Oxonium Ion-Initiated Pinacolic Ring Expansion Reactions. Application to the Enantioselective Synthesis of the Spirocyclic Sesquiterpene Ethers Dactyloxene-B and -C

Marc D. Lord, Joanna T. Negri, and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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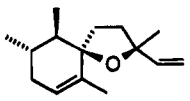
A convergent synthesis of dactyloxene-B (**1**) and -C (**2**) from a common optically active intermediate in seven steps has been achieved. Ozonolysis of (*R*)-(−)-linalool proceeded regioselectively to deliver a lactol, the benzoate of which when thermolyzed gave dihydrofuran **7**. The second building block, levorotatory cyclopentanone **8**, was produced by kinetically controlled lipase-induced hydrolysis of chloroacetate **15b**. Saponification and oxidation of the less reactive ester was sufficient to provide (−)-**8** whose condensation with the cerate of **7** gave rise to **19** and set the stage for implementation of the key structural rearrangement step. When stirred with Dowex resin, **19** was isomerized to four ketones. Following chromatographic separation, **20** and **21** were independently transformed into the target molecules via a two-step sequence. The spectral and optical properties of the two dactyloxenes compared very favorably with those reported earlier.

More than a decade ago, Schmitz and his co-workers succeeded in isolating from the sea hare *Aplysia dactylomela* the spirocyclic tetrahydrofuranyl ethers dactyloxene-B (**1**)[1] and dactyloxene-C (**2**).[2] These marine metabolites were subsequently accorded considerable attention by the Firmenich Co.[3] because of their close structural relationship to the theaspiranes (**3** and **4**), components of raspberry,[4] passion fruit,[5] tea,[6] and vanilla[7] valued for their tang and aroma. Several synthetic routes to the latter pair of molecules have consequently been devised as well.[8]



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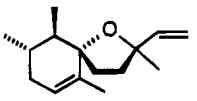

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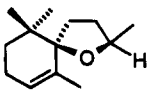

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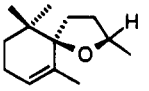

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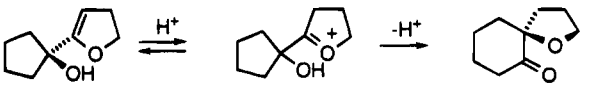
Our laboratory has been engaged in studying the response of tertiary allylic alcohols such as **5** to acidic conditions. Strikingly, allyl cation formation is skirted in favor of oxonium ion generation, thereby setting the stage for ring expansion if strain release is realized.[9] Should the dihydrofuran subunit in **5** contain preexisting chirality, the issue of diasterofacial preference requires consideration. If the ring involved in the Wagner-

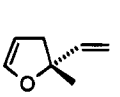


5 **6**

Meerwein 1,2-shift is unsymmetrically substituted, the matter of migratory aptitude must also be addressed. Although these fundamental issues are presently under active investigation, we have forged ahead to evaluate the utility of this rearrangement in the context of natural products synthesis by undertaking enantioselective syntheses of **1** and **2** from a common optically active intermediate. The details of this investigation are presented herein.[10]

Results and Discussion

Our retrosynthetic plan was based on the preparation of (2*R*)-2,3-dihydro-2-methyl-2-vinylfuran (**7**) and (2*R*,3*S*)-2,3-dimethylcyclopentanone (**8**) prior to their coupling. Initially, the source of **7** was envisaged to be the known lactone **13**,[11] the stereogenicity of which derives from the



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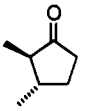

8

natural oil (*R*)-(−)-linalool (**9**, Scheme 1). When **9** was treated with freshly recrystallized NBS in CCl_4,[12] a mixture of diastereomeric tertiary bromides **10** was

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1994.

(1) Schmitz, F. J.; McDonald, F. J. *Tetrahedron Lett.* **1974**, 2541.

(2) Schmitz, F. J.; McDonald, F. J.; Vanderah, D. J . *J. Org. Chem.* **1978**, *43*, 4220.

(3) (a) Maurer, B.; Hauser, A.; Thommen, W.; Schulte-Elte, K. H.; Ohloff, G. *Helv. Chim. Acta* **1980**, *63*, 293. (b) Maurer, B.; Hauser, A.; Ohloff, G. *Helv. Chim. Acta* **1980**, *63*, 2503.

(4) Winter, M.; Enggist, P. *Helv. Chim. Acta* **1971**, *54*, 1891.

(5) Winter, M.; Klöti, R. *Helv. Chim. Acta* **1972**, *55*, 1916.

(6) Renold, W.; Näf-Müller, R.; Keller, U.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1974**, *57*, 1301.

(7) Naegeli, P. D.O.S. 2610238 (Sept 23, 1976); *Chem. Abstr.* **1977**, *86*, P95876c.

