcohol with CBr_4 and PPh_3 in CH_2Cl_2.

The allylation of **16** using allyl bromide **32** was successful, albeit in a modest yield of 47%. Any attempts at ameliorating this problem by varying reaction conditions and leaving groups in the allyl fragment were fruitless. The microwave irradiation of **33** gave **34** as the sole diastereomer in 59% yield (Scheme 7). In light of these results, we had effectively solved the problem of not being able to install the furan via an alkylation protocol.

We were then prepared to advance our synthesis to a point where we could attempt to install the quaternary carbon at the C5 ring junction of the *trans*-decalin in **3**. Exposure of **34** to OsO_4 and NMO followed by treatment with $NaIO_4$ smoothly oxidized the olefins, generating hemiacetal **35** in 72% yield. As we expected, and as proven by extensive 2D NMR experiments, the stereochemistry at the hemiacetal anomeric center is the same as that at the hemiacetal anomeric center in the natural product **3**. Treatment of **35** with catalytic PTSA in MeOH served the double purpose of removing the acetonide

SCHEME 8



and protecting the hemiacetal as the mixed acetal **36** in 95% yield. Formation of carbonate **37** using triphosgene was achieved in quantitative yield. The treatment of **37** with DBU afforded the α,β-unsaturated ketone **38** in 98% yield. The secondary alcohol in **38** was easily protected as the TES ether **39** using TESCl, Et_3N, and DMAP in 97% yield.

We foresee several methods by which we can overcome the last major hurdle of installing the remaining quaternary center at C5. Currently, we are examining several routes which include a 2,3-Wittig rearrangement, **40**→ **41**, and a 1,4-addition/enolate trapping sequence, **39**→ **42** (Scheme 8).

In conclusion, we have described the rapid synthesis of the *trans*-decalin core of teucrolivin A (**1**) in 16 steps from 1,3-cyclohexadiene using a cascading oxy-Cope/Claisen/ene reaction as the key step. This synthesis demonstrates the usefulness of this tandem process to construct decalin frameworks, embedding sufficient functionality to further advance intermediates toward the goal of total synthesis. A description of our studies to install the remaining quaternary carbon at C5, subsequent elaboration of the ketone and epoxide moieties in the A ring, and finally completion of teucrolivin A (**3**) synthesis will be reported in due course.

Experimental Section

8: 2,3-Dioxa-bicyclo[2.2.2]oct-5-ene. A solution of 1,3-cyclohexadiene (10.00 g, 124.8 mmol) in CH_2Cl_2 (500 mL) was degassed with O_2 for 15 min, after which was added 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) (275.2 mg, 0.4480 mmol). The resulting deep purple solution was irradiated with a 200 W tungsten lamp for 8 h while being bubbled with a constant stream of O_2. The reaction mixture was then concentrated under reduced pressure to a total volume of 50 mL, and this crude mixture was used directly in the next reaction.

9: *cis*-Cyclohex-2-ene-1,4-diol. To a solution of crude mixture **8** in MeOH (500 mL) was added thiourea (11.40 g, 149.8 mmol). The resulting mixture was stirred at room temperature for 18 h, after which it was filtered through a short pad of Celite. The resulting clear orange solution was concentrated under reduced pressure, and the residue was preadsorbed onto silica gel (20 g). The product was isolated by flash chromatography (EtOAc) to afford **9** as a white solid (11.87 g, 104.0 mmol, 83% over two steps). All spectral data are in agreement with that found in the literature.[11]

16: *E*-4-Isopropenyl-2,2-dimethyl-5-(1-methylpropenyl)hexahydro-benzo[1,3]dioxol-5-ol. To a solution of *E*-2-bromo-2-butene (3.74 mL, 36.9 mmol) in ether (100 mL) cooled at −78 °C was added *t*-BuLi (1.70 M, 43.4 mL, 73.8 mmol), and the resulting solution was stirred for 2 h. After this, a solution of **15** (2.22 g, 10.5 mmol) in ether (50 mL) was added, and the solution was stirred for 2 h while warming to room temperature and then for a further

16 h at room temperature. The reaction was quenched with aqueous saturated NH_4Cl, and the layers were separated. The aqueous layer was extracted with ether (3 × 75 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% EtOAc/Hex) afforded **16** (0.984 g, 3.68 mmol, 35%) as a pale yellow solid. Mp: 85−86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.44 (q, J = 6.5 Hz, 1H), 4.96 (s, 1H), 4.78 (s, 1H), 4.28−4.24 (m, 2H), 2.45 (d, J = 8.7 Hz, 1H), 2.19−1.90 (m, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.56 (d, J = 7.2 Hz, 3H), 1.51 (s, 3H), 1.34 (s, 3H), 1.27−1.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.7, 139.7, 116.8, 113.5, 107.7, 76.6, 73.0, 51.4, 30.8, 28.8, 26.3, 24.0, 22.2, 13.6, 13.3. IR (neat): ν_{max} = 3478 (b), 3072 (w), 2987 (s), 2931 (s), 2874 (m), 1643 (m), 1449 (m), 1377 (s), 1365 (s), 1243 (s), 1218 (s), 1159 (m), 1061 (s), 1026 (s). HRMS (EI): calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1921.

