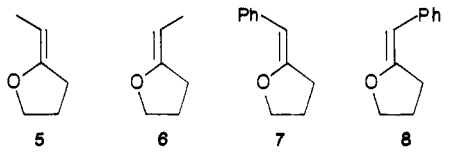
This is a process that puts positive charge on the substrate, and that positive charge can be stabilized by Coulombic interaction with a negative charge in sufficiently close proximity. Conversion of a carboxylic acid to a carboxylate group at the meta position of a β-phenyl substituent, such as occurs in the acid ionization of **2** or **4**, should therefore accelerate the rate of the vinyl ether hydrolysis reaction. The effect, moreover, can be expected to be greater for proton transfer from positively charged acid catalysts, such as H_3O^+, than from uncharged catalysts such as RCO_2H, as is observed here: the rate accelerations given by the present data for H_3O^+ catalysis are $k'_{H^+}/k_{H^+} = 2.6 \pm 0.7$ for **2** and $k'_{H^+}/k_{H^+} = 3.0 \pm 1.4$ for **4**, whereas those for CH_3CO_2H catalysis are $k'_{HA}/k_{HA} = 1.3 \pm 0.1$ for **2** and $k'_{HA}/k_{HA} = 1.6 \pm 0.1$ for **4**. Electrostatic effects similar to these have been observed for other vinyl ether hydrolysis reactions.[13]

Reactivity. The present rate measurements give the prostacyclin analogue **2** a hydrolytic lifetime at physiological pH of 9 days. This is half as long as the prediction of 20 days,[6] but that estimate was made without knowledge of the electrostatic effect discovered here, which shortens the lifetime by a factor of 2.6. At any rate, a lifetime of 9 days is certainly adequate for any therapeutic or other biomedical application.

The trans isomer **4** is less reactive than **2** by a factor of about 2. Such a difference between cis and trans isomers is usually observed in vinyl ether hydrolysis; for example, for the isomeric 2-ethylidenetetrahydrofurans **5** and **6**, whose vinyl ether ring system is closely similar to that of **2** and **4**, $k_{H^+} = 640\ M^{-1}\ s^{-1}$ for **5** and $k_{H^+} = 290\ M^{-1}\ s^{-1}$ for **6**.[14] This could be the result of initial-state energy differences: ab initio calculations suggest that the π-electronic systems of trans vinyl ethers are slightly more stable than those of the cis isomers;[15] such differences would of course be lost upon protonation of the vinyl ether double bond, and that would lead to more rapid hydrolysis reactions for the cis compounds.



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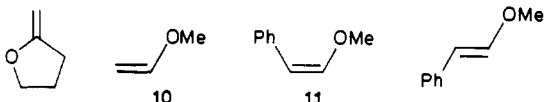
It is instructive to predict the reactivities of the styrylidene derivatives of tetrahydrofuran, **7** and **8**. This may be done by applying to $k_{H^+} = 3.3 \times 10^3\ M^{-1}\ s^{-1}$ for 2-methylenetetrahydrofuran (**9**)[14] the factors by which β-phenyl substitution retards vinyl ether hydrolysis, as obtained, for example, by a comparison of $k_{H^+} = 0.76\ M^{-1}\ s^{-1}$ for methyl vinyl ether[12b] with $k_{H^+} = 2.7 \times 10^{-3}\ M^{-1}\ s^{-1}$ and $7.0 \times 10^{-4}\ M^{-1}\ s^{-1}$ for the cis and trans isomers of β-methoxystyrene (**11** and **12**).[4b] Such a treatment gives $k_{H^+} = 12\ M^{-1}\ s^{-1}$ for **11**, in reasonable agreement with $k_{H^+} = 4.9\ M^{-1}\ s^{-1}$ measured here for the cis substrate **2**, and $k_{H^+} = 3.0\ M^{-1}\ s^{-1}$ for **12**, in remarkably good agreement with $k_{H^+} = 2.6\ M^{-1}\ s^{-1}$ measured here for the trans substrate **4**. This good accord between measured and expected values serves to underscore the fact that the prostacyclin analogues investigated here are entirely normal in their vinyl ether reactivity.