(8) (a) Ohloff, G.; Rautenstrauch, V.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1973**, *56*, 1503. (b) Bellas, T. E.; Brownlee, R. G.; Silverstein, R. M. *Tetrahedron* **1974**, *30*, 2267. (c) Okawara, H.; Kobayashi, S.; Ohno, M. *Heterocycles* **1979** *13*, 191. (d) Torii, S.; Unemaya, K.; Nakai, T.; Yasuda, T. *Tetrahedron Lett.* **1981**, *22*, 2291. (e) Masuda, H.; Mihara, S. *Agric. Biol. Chem.* **1985**, *49*, 861.

(9) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

(10) Preliminary report: Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693.

(11) Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* **1987**, 1175.

(12) Demole, E.; Enggist, P. *Helv. Chim. Acta* **1971**, *54*, 456.

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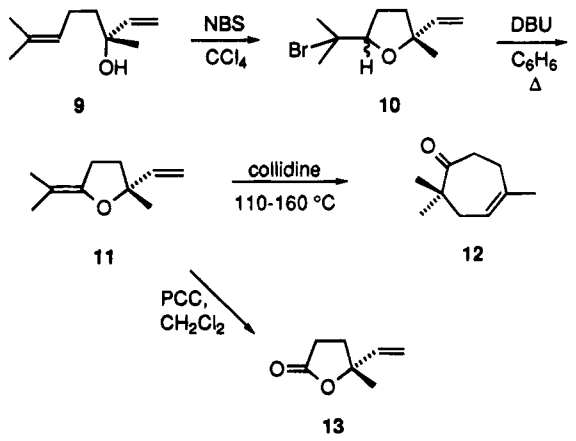
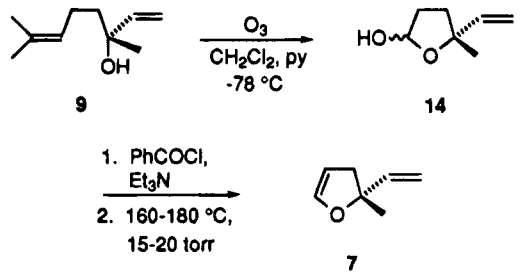
Scheme 1



Scheme 2

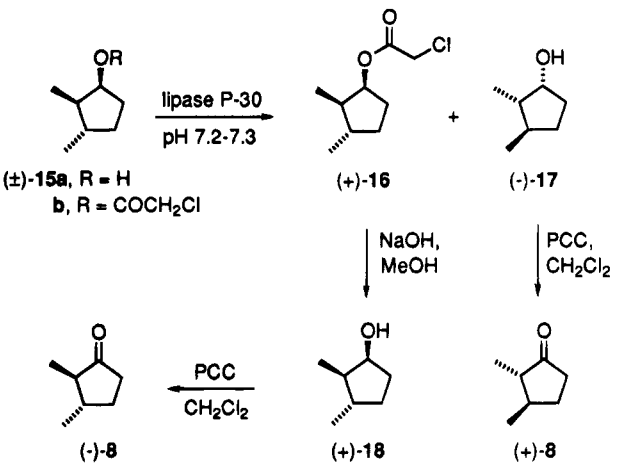


isolated in 67% yield after distillation. Initial attempts to dehydrobrominate **10** with collidine[12] proved sluggish and required temperatures in the range of 110–160 °C. Under these conditions, the desired **11** was transformed into the seven-membered ketone **12** by [3,3] sigmatropy. This unwelcomed event could be skirted by making recourse instead to 1.5 equiv of DBU in refluxing benzene.[13] The ensuing oxidation of **11** to **13** with PCC in CH_2Cl_2 has been reported to proceed in 90% yield.[11] Several modifications[14] of this reagent were examined; in no instance was greater than 25% of **13** formed and purification proved difficult to implement. This tactic was therefore abandoned.

At this point, we investigated instead the possibility of regiocontrolled ozonolysis of **9**.[15] By performing this reaction at −78 °C in CH_2Cl_2–pyridine as solvent,[16] the more electron-rich double bond was indeed attacked preferentially to deliver **14** as a mixture of diastereomers in a 1:1 ratio (Scheme 2). Best results (68% of **14**) were obtained if overoxidation was minimized by carrying the bond cleavage to approximately 65–70% completion. The unreacted linalool could be recovered quantitatively and recycled.