17: *E*-5-Allyoxy-4-iospropenyl-2,2-dimethyl-5-(1-methylpropenyl)hexahydro-benzo[1,3]dioxol-5-ol. A mixture of NaI (0.0042 g, 0.028 mmol) and KH (30% dispersion in oil, 0.0750 g, 0.561 mmol) was washed with hexanes to remove mineral oil and was dried under high vacuum. These solids were suspended in DME (1.5 mL), and the mixture was cooled to 0 °C, whereupon a solution of **16** (0.0217 g, 0.0691 mmol) in DME (1 mL) was added followed by 10 min of stirring. To this mixture was added allyl bromide (0.07 mL, 0.8 mmol), and the mixture was stirred while warming to room temperature for 2 h and then stirred at room temperature for 16 h. The reaction was quenched by adding aqueous saturated NH_4Cl (5 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% EtOAc/Hex) afforded **17** (0.0178 g, 0.0567 mmol, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.91−5.78 (m, 1H), 5.39 (q, J = 6.7 Hz, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 9.9 Hz, 1H), 4.88 (s, 1H), 4.72 (s, 1H), 4.41 (q, J = 4.9 Hz, 1H), 4.32−4.30 (m, 1H), 3.67 (m, 2H), 2.18 (d, J = 9.9 Hz, 1H), 2.07−1.83 (m, 2H), 1.79 (s, 3H), 1.69−1.62 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H), 1.50 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.2, 136.3, 135.7, 120.8, 111.5, 114.8, 108.1, 85.4, 83.9, 77.6, 73.4, 62.8, 56.3, 29.1, 26.9, 26.2, 22.8, 13.9, 13.8. IR (neat): ν_{max} = 3071(w), 2984 (s), 2968 (s), 2933 (s), 2871 (s), 1643 (m), 1453 (m), 1434 (m), 1379 (s), 1366 (s), 1243 (s), 1216 (s), 1162 (s), 1118 (m), 1060 (s), 1028 (s), 923 (m), 887 (m), 861 (m), 816 (w), 792 (w). HRMS (EI): calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2333.

18: 6-Allyl-2,2,6,7-tetramethyl-9-methylene-octahydro-naptho[1,2-d][1,3]dioxol-5a-ol. A solution of **17** (0.0255 g, 0.0832 mmol) in toluene (12 mL) was transferred to a microwave cell, whereupon it was degassed by bubbling with argon for 15 min. The resulting solution was heated in a microwave oven (20 min heat ramp to 220 °C followed by 1 h at 220 °C). After cooling, the solution was concentrated and the major product was isolated by flash chromatography (10% EtOAc/Hex) to afford **18** (0.0199 g, 0.0649 mmol, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.11−6.02 (m, 1H), 5.06 (d, J = 17.2 Hz, 1H), 5.02 (s, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.94 (s, 1H), 4.33 (dd, J = 8.6, 5.4 Hz, 1H), 4.27−4.24 (m, 1H), 2.34 (dd, J = 15.4, 9.2 Hz), 2.29 (d, J = 8.8 Hz, 1H), 2.20−2.04 (m, 5H), 1.95−1.88 (m, 2H), 1.68−1.61 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H), 0.89 (d, J = 6.3 Hz, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.1, 138.2, 116.4, 109.5, 107.8, 79.5, 74.9, 72.8, 47.1, 44.8, 41.1, 40.0, 34.2, 28.6, 26.3, 26.2, 22.5, 16.9, 15.9. IR (neat): ν_{max} = 3561 (b), 3074 (w), 2983 (s), 2956 (m), 2937 (s), 2880 (s), 1645 (m), 1462 (m), 1447 (m), 1382 (m), 1367 (m), 1246 (s), 1219 (s), 1161 (m), 1055 (s), 1014 (m), 968 (w), 934 (w), 903 (w), 869 (w), 839 (w), 793 (w). HRMS (EI): calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2199.

21: 7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[*d*]naphthalene-2-ol-6-one. A solution of **18** (0.1311 g, 0.4278 mmol) in CH_2Cl_2 (25 mL) was degassed by bubbling with O_2 for 10 min. The resulting mixture was then cooled to −78 °C and bubbled with O_3 until a pale blue color persisted in the solution. The reaction was quenched by adding Me_2S, followed by stirring while warming to room temperature over 0.5 h. The resulting solution was concentrated under reduced pressure to give an orange oil (0.1335 g), which was used without purification in the next step of the synthesis.