Mindful of the success enjoyed by Sosnovsky[17] and others in promoting dehydration by ester pyrolysis, we transformed **14** into its benzoate and heated it to 160–180 °C at 15–20 Torr in a Kugelrohr apparatus. Although the conversion to **7** proceeded smoothly, the high volatility of this dihydrofuran resulted in modest losses in its recovery. Unoptimized yields often fell in the 50%

Scheme 3



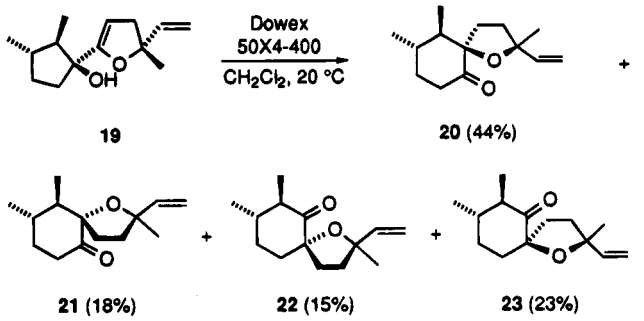
range. The specific rotation recorded for **7** was $[\alpha]^{20}_D$ +0.42° (*c* 0.74, $CHCl_3$).[18]

Having obtained **7** in three steps, we proceeded to produce **8** in acceptable fashion. This levorotatory ketonic building block, known in racemic form,[19] was accessed by controlled reduction to (±)-**15a** with L-Selectride[20] and conversion to chloroacetate **15b** in advance of its hydrolysis with lipase P-30[21] (Scheme 3). This enantioselective process, when allowed to proceed to the 54% level, returned the slower reacting 1*S*,2*R*,3*S* ester **16** in optically enriched condition. Following its saponification to (+)-**18**, the alcohol was judged to be of 79% ee by Mosher ester analysis.[22] The absolute configurations of **8**, **17**, and **18** were assigned on the strength of Varech's earlier investigation of these compounds.[23]

With both **7** and **8** in hand, their coupling was realized by deprotonation of the vinyl ether with *tert*-butyllithium[24] and transmetalation with anhydrous cerium trichloride[25] prior to introduction of the ketone. The reduced basicity of the organocerate curtails simple enolization, thereby fostering efficient 1,2-addition.[26,27] Alcohol **19** was not purified because of its expected sensitivity; its direct admixture with Dowex-50 × 4-400 resin in CH_2Cl_2 at 20 °C for 2 days provided in 63% overall yield the four chromatographically separable spirocyclic ketones identified as **20**–**23** (Scheme 4). The

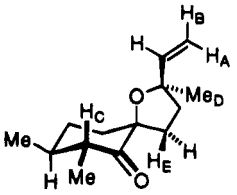
(13) Jäger, V.; Günther, H. *J. Tetrahedron Lett.* **1977**, 2543.
(14) For example: Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. *Synthesis* **1980**, 223.
(15) Ozonolysis of the TMS-ether of **9** has previously been reported: Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1978**, 297.
(16) Slomp, G., Jr.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.
(17) Sosknovsky, G. *Tetrahedron* **1961**, *13*, 241.
(18) The commercial sample of linalool used in this study was of 96.5% purity and exhibited $[\alpha]^{20}_D$ −16.4°. After preparative GC purification, the specific rotation was raised to only −16.8°. Recorded values for **9** are −19.7° [12] and -20.1° [*Merck Index*, 11th ed.; Merck Rahway, NJ, 1989; p 5375].
(19) Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2662.
(20) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885.
(21) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1.
(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(23) Varech, D.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1965**, 1662.
(24) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187. (b) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107 and relevant references cited therein.
(25) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed.; John Wiley and Sons, Chichester, England, in press.
(26) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(27) (a) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879. (b) Paquette, L. A. DeRussy, D. T.; Cottrell, C. E. *J. Am. Chem. Soc.* **1988**, *110*, 890. (c) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291.

Scheme 4

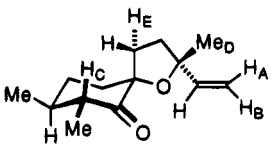


indicated structural assignments follow on the basis of NOE studies and the subsequent conversion of **20** and **21** to **1** and **2**, respectively.

More specifically, ketone **22** was distinguished from its diastereomer **23** by performing a double irradiation of H_A positioned at δ 4.98 in $CDCl_3$. The following integral enhancements were seen: 9% at H_B, 2% at H_C, and 1% at Me_D (see **A**). The diagnostic NOE effect is at H_C since irradiation of H_A in **23** would not have produced the same observation (see **B**). Further, the diaxial interactions involving H_C and the oxygen of the tetrahydrofuran ring as well as H_E and the carbonyl oxygen in **A** results in significant deshielding of these protons (δ 2.82 and 2.60, respectively). Similar interactions are not possible in **B**, resulting in more upfield shifts for these alicyclic protons (above δ 2.10).[28]

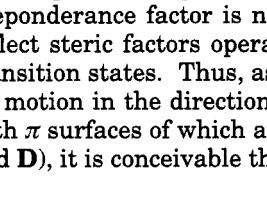


A

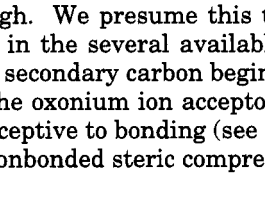


B

The relative proportions of **20** + **21** and **22** + **23** are indicative that the secondary carbon in **19** migrates to the electron-deficient center only somewhat more effectively than the methylene carbon. Although this ordering is as expected on electronic grounds,[29] the preponderance factor is not high. We presume this to reflect steric factors operating in the several available transition states. Thus, as the secondary carbon begins its motion in the direction of the oxonium ion acceptor, both π surfaces of which are receptive to bonding (see **C** and **D**), it is conceivable that nonbonded steric compression begins to materialize between the methyl substituent on the migrating center and those substituents adjacent to positively charged oxygen. Since a methyl–methyl interaction is likely to be less costly than methyl–vinyl compression, the transition state related to **C** is followed more readily (by a factor of 2) to produce greater levels of **20** than **21**. The endothermicity required of these two pathways is clearly sufficient to allow methylene migration to be kinetically competitive. When this occurs, the relative steric bulk of the substituents flanking the electrophilic center is not as clearly distinguished (approximately equal amounts of **22** and **23**).

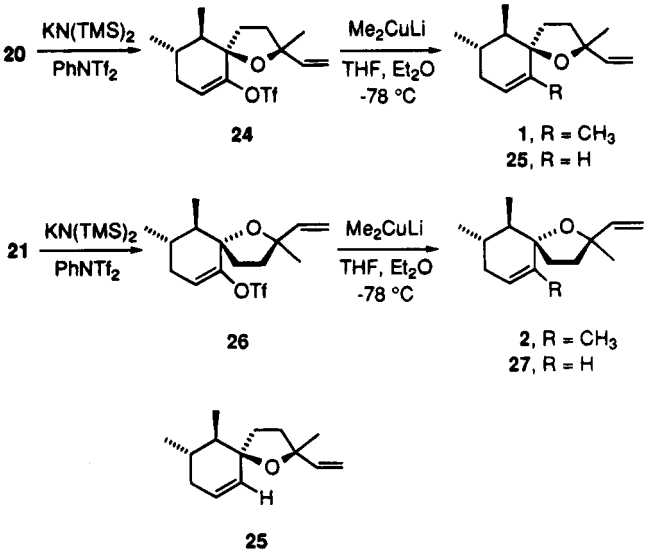


C



D

Scheme 5



Scheme 5 outlines the completion of the synthesis of both spirocyclic ethers. Following independent conversion of **20** and **21** to their enolate anions, exposure to *N*-phenyltriflimide led to the enol triflates **24** and **26**, respectively.[30] These intermediates were reacted in turn with lithium dimethylcuprate in order to effect carbon–carbon bond formation.[31] The latter reaction was considered to be an interesting test of its efficacy, since the seats of substitution in **24** and **26** are neopentyl-like and therefore rather excessively crowded. Notwithstanding, **1** and **2** were indeed formed satisfactorily under these conditions. The congestion was not without consequences, however, since **25** and **27**, products of simple reductive cleavage of the C–O bond, also made their appearance. Separation of each mixture was readily accomplished by medium pressure liquid chromatography (MPLC) on silica gel. Through direct comparison of spectral properties, it was possible to assert with confidence that dactyloxenes-B and -C had been synthesized. Furthermore, the respective $[\alpha]_D$ values determined for **1**, +105.6° (*c* 0.65, $CHCl_3$), and for **2**, +42.6° (*c* 0.72, $CHCl_3$) compare closely to specific rotations previously recorded.[32]

Construction of the natural dactyloxenes has therefore been accomplished in seven steps from (*R*)-(−)-linalool by way of a common intermediate. The spirocyclic nature of both sesquiterpenes was established by oxonium ion-initiated pinacol rearrangement, thus extending the scope of this reaction to include enantioenriched structural components. The results suggest that the Wagner–Meerwein step is sensitive to preexisting substitution in

(28) For spectral information on related systems, see Klemeyer, H. J.; Paquette, L. A. *J. Org. Chem.*, in press and relevant references cited therein.

(29) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956.

(30) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

(31) (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. (b) Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676.

(32) Dactyloxene-B: 106° (*c* 0.74, $CHCl_3$);[1] +110.2° (*c* 0.74, $CHCl_3$);[2] +111.6° (*c* 1.3, $CHCl_3$).[3b] Dactyloxene-C: +45.6° (*c* 0.9, $CHCl_3$);[2] +48.8° (*c* 1.3, $CHCl_3$).[3b]

both the donor and acceptor regions of the cationic intermediate. It is expected that these lessons will be fruitfully applied to future synthetic endeavors involving this chemistry.