22: 7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[*d*]naphthalene-2,6-dione. To a crude solution of **21** (0.1335 g) in CH_2Cl_2 (25 mL) was added 4 Å molecular sieves (0.2139 g, 500 mg/mmol starting material), NMO (0.0752 g, 0.642 mmol), and TPAP (0.0065 g, 0.018 mmol). The resulting dark orange solution was stirred for 2 h, whereupon it had turned opaque black. The solution was filtered through a short pad of silica, and the filter cake was washed with 10% MeOH/EtOAc (100 mL). The mother liquor was concentrated under reduced pressure, and the product was isolated by flash chromatography (60% EtOAc/Hex) to afford **22** (0.1279 g, 0.4149 mmol, 97% over two steps) as a white solid. Mp: 169−170 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.66 (dd, J = 8.8, 5.0 Hz, 1H), 4.33−4.30 (m, 1H), 2.53 (d, J = 9.1 Hz, 1H), 2.44 (d, J = 8.3 Hz, 2H), 2.31 (dt, J = 13.9, 4.0 Hz, 2H), 2.15−1.91 (m, 3H), 1.67−1.61 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 204.8, 173.9, 108.4, 93.3, 72.0, 71.7, 53.4, 45.1, 44.9, 40.4, 38.4, 28.2, 27.7, 26.1, 22.1, 17.1, 12.0. IR (neat): ν_{max} = 2959 (s), 2927 (s), 2854 (m), 1780 (s), 1727 (s), 1457 (m), 1381 (m), 1244 (m), 1220 (m), 1170 (w), 1160 (m), 1045 (m), 1037 (s), 922 (m). HRMS (EI): calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1629.

23: 7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[*d*]naphthalene-6-ol-2-one. To a solution of **22** (0.0385 g, 0.124 mmol) in MeOH (5 mL) was added $NaBH_4$ (0.0323 g, 0.373 mmol), and the resulting solution was stirred at room temperature for 3 h. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL) followed by 1 h of vigorous stirring. MeOH was removed by evaporation, and the resulting aqueous solution was extracted with EtOAc (4 × 10 mL). The layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (60% EtOAc/Hex) afforded **23** (0.0349 g, 0.1123 mmol, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.46 (dd, J = 9.6, 4.8 Hz, 1H), 4.33−4.28 (m, 1H), 4.12−4.08 (m, 1H), 2.44−2.37 (m, 2H), 2.12−2.02 (m, 3H), 1.95−1.91 (m, 1H), 1.82−1.78 (m, 1H), 1.73 (dt, J = 13.2, 5.5 Hz, 2H), 1.57−1.54 (m, 2H), 1.43 (s, 3H), 1.35 (s, 3H), 0.95 (s, 3H), 0.90 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.1, 108.3, 89.3, 73.7, 72.4, 64.1, 44.5, 43.5, 40.4, 36.3, 28.8, 28.5, 27.7, 26.4, 22.1, 16.6, 12.0. IR (neat): ν_{max} = 3492 (b), 2982 (m), 2964 (m), 2933 (m), 2881 (m), 1772 (s), 1451 (w), 1381 (m), 1368 (m), 1245 (s), 1213 (s), 1182 (m), 1164 (s), 1135 (w), 1085 (w), 1066 (s), 1050 (s), 1033 (s), 981 (m), 944 (m), 918 (m), 858 (m), 790 (w), 732 (m), 672 (w). HRMS (EI): calcd for $C_{17}H_{26}O_5$ 310.1780, found ($M^+ - CH_3$) 295.1530, actual 295.1546.

24: 7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-6-(trimethylsilyloxy)-octahydro-1-oxa-cyclopenta[*d*]naphthalene-2-one. A solution of **23** (0.0101 g, 0.0325 mmol) in CH_2Cl_2 (2 mL) cooled at −78 °C was treated with 2,6-lutidene (0.02 mL, 0.172 mmol) followed by TMSOTf (0.01 mL, 0.0579 mmol), and the resulting mixture was stirred for 0.5 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (5 mL) and warming to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). Then, the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (30% EtOAc/Hex) yielded **24** (0.0120 g, 0.0314 mmol, 96%) as a white solid. Mp: 187−188 °C. ^{1}H NMR (C_6D_6, 300 MHz): δ = 4.53 (dd, J = 9.7, 4.8 Hz, 1H), 4.21 (q, J = 3.2 Hz, 1H), 4.08−4.06 (m, 1H), 2.12−2.09 (m, 2H), 1.88−1.84 (m, 3H), 1.44 (dt, J = 14.0, 3.3 Hz, 2H), 1.41−1.34 (m, 4H), 1.29 (s, 3H), 1.05−0.95 (m, 2H), 0.51 (d, J = 7.0 Hz, 3H), 0.39 (s, 3H), 0.19 (s, 9H). ^{13}C NMR (C_6D_6, 75 MHz): δ = 173.8, 107.7, 100.2, 87.3, 74.6, 72.8, 64.4, 44.7, 43.9, 40.4, 37.1, 29.1, 28.4, 26.6, 22.7, 16.6, 11.8, 0.2. IR (neat): ν_{max} = 2982 (m), 2960 (m), 2934 (m),

2895 (m), 2888 (m), 1774 (s), 1451 (w), 1438 (w), 1380 (m), 1367 (m), 1349 (w), 1323 (w), 1291 (w), 1249 (s), 1212 (s), 1184 (m), 1164 (m), 1137 (w), 1093 (m), 1069 (s), 1058 (s), 1036 (s), 1014 (w), 996 (m), 971 (m), 946 (m), 923 (m), 883 (m), 842 (s), 793 (w), 749 (w), 667 (w). HRMS (EI): calcd for $C_{20}H_{34}O_5Si$ 310.2144, found ($M^+ - CH_3$) 367.1942, actual 367.1941.

27: (*tert*-Butyl-dimethylsilanyloxy)-acetic Acid Methyl Ester. A solution of **26** (27.29 g, 303.0 mmol) in THF (600 mL) was treated with imidazole (61.88 g, 909.0 mmol) followed by TBDMSCl (54.80 g, 364.0 mmol), and the mixture was stirred at room temperature for 16 h. The reaction was then quenched by adding saturated aqueous NH_4Cl (500 mL). The layers were separated. The aqueous layer was extracted with Et_2O (3 × 400 mL), and the combined organic layers were washed with H_2O (200 mL), 1 M HCl (300 mL), and saturated aqueous NaCl (200 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/Hex) afforded **27** (58.81 g, 287.8 mmol, 95%) as a clear pale yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.20 (s, 2H), 3.68 (s, 3H), 0.87 (s, 9H), 0.05, (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 61.6, 51.6, 25.7, 18.3, −5.6. IR (neat): ν_{max} = 2954 (m), 2931 (m), 2896 (m), 2859 (m), 1765 (s), 1473 (m), 1464 (m), 1437 (m), 1389 (w), 1362 (m), 1256 (m), 1213 (m), 1189 (w), 1150 (s), 1007 (w), 939 (w), 888 (w), 840 (s), 817 (m), 780 (s), 695 (w), 663 (w). HRMS (EI): calcd for $C_9H_{20}O_3Si$ 204.1182, found ($M^+ - CH_3$) 189.0958, actual 189.0947, found ($M^+ - {}^t$Bu) 147.0480, actual 147.0477.

28: 2-(*tert*-Butyl-dimethylsilanyloxy)-*N*-methoxy-*N*-methylacetamide. To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (15.64 g, 106.3 mmol) in CH_2Cl_2 (350 mL) cooled at 0 °C was added trimethylaluminum (2 M in hexanes, 80.16 mL, 160.3 mmol), and the resulting solution was stirred at 0 °C for 25 min. To this was added a solution of **27** (11.90 g, 58.20 mmol) in CH_2Cl_2 (150 mL), and the mixture was stirred at 0 °C for 20 min, whereupon the reaction was quenched by the careful addition of an aqueous solution of 1 M sodium tartrate/1 M NH_4Cl (300 mL). After 1 h of vigorous stirring, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% EtOAc/Hex) afforded **28** (11.11 g, 46.59 mmol, 80%) as a clear yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.41 (s, 2H), 3.65 (s, 3H), 3.16 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.0, 61.7, 61.3, 60.3, 25.7, 18.4, −5.5. IR (neat): ν_{max} = 2954 (s), 2931 (s), 2897 (m), 2857 (s), 2824 (w), 1695 (s), 1472 (m), 1464 (m), 1443 (m), 1415 (m), 1390 (m), 1361 (m), 1329 (m), 1254 (m), 1161 (s), 1089 (s), 997 (s), 939 (w), 921 (w), 839 (w), 780 (s), 738 (w), 683 (w), 663 (w), 611 (w). HRMS (EI): calcd for $C_{10}H_{23}NO_3Si$ 204.1182, found ($M^+ - CH_3$) 218.1221, actual 218.1213, found ($M^+ - {}^t$Bu) 176.0762, actual 176.0743.

29: 2-(*tert*-Butyl-dimethylsilanyloxy)-1-furan-3-yl-ethanone. To a solution of freshly prepared 3-bromofuran (3.90 mL, 43.1 mmol) in THF (150 mL) cooled at −78 °C was added ^{t}BuLi (1.70 M in hexanes, 50.80 mL, 86.40 mmol), and the mixture was stirred for 2 h at −78 °C, giving a clear orange solution. To this mixture was added a solution of **28** (5.03 g, 21.5 mmol) in THF (50 mL), followed by 0.5 h of stirring at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (200 mL) at −78 °C and then warming to room temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Subsequent purification by flash chromatography (10% EtOAc/Hex) afforded **29** (4.27 g, 17.8 mmol, 83%) as a clear colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.27−8.26 (m, 1H), 7.41 (t, J = 1.7 Hz, 1H), 6.79 (dd, J = 1.9, 0.7 Hz, 1H), 4.52 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.1, 148.4, 143.4, 124.5, 108.7, 69.0, 25.8, 18.3, −5.5. IR (neat): ν_{max} = 3133 (w), 2955 (s), 2931 (s), 2887 (m), 2858 (s), 1674 (s), 1563 (s), 1511 (s), 1472 (m), 1464 (m), 1440 (w), 1409 (w), 1390 (m), 1362 (m), 1314 (m), 1287 (w), 1256 (s), 1228 (w), 1154 (s), 1128 (m), 1092 (s), 1069 (w), 1034 (m), 1004 (m), 940 (w), 922 (m). HRMS (EI): calcd for $C_{12}H_{20}O_3Si$ 240.1182, found ($M^+ - CH_3$) 225.0929, actual 225.0947, found ($M^+ - {}^t$Bu) 183.0476, actual 183.0477.