Experimental Section

Mass spectra were measured at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All flash chromatographic separations were carried out on Merck silica 60 (60–200 mesh). MPLC purifications were accomplished on Merck Lichroprep Si 60 columns. All reactions were routinely performed under a nitrogen atmosphere. Solvents were reagent grade and dried prior to use.

(5*R*)-Tetrahydro-5-methyl-5-vinyl-2-furanol (14). A solution of (*R*)-(−)-linalool[18] (51.0 g, 330.6 mmol) in CH_2Cl_2 (2700 mL) and pyridine (80 mL) was stirred mechanically in a Morton flask and cooled to −78 °C. Ozone was bubbled through the reaction mixture for 4 h. After purging with O_2 and the slow addition of methyl sulfide via syringe, the solution was allowed to warm slowly to rt overnight, washed successively with brine, aqueous $CuSO_4$ solution, brine, and water, and then dried and concentrated. The residual brown oil was purified by flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 29.01 g (68%) of **14** as a colorless liquid (1:1 diastereomeric mixture). The unreacted linalool was recovered quantitatively (32%).

For **14**: IR (neat, cm^{-1}) 3420, 1640, 1350–1345, 1000; ^1H NMR (300 MHz, C_6D_6) δ 6.08 (dd, J = 17.4, 10.7 Hz, 0.5 H), 5.66 (dd, J = 17.1, 10.6 Hz, 0.5 H), 5.52 (m, 1 H), 5.29 (dd, J = 17.4, 1.4 Hz, 0.5 H), 5.16 (dd, J = 17.1, 1.8 Hz, 0.5 H), 4.96 (dd, J = 10.7, 1.4 Hz, 0.5 H), 4.87 (dd, J = 10.6, 1.8 Hz, 0.5 H), 4.46 (s, 1 H), 1.93–1.54 (m, 4 H), 1.42 (s, 1.5 H), 1.14 (s, 1.5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 145.5, 143.9, 111.7, 111.2, 99.1, 99.0, 84.4, 84.1, 36.0, 35.6, 33.4, 33.1, 28.4, 26.2; MS m/z (M^+ − OH) calcd 111.0810, obsd 111.0785.

(*R*)-2,3-Dihydro-2-methyl-2-vinylfuran (7). A solution of **14** (19.68 g, 154 mmol) in CH_2Cl_2 (100 mL) containing freshly distilled triethylamine (68.4 mL, 490 mmol) was cooled to 0 °C, treated dropwise with benzoyl chloride (19.6 mL, 169 mmol), and stirred at 0 °C overnight. The reaction mixture was poured onto cold $NaHCO_3$ solution and the separated organic layer was washed with 0.1 M HCl, saturated $NaHCO_3$ solution, and brine prior to drying and concentration.

The residual brown oil (42.4 g) was heated to 160–180 °C at 15–20 Torr for 2 h in a Kugelrohr apparatus. The volatile yellowish oil that was collected was further purified by bulb-to-bulb distillation (70 °C and 10 Torr) to furnish 7.90 g (47%) of **7** as a colorless liquid: IR (neat, cm^{-1}) 1620, 1450–1375; ^1H NMR (300 MHz, C_6D_6) δ 6.14 (m, 1 H), 5.86 (dd, J = 17.2, 10.7 Hz, 1 H), 5.22 (dd, J = 17.2, 1.3 Hz, 1 H), 4.91 (dd, J = 10.7, 1.3 Hz, 1 H), 4.56 (m, 1 H), 2.40 (dt, J = 15.0, 2.3 Hz, 1 H), 2.19 (dt, J = 15.0, 2.3 Hz, 1 H), 1.29 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 144.7, 142.9, 111.5, 97.9, 85.7, 41.8, 26.3; MS m/z (M^+) calcd 110.0732, obsd 110.0723. Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.59; H, 9.17.

(±)-(1*R,2*S**,3*R**)-2,3-Dimethylcyclopentanol (15a).** A cold (-78 °C) solution of racemic 2,3-dimethylcyclopentanone[19] (9.64 g, 85.9 mmol) in anhydrous THF was treated dropwise during 1 h with L-Selectride (94 mL of 1.0 M in THF, 94 mmol), stirred at −78 °C for 45 min and at rt for the same amount of time. The reaction mixture was returned to 0 °C, treated sequentially with water (25 mL), ethanol (50 mL), and 30% hydrogen peroxide (100 mL over 30 min), and then saturated with K_2CO_3 and stirred overnight at rt. The resulting slurry was filtered, extracted with a 1:1 THF–ether mixture, dried, and concentrated. Kugelrohr distillation (80–100 °C, 30 Torr) of the residue gave (±)-**15a** as a colorless liquid (8.58 g, 87%): IR (neat, cm^{-1}) 3380; ^1H NMR (300 MHz, C_6D_6) δ 3.62 (m, 1 H), 1.91 (m, 1 H), 1.83–1.67 (m, 2 H), 1.49 (m, 1 H), 1.04–0.94 (m, 3 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 76.5, 47.8, 38.2, 34.1, 32.3, 19.0, 12.2; MS m/z (M^+ − OH) calcd 97.1017, obsd 97.1003.