30: *tert*-Butyl-(2-furna-3-yl-allyloxy)-dimethylsilane. To a suspension of methyltriphenylphosphonium iodide (10.50 g, 26.00 mmol) in THF (100 mL) cooled at 0 °C was added KHMDS (5.18 g, 26.0 mmol), and the resulting yellow mixture was stirred at 0 °C for 0.5 h. To this was then added a solution of **29** (4.27 g, 17.6 mmol) in THF (50 mL), followed by stirring at 0 °C for a further 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% EtOAc/Hex) afforded **30** (3.95 g, 16.6 mmol, 93%) as a clear yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.46 (s, 1H), 7.35 (t, J = 1.7 Hz, 1H), 6.52 (dd, J = 1.8, 0.8 Hz, 1H), 5.29 (s, 1H), 5.24 (s, 1H), 4.36 (s, 2H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 142.8, 138.8, 138.6, 124.0, 109.5, 108.1, 64.6, 25.9, 18.3, −5.4. IR (neat): ν_{max} = 2956 (m), 2930 (m), 2886 (m), 2857 (m), 1642 (w), 1511 (w), 1472 (m), 1463 (m), 1390 (w), 1361 (m), 1254 (m), 1167 (w), 1149 (s), 1097 (s), 1068 (s), 1024 (m), 1007 (w), 939 (w), 893 (m), 873 (m), 838 (s), 777 (s), 738 (m), 695 (w), 595 (s). HRMS (EI): calcd for $C_{13}H_{22}O_2Si$ 238.1389, found 238.1386, found ($M^+ - CH_3$) 223.1148, actual 223.1154, found ($M^+ - {}^t$Bu) 181.0678, actual 181.0685.

31: 2-Furan-3-yl-prop-2-en-1-ol. A solution of **30** (3.95 g, 16.6 mmol) in THF (160 mL) was treated with TBAF (8.66 g, 33.1 mmol), and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL), whereupon the layers were separated and the aqueous layer was extracted with Et_2O (3 × 75 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (40% EtOAc/Hex) afforded **31** (1.57 g, 12.6 mmol, 76%) as a clear yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (s, 1H), 7.35 (s, 1H), 6.51 (s, 1H), 5.30 (s, 1H), 5.19 (s, 1H), 4.32 (s, 2H), 2.43 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.1, 138.9, 138.8, 123.8, 110.4, 108.0, 64.6. IR (neat): ν_{max} = 3347 (b), 2935 (m), 2870 (m), 1641 (m), 1560 (w), 1509 (m), 1457 (w), 1418 (w), 1321 (w), 1234 (w), 1165 (s), 1137 (m), 1071 (m), 1045 (s), 1024 (s), 964 (m), 898 (m), 873 (s), 792 (s), 738 (m), 695 (w), 594 (s). HRMS (EI): calcd for $C_7H_8O_2$ 124.0524, found 124.0525.

32: 3-(1-Bromomethyl-vinyl)-furan. To a solution of **31** (1.57 g, 12.6 mmol) in CH_2Cl_2 (100 mL) was added CBr_4 (5.24 g, 15.8 mmol), and the mixture was stirred for 5 min. To this was added a solution of PPh_3 (4.97 g, 18.9 mmol) in CH_2Cl_2 (25 mL). The resulting solution was stirred at room temperature for 2 h, after which the reaction was quenched by the addition of hexanes (300 mL) which produced a white precipitate of triphenylphosphine oxide. The precipitate was removed by repeated filtration through a pad of Celite (3×) followed by concentration under reduced pressure. Flash chromatography (10% EtOAc/Hex) afforded **32** (1.63 g, 8.7 mmol, 69%) as a clear yellow liquid. ^{1}H NMR (C_6D_6, 300 MHz): δ = 7.31 (s, 1H), 6.95 (t, J = 1.7 Hz, 1H), 6.16−6.15 (m, 1H), 5.03 (s, 1H), 4.88 (s, 1H), 3.66 (s, 2H). ^{13}C NMR (C_6D_6, 75 MHz): δ = 143.5, 140.1, 136.5, 124.0, 114.8, 108.4, 33.3. IR (neat): ν_{max} = 3148 (w), 3125 (w), 3095 (w), 2969 (w), 1635 (m), 1584 (w), 1560 (w), 1510 (m), 1443 (w), 1403 (w), 1357 (w), 1322 (w), 1241 (w), 1214 (s), 1175 (w), 1160 (s), 1106 (w), 1072 (s), 1024 (s), 971 (m), 905 (s), 872 (s), 792 (s), 734 (m), 688 (w), 595 (s). HRMS (EI): calcd for C_7H_7BrO 185.9680, found 185.9664.

33: 5-(2-Furan-3-yl-allyloxy)-4-isopropenyl-2,2-dimethyl-5-(1-methylpropenyl)hexahydro-benzo[1,3]dioxole. A mixture of NaI (0.0139 g, 0.0927 mmol) and KH (60% dispersion in oil, 1.7370 g, 13.0 mmol) was washed with hexanes to remove mineral oil and was dried under high vacuum. These solids were suspended in DME (10 mL), and the mixture was cooled to 0 °C whereupon a

solution of **16** (0.4944 g, 1.86 mmol) in DME (10 mL) was added followed by 10 min of stirring. To this mixture was added **32** (1.2621 g, 6.75 mmol), and the mixture was stirred while warming to room temperature for 2 h and then stirred at room temperature for 16 h. The reaction was quenched by adding aqueous saturated NH_4Cl (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% EtOAc/Hex) afforded **33** (0.1489 g, 0.400 mmol, 47%) as a yellow oil. ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.22 (s, 1H), 7.06 (s, 1H), 6.34 (s, 1H), 5.50 (q, J = 6.7 Hz, 1H), 5.44 (s, 1H), 5.33 (s, 1H), 5.06 (s, 1H), 4.98 (dd, J = 9.9, 4.8 Hz, 1H), 4.18−4.17 (m, 1H), 3.87 (d, J_{ab} = 13.5 Hz, 2H), 2.45 (d, J = 10.0 Hz, 1H), 2.08−2.02 (m, 2H), 1.99 (s, 3H), 1.75−1.67 (m, 2H), 1.56 (s, 3H), 1.55 (s, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.38 (s, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ = 144.0, 143.0, 138.4, 137.0, 136.3, 128.0, 142.7, 120.4, 115.0, 109.5, 108.0, 108.5, 84.3, 76.7, 72.9, 62.8, 56.2, 28.8, 26.5, 26.0, 22.6, 13.5, 13.2. IR (neat): ν_{max} = 2983 (m), 2972 (m), 2932 (m), 2872 (w), 1641 (m), 1514 (w), 1500 (w), 1453 (m), 1433 (w), 1379 (m), 1366 (m), 1242 (s), 1216 (s), 1162 (s), 1108 (w), 1060 (s), 1025 (m), 965 (w), 923 (w), 890 (m), 873 (m), 860 (w), 816 (w), 791 (m), 765 (m). HRMS (EI): calcd for $C_{23}H_{32}O_4$ 372.2301, found 372.2299.

34: 6-(2-Furan-3-yl-allyl)-2,2,6,7-tetramethyl-9-methylene-octahydro-naphtho[1,2-*d*][1,3]dioxol-5a-ol. A solution of **33** (0.1172 g, 0.3146 mmol) in toluene (12 mL) was transferred to a microwave cell, whereupon it was degassed by bubbling with argon for 15 min. The resulting solution was heated in a microwave oven (20 min heat ramp to 220 °C followed by 1 h at 220 °C). After cooling, the solution was concentrated and the major product was isolated by flash chromatography (10% EtOAc/Hex) to afford **34** (0.0691 g, 0.186 mmol, 59%) as a yellow oil. ^{1}H NMR (C_6D_6, 300 MHz): δ = 7.47 (s, 1H), 7.04 (t, J = 1.7 Hz, 1H), 6.29 (t, J = 0.9 Hz, 1H), 5.22 (s, 1H), 5.17 (s, 1H), 5.01 (s, 1H), 4.94 (s, 1H), 4.31 (dd, J = 8.8, 5.7 Hz, 1H), 4.12 (q, J = 4.0 Hz, 1H), 2.45−2.31 (m, 3H), 1.97−1.74 (m, 5H), 1.67−1.51 (m, 3H), 1.48 (s, 3H), 1.32 (s, 3H), 0.79 (s, 3H), 0.70 (d, J = 6.5 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz): δ = 145.7, 143.3, 140.3, 139.6, 129.6, 114.9, 110.5, 109.3, 107.7, 78.6, 74.8, 73.2, 48.1, 46.4, 42.0, 39.8, 37.7, 28.7, 26.8, 26.2, 23.1, 17.6, 15.1. IR (neat): ν_{max} = 3552 (b), 2983 (m), 2933 (m), 2873 (w), 1646 (m), 1622 (m), 1561 (m), 1542 (m), 1512 (w), 1457 (m), 1380 (m), 1366 (w), 1244 (s), 1219 (s), 1162 (s), 1052 (s), 1017 (m), 964 (w), 934 (w), 889 (s), 872 (s), 839 (m), 793 (m), 729 (m). HRMS (EI): calcd for $C_{23}H_{32}O_4$ 372.2301, found 372.2280, found $M^+ - CH_3$ 354.2200, calcd 354.2195.