(±)-(1*R,2*S**,3*R**)-2,3-Dimethylcyclopentyl Chloroacetate (15b).** A magnetically stirred solution containing **15a** (6.73 g, 58.9 mmol), freshly distilled triethylamine (12.3 mL, 88.4 mmol), and DMAP (0.02 g) in CH_2Cl_2 (150 mL) was treated dropwise with choroacetyl chloride (7.04 mL, 88.4 mmol) and stirred overnight at rt. The mixture was quenched with water, washed with $NaHCO_3$ solution, dried, and concentrated to leave a brown oil. Purification by flash chromatography on silica gel (elution with 25% ether in petroleum ether) gave **15b** (10.86 g, 97%) as a faintly yellow liquid; IR (neat, cm^{-1}) 1750, 1455–1380, 1190; ^1H NMR (300 MHz, C_6D_6) δ 5.11 (m, 1 H), 3.50 (s, 2 H), 1.71 (m, 2 H), 1.50 (m, 2 H), 1.05 (m, 1H), 0.86–0.78 (m, 1 H), 0.82 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 166.5, 81.2, 46.2, 40.9, 39.0, 32.1, 31.3, 18.5, 12.1; MS m/z (M^+) calcd 190.0760, obsd 190.0774.

Lipase-Catalyzed Kinetic Resolution. Racemic **15b** (5.49 g, 28.79 mmol) and water (150 mL) was stirred vigorously with pH 7.00 phosphate buffer (25 mL) and lipase P-30 (Amano, 150 mg). A syringe charged with 0.5 M NaOH (31.67 mL, 15.8 mmol) connected to a syringe pump was adjusted to exit into the reaction flask. The pH of the mixture was maintained between 7.23–7.32 by controlled additon of the NaOH solution as regulated by a pH-stat. After 6 h, all of the NaOH had been added and GC analysis confirmed that 47% hydrolysis had occurred. Following extraction (3x) into ether, the combined organic phases were filtered through a pad of Celite, dried, and evaported. Flash chromatography of the residue on silica gel (elution with 5% ether in petroleum ether) furnished **17** (1.57 g), $[\alpha]^{23}_D$ −61.3° (*c* 1.1, $CHCl_3$) and unreacted chloroacetate (2.56 g, 89%), $[\alpha]^{23}_D$ +67.5° (*c* 1.6, $CHCl_3$).

This ester (2.56 g, 13.43 mmol) was dissolved in methanolic sodium hydroxide (13.5 mL of 3 M NaOH in 27 mL of MeOH, 40.3 mmol of base) and stirred for 4 h at rt. The pH of this mixture was returned to 7 by dropwise addition of 3 M H_2SO_4. The product was extracted into CH_2Cl_2 and the combined organic layers were washed with $NaHCO_3$ solution, dried, and concentrated to give **18** (1.53 g, 100%); $[\alpha]^{23}_D$ +49.4° (*c* 1.4, $CHCl_3$).

Alcohol **18** (1.53 g, 13.39 mmol) was dissolved in CH_2Cl_2 (25 mL), treated with pyridinium chlorochromate (4.33 g, 20.09 mmol) and stirred at rt for 24 h. The mixture was diluted with ether, filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by Kugelrohr distillation (50–70 °C at 15 Torr) to give 1.21 g (81%) of (−)-**8**, $[\alpha]^{23}_D$ −137.2° (*c* 2.5, $CHCl_3$).

Entirely comparable oxidation of (−)-**17** (0.20 g, 1.75 mmol) afforded (+)-**8** (0.17 g, 85%), $[\alpha]^{23}_D$ +152.5° (*c* 2.0, $CHCl_3$).

Coupling and Pinacolic Rearrangement. Cerium trichloride heptahydrate (5.0 g, 13.4 mmol) was dried (20 ° → 140 °C, 0.1 Torr)[25] and slurried in anhydrous THF (20 mL) for 2 h at rt. Meanwhile, a solution of **7** (1.20 g, 10.9 mmol) in THF (5 mL) was cooled to −78 °C, treated with *tert*-butyllithium (7.0 mL of 1.7 M, 11.9 mmol), and stirred for 1 h. The $CeCl_3$ slurry was also cooled to −78 °C and *tert*-butyllithium was added dropwise until a peach color persisted (1–2 mL). The solution containing lithiated **7** was next introduced via cannula to give a yellow color. A solution of (−)-**8** (0.60 g, 5.35 mmol) in THF (2 mL) was added and the mixture was stirred at −78 °C for 3 h before being allowed to warm slowly to rt overnight. Saturated NH_4Cl solution was added, the mixture was filtered through Celite, and the filtrate was dried and concentrated.

The resulting yellow oil was dissolved in CH_2Cl_2 (25 mL) and stirred with Dowex 50 × 4-400 resin (1.2 g) for 2 days. This slurry was concentrated, diluted with 10% ether in petroleum ether, filtered through silica gel, and evaporated to leave a yellow oil (0.75 g, 63%). Ketones **20–23**, which were the major constituents of this oil, were obtained isomerically pure by MPLC and HPLC on silica gel (elution with 5% ether in petroleum ether).

For **20**: colorless oil; IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, C_6D_6) δ 5.71 (dd, J = 17.3, 10.7 Hz, 1 H), 5.03 (dd, J = 17.3, 1.3 Hz, 1 H), 4.83 (dd, J = 10.7, 1.3 Hz, 1 H), 3.09 (ddd,

J = 14.4, 11.8, 6.0 Hz, 1 H), 2.80 (m, 1 H), 2.22 (ddd, J = 11.8, 4.0, 2.8 Hz, 1 H), 1.78 (m, 2 H), 1.60 (m, 1 H), 1.45 (m, 2 H), 1.20 (s, 3 H), 0.92–0.82 (m, 2 H), 0.85 (s, 3 H), 0.68 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.1, 144.3, 111.8, 90.3, 84.3, 48.4, 38.5, 37.9, 36.1, 33.8, 27.5, 26.7, 19.8, 12.6; MS m/z (M^+) calcd 222.1620, obsd 222.1630; $[\alpha]^{23}_D$ −39.9° (c 3.5, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 76.09; H, 10.10.

For **21**: colorless oil; IR (neat, cm^{-1}) 1730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, J = 17.5, 10.8 Hz, 1 H), 5.19 (dd, J = 17.5, 1.3 Hz, 1 H), 4.99 (dd, J = 10.8, 1.3 Hz, 1 H), 2.49 (m, 2 H), 2.05 (m, 1 H), 1.97–1.84 (m, 3 H), 1.76–1.53 (m, 4 H), 1.37 (s, 3 H), 1.01 (d, J = 6.1 Hz, 3 H), 0.97 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.4, 143.8, 111.4, 92.0, 83.9, 47.8, 38.5, 36.2, 36.1, 34.4, 29.2, 26.6, 19.7, 13.2; MS m/z (M^+) calcd 222.1620, obsd 222.1615; $[\alpha]^{23}_D$ −31.5° (c 0.63, $CHCl_3$).

For **22**: colorless oil; IR (neat, cm^{-1}) 1717; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (dd, J = 17.3, 10.7 Hz, 1 H), 4.98 (dd, J = 17.3, 1.2 Hz, 1 H), 4.89 (dd, J = 10.7, 1.2 Hz, 1 H), 2.82 (dq, J = 11.3, 6.2 Hz, 1 H), 2.60 (m, 1 H), 1.96 (m, 1 H), 1.90–1.75 (m, 3 H), 1.71–1.49 (m, 4 H), 1.31 (s, 3 H), 1.03 (d, J = 6.4 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.6, 143.9, 111.6, 87.2, 84.2, 47.7, 41.9, 39.9, 37.1, 30.6, 30.4, 27.4, 20.3, 11.4; MS m/z (M^+) calcd 222.1620, obsd 222.1633; $[\alpha]^{23}_D$ −51.2° (c 1.42, $CHCl_3$).

For **23**: colorless oil; IR (neat, cm^{-1}) 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (dd, J = 17.1, 10.6 Hz, 1 H), 5.12 (dd, J = 17.1, 1.7 Hz, 1 H), 4.85 (dd, J = 10.6, 1.7 Hz, 1 H), 2.00 (m, 2 H), 1.83 (m, 2 H), 1.72 (m, 2 H), 1.58 (m, 2 H), 1.31 (s, 3 H), 1.03 (d, J = 6.0 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.77 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.3, 144.3, 111.4, 89.1, 83.5, 48.9, 40.3, 38.7, 36.3, 34.7, 32.0, 26.4, 20.3, 11.8; MS m/z (M^+) calcd 222.1620, obsd 222.1612; $[\alpha]^{23}_D$ −82.7° (c 1.39, $CHCl_3$).