35: 2-Furan-3-yl-2-hydroxy-3a,4,8,8-tetramethyl-octahydro-1,7,9-tridicyclopenta[*d*,*h*]naphthalene-6-one. To a solution of **34** (0.0100 g, 0.0268 mmol) in a 5:1 mixture of THF/H_2O (3 mL) was added NMO (0.0126 g, 0.108 mmol) followed by OsO_4 (4% solution in H_2O, 0.02 mL, 0.00314 mmol), and the mixture was stirred at room temperature for 4 h. After this, solid $NaIO_4$ (0.0689 g, 0.322 mmol) was added to the mixture, which was stirred for a further 16 h. The reaction was quenched by the addition of saturated Na_2SO_3 followed by 0.5 h of vigorous stirring. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (60% EtOAc/Hex) afforded **35** (0.0073 g, 0.0194 mmol, 72%) as a white solid. Mp: 166−167 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.50 (d, J = 0.07 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 6.31 (s, 1H), 5.19 (dd, J = 8.8, 5.2 Hz, 1H), 4.44−4.42 (m, 1H), 2.64 (d, J = 8.9 Hz, 1H), 2.38 (s, 1H), 2.25−2.15 (m, 3H), 2.05−1.92 (m, 3H), 1.87−1.81 (m, 1H), 1.66 (s, 2H), 1.61 (s, 3H), 1.52 (s, 3H), 0.73 (s, 3H), 0.45 (d, J = 6.8 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ = 205.9, 143.5, 139.6, 133.0, 128.3, 108.8, 107.7, 101.6, 92.9, 72.9, 55.5, 49.2, 48.9, 45.7, 38.2, 29.2, 28.0, 26.6, 23.0, 16.7, 12.6. IR (neat): ν_{max} = 3411(b), 2981 (m), 2934 (m), 2878 (m), 1722 (s), 1659 (w), 1502 (w), 1459 (m), 1429 (w), 1380 (m), 1244 (m), 1216 (m), 1160 (m), 1103 (w), 1054 (s), 1005 (m), 990 (m), 950 (w), 914 (w), 904 (w), 874 (m), 806 (m), 733 (m), 602 (w). HRMS (EI): calcd for $C_{21}H_{28}O_6$ 376.1886, found ($M^+ - H_2O$) 358.1791, actual 358.1780.

36: 2-Furan-3-yl-7,8-dihydroxy-2-methoxy-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[*d*]naphthalene-6-one. A solution of **35** (0.0345 g, 0.0916 mmol) in MeOH (5 mL) was treated with PTSA (0.0017 g, 0.00916 mmol), and the resulting solution was stirred at room temperature for 1 h. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (80% EtOAc/Hex) afforded **36** (0.0306 g, 0.0873 mmol, 95%) as a white solid. Mp: 160−161 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.48 (d, J = 0.7 Hz, 1H), 7.09 (t, J = 1.7 Hz, 1H), 6.20−6.19 (m, 1H), 4.60 (dd, J = 9.9, 2.6 Hz, 1H), 4.29−4.28 (m, 1H), 4.18 (s, 1H), 3.03 (s, 3H), 2.85 (d, J = 9.9 Hz, 1H), 2.24 (s, 2H), 2.21−2.15 (m, 1H), 2.10−2.04 (m, 2H), 2.00−1.92 (m, 3H), 1.81−1.75 (m, 2H), 0.73 (s, 3H), 0.43 (d, J = 6.8 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ = 212.8, 143.9, 141.1, 129.0, 108.9, 105.1, 93.4, 69.6, 68.1, 52.9, 50.7, 50.1, 48.1, 45.2, 37.3, 27.6, 26.0, 16.5, 12.6. IR (neat): ν_{max} = 3450 (b), 2966 (s), 2935 (s), 2882 (m), 2826 (w), 1712 (s), 1503 (m), 1461 (m), 1437 (m), 1384 (m), 1341 (m), 1305 (m), 12870 (m), 1252 (w), 1196 (w), 1158 (m), 1139 (m), 1064 (s), 1031 (s), 978 (s), 957 (m), 930 (w), 873 (m), 805 (m), 676 (w). HRMS (EI): calcd for $C_{19}H_{26}O_6$ 350.1729, found 350.1709, found ($M^+ - OCH_3$) 319.1534, actual 319.1545.

37: 2-Furan-3-yl-2-methoxy-3a,4-dimethyl-octahydro-1,7,9-trioxa-dicyclopenta[*d*,*h*]naphthalene-6,8-dione. To a solution of pyridine (0.06 mL, 0.796 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C was added triphosgene (0.0354 g, 0.119 mmol) followed by 10 min of stirring. To this mixture was added a solution of **36** (0.0279 g, 0.0796 mmol) in CH_2Cl_2 (5 mL) followed by stirring at 0 °C for 0.5 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% EtOAc/Hex) afforded **37** (0.0300 g, 0.0796 mmol, 100%) as a white solid. Mp: 189−190 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.40 (s, 1H), 7.06 (s, 1H), 6.10 (s, 1H), 5.24 (dd, J = 9.2, 6.2 Hz, 1H), 4.15−4.14 (m, 1H), 2.28 (s, 3H), 2.37 (d, J = 9.4 Hz, 1H), 2.08−2.02 (m, 1H), 2.07 (dd, J_{ab} = 13.6 Hz, 2H), 1.91−1.87 (m, 2H), 1.75−1.70 (m, 2H), 1.64 (t, J = 13.3 Hz, 1H), 1.44−1.37 (m, 1H), 0.50 (s, 3H), 0.36 (d, J = 6.8 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ = 203.9, 154.8, 144.1, 141.1, 128.3, 108.6, 105.8, 91.6, 75.1, 73.9, 53.5, 50.9, 49.7, 48.4, 44.7, 37.9, 27.3, 22.1, 16.4, 12.4. IR (neat): ν_{max} = 2963 (m), 2939 (m), 2887 (m), 1806 (s), 1717 (s), 1550 (w), 1453 (m), 1421 (m), 1385 (m), 1361 (w), 1318 (m), 1292 (w), 1232 (w), 1140 (m), 1123 (m), 1107 (w), 1048 (s), 1027 (s), 999 (w), 946 (m), 920 (m), 871 (m), 804 (m), 771 (m). HRMS (EI): calcd for $C_{20}H_{24}O_7$ 376.1522, found 376.1520, found ($M^+ - OCH_3$) 345.1397, actual 345.1337.