Dactyloxene-B (1). A solution of **20** (24.8 mg, 0.11 mmol) in THF (1 mL) was cooled to −78 °C and treated dropwise with a solution of potassium hexamethyldisilazide in toluene (0.45 mL of 0.5 M, 0.22 mmol). Next, a solution of *N*-phenyltriflimide (80 mg, 0.22 mmol) in THF (1 mL) was introduced via cannula and stirring was continued for 2 h at −78 °C prior to quenching with saturated NH_4Cl solution. The reaction mixture was diluted with water and extracted with ether. The combined organic phases were washed with brine and water and then dried and concentrated. Flash chromatograpy of the residue on silica gel (elution with 5% ether in petroleum ether) gave pure **24** (34 mg, 86%), which was used directly in the next step: ^{1}H NMR (300 MHz, C_6D_6) δ 6.10 (dd, J = 17.4, 10.3 Hz, 1 H), 5.63 (m, 1 H), 5.18 (dd, J = 17.4, 1.3 Hz, 1 H), 4.97 (dd, J = 10.3, 1.3 Hz, 1 H), 2.24–2.00 (m, 2 H), 1.78–1.49 (m, 3 H), 1.37–1.25 (m, 3 H), 1.15 (s, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.63 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 152.2, 144.8, 117.9, 111.2, 84.7, 84.6, 45.5, 38.1, 33.0, 32.3, 30.6, 27.3, 19.2, 13.1 (CF_3 not observed).

A slurry of copper bromide–dimethyl sulfide complex (0.25 g, 0.82 mmol) in THF (2 mL) was cooled to −40 °C and treated sequentially with methyllithium (1.1 mL of 1.5 M in ether, 1.64 mmol) and the above triflate (98 mg, 0.275 mmol) dissolved in THF (2 mL). The reaction mixture was stirred at −20 °C for 3 h, quenched with saturated NH_4Cl solution, diluted with ether, and washed with NH_4OH and brine prior to drying and solvent evaporation. MPLC purification of the residual oil (silica gel, elution with 1% ether in petroleum ether) furnished **25** (23 mg, 41%) and **1** (21 mg, 35%).

For **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, J = 17.4, 10.7 Hz, 1H), 5.56–5.49 (m, 2 H), 5.06 (dd, J = 17.4, 1.4 Hz, 1 H), 4.84 (dd, J = 10.7, 1.4 Hz, 1 H), 2.01–1.88 (m, 3 H), 1.74–1.59 (m, 3 H), 1.48 (m, 1 H), 1.21 (m, 1 H), 1.18 (s, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.81 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.9, 133.8, 126.9, 110.8, 83.1, 82.8, 44.0, 37.4, 36.3, 34.6, 30.9, 26.4, 19.6, 11.9; MS m/z (M^+) calcd 206.1671, obsd 206.1635.

For **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, J = 17.5, 10.8 Hz, 1 H), 5.30 (m, 1 H), 5.01 (dd, J = 17.5, 1.2 Hz, 1 H), 4.86 (dd, J = 10.8, 1.2 Hz, 1 H), 2.07–1.89 (m, 4 H), 1.77 (m, 1 H), 1.64 (m, 1 H), 1.60 (s, 3 H), 1.50–1.36 (m, 2 H), 1.22 (s, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.6, 136.8, 124.3, 110.8, 86.1, 83.2, 45.5, 38.0, 34.9, 32.7, 32.1, 27.8, 20.9, 20.0, 15.0; MS m/z (M^+) calcd 220.1827, obsd 220.1814; $[\alpha]^{23}_D$ +105.6° (c 0.7, $CHCl_3$).

Dactyloxene-C (2). Ketone **21** (0.101 g, 0.455 mmol, 70% pure by GC) was treated as above to furnish 0.25 g of crude triflate, which was exposed directly to lithium dimethylcuprate to give 78 mg (77%) of a pale yellow oil. MPLC purification of this material (silica gel, elution with 0.5% ether in petroleum ether) furnished **2** as the major constituent (29 mg, 29%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (dd, J = 17.5, 10.8 Hz, 1 H), 5.37 (m, 1 H), 5.14 (dd, J = 17.5, 1.3 Hz, 1 H), 4.96 (dd, J = 10.8, 1.3 Hz, 1 H), 2.05–1.88 (m, 3 H), 1.77 (s, 3 H), 1.70–1.46 (m, 3 H), 1.35 (s, 3 H), 1.24 (m, 2 H), 0.90 (d, J = 6.1 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.2, 139.2, 124.0, 110.8, 89.3, 83.9, 45.7, 37.9, 35.0, 32.9, 31.5, 28.6, 20.02, 19.95, 13.3; MS m/z (M^+) calcd 220.1827, obsd 220.1817; $[\alpha]^{23}_D$ +42.6° (c 0.7, $CHCl_3$).

The companion product **27** was not completely characterized.

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Supplementary Material Available: 300-MHz ^{1}H and 75-MHz ^{13}C spectra of new compounds lacking combustion data (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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