38: 2-Furan-3-yl-8-hydroxy-2-methoxy-3a,4-dimethyl-3,-3a,4,5,9,10-hexahydro-2*H*,8*H*-a-oxa-cyclopenta[*d*]naphthalene-6-one. To a solution of **37** (0.0116 g, 0.0308 mmol) in benzene (3 mL) was added DBU (0.04 mL, 0.267 mmol), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (80% EtOAc/Hex) afforded **38** (0.0100 g, 0.0301 mmol, 98%) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz): δ = 7.27 (q, J = 0.8 Hz, 1H), 6.97 (t, J = 1.7 Hz, 1H), 6.94 (dd, J = 4.3, 1.5 Hz, 1H), 6.13−6.12 (m, 1H), 3.92−3.89 (m, 1H), 3.05 (s, 3H), 2.33 (dd, J_{ab} = 13.6 Hz, 2H), 2.23−2.13 (m, 3H), 2.11−2.06 (m, 1H), 1.94−1.80 (m, 2H), 1.73−1.64 (m, 2H), 0.67 (s, 3H), 0.41 (d, J = 6.8 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ = 198.5,

143.8, 141.0, 140.3, 137.3, 128.8, 109.0, 105.1, 85.8, 63.2, 51.5, 50.4, 48.3, 43.6, 32.8, 27.2, 26.3, 15.8, 14.0. IR (neat): ν_{max} = 3414 (b), 2971 (m), 2943 (m), 2891 (m), 2830 (w), 1694 (s), 1624 (m), 1502 (w), 1461 (m), 1409 (m), 1377 (w), 1337 (w), 1317 (w), 1280 (m), 1196 (w), 1159 (m), 1103 (w), 1073 (m), 1042 (s), 993 (m), 964 (s), 927 (m), 873 (m), 803 (m). HRMS (EI): calcd for $C_{19}H_{24}O_5$ 332.1624, found ($M^+ - H_2O$) 314.1518, actual 314.1508, found ($M^+ - OCH_3$) 301.1439, actual 301.1439.

39: 2-Furan-3-yl-2-methoxy-3a,4-dimethyl-8-triethylsilanyloxy-3,3a,4,5,9,10-hexahydro-2*H*,8*H*-1-oxa-cyclopenta[*d*]-naphthalen-6-one. A solution of **38** (0.0114 g, 0.0342 mmol) in THF (5 mL) was treated with Et_3N (0.05 mL, 0.359 mmol), DMAP (0.0004 g, 0.00342 mmol), and TESCl (0.01 mL, 0.0595 mmol), and the resulting solution was stirred at room temperature for 18 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, the aqueous phase was extracted with Et_2O (3 × 10 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography afforded **39** (0.0148 g, 0.0331 mmol, 97%) as a colorless oil. ^{1}H NMR (d_6-acetone, 500 MHz): δ = 7.52 (t, J = 1.7 Hz, 1H), 7.40 (d, J = 0.7 Hz, 1H), 6.64 (dd, J = 4.2, 1.5 Hz, 1H), 6.32 (d, J = 1.0 Hz, 1H), 4.43−4.41 (m, 1H), 3.01 (s, 3H), 2.62 (d, J_{ab} = 13.7 Hz, 1H), 2.36 (d, J_{ab} = 13.7 Hz, 1H), 2.30−2.13 (m, 5H), 1.93 (dt, J = 13.1, 3.0 Hz, 1H), 1.78−1.75 (m, 1H), 1.09 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.65 (q, J = 7.9 Hz, 6H). ^{13}C NMR (d_6-acetone, 125 MHz): δ = 200.1, 145.2, 142.0, 141.4, 138.1, 130.0, 110.4, 106.3, 87.0, 65.1, 52.3, 51.1, 49.6, 44.5, 34.0, 29.2, 27.4, 16.8, 14.9, 7.7, 6.0. IR (neat): ν_{max} = 2957 (s), 2915 (m), 2877 (m), 2822 (w), 1698 (s), 1631 (m), 1559 (w), 1458 (m), 1251 (m), 1200 (w), 1159 (m), 1103 (w), 1075 (m), 1043 (s), 1010 (m), 972 (s), 946 (m), 925 (m), 874 (m), 803 (m), 745 (m), 728 (m). HRMS (EI): calcd for $C_{25}H_{38}O_5Si$ 446.2489, found 446.2494, found ($M^+ - Et$) 417.2115, actual 417.2097.

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Supporting Information Available: Spectral data for all new compounds (^{1}H and ^{13}C NMR, IR, HRMS) and general experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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