9 10 11 12

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Supplementary Material Available: Tables of rate and equilibrium data (9 pages). Ordering information is given on any current masthead page.

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Exploration of a Novel Cyclization Reaction. A Synthesis of (±)-β-Eudesmol

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An attempt was made to develop a variation of the Lewis acid catalyzed addition of trimethylsilyl enol ethers to ketals in which carbon–carbon bond formation occurs at one of the alcohol carbon atoms rather than at the ketal carbon. Specifically, a variety of conditions was employed in an unsuccessful effort to cause ketal **3**, prepared by conjugate addition of **12** to **8**, to cyclize to **4**, which was to be converted to **5**, a known precursor of β-eudesmol (**6**). In a related but more conventional approach to such a cyclization, ditosylate **20**, which, like **3**, has a prochiral carbon in its side chain, was cyclized diastereoselectively to the 7β-substituted **25**, which was readily converted to **5**.

The Lewis acid catalyzed addition of trimethylsilyl enol ethers to ketals (Mukaiyama reaction) has found widespread use in organic synthesis.[1] In all reported cases carbon–carbon bond formation occurs at the ketal carbon,

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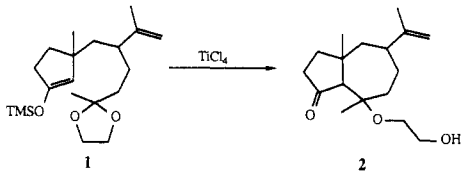
as in the intramolecular example 1 → 2 reported by Posner.[2] The current investigation was initiated to see if,

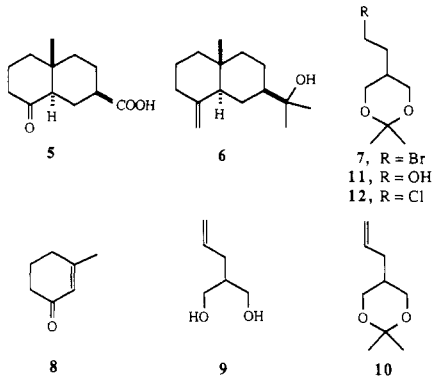


1 2

under favorable circumstances, carbon–carbon bond formation could be effected at an alternate site. Specifically, we wished to determine if the kinetic preference for formation of a six-membered ring would allow compound **3** to react as shown in Scheme I to form annulation product **4**. Furthermore, if the cyclization of **3** occurred in a concerted manner, as depicted in Scheme I, the possibility would exist for diastereoselective formation of functionality at C7 in **4**, owing to the prochiral nature of that carbon in **3**.

If the proposed cyclization were successful, it was anticipated that it would be easy to convert any isomer of structure **4** to keto acid **5**, an intermediate in two[3,4] of the numerous[5] syntheses of β-eudesmol (**6**). Such a conversion would not only constitute an additional formal total synthesis of (±)-β-eudesmol, it would also be a convenient way to determine the stereochemistry of the C7 substituent in **4**. The cyclization of **3** presumably would initially yield **4** with a cis ring fusion,[6] but epimerization via enolization would readily afford the more stable trans ring fusion found in **5**. If epimerization were also required at C7 in order to obtain **5** with its equatorial 7β carboxyl group, then it would be established that **4** had been formed with a 7α substituent.

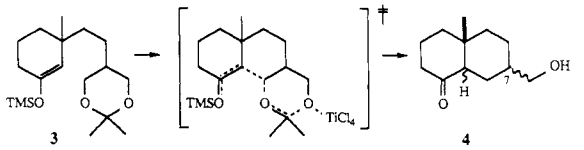
The synthesis of reactant **3** initially was envisioned as involving as its key step conjugate addition of the Grignard reagent derived from alkyl bromide **7** to 3-methylcyclohex-2-en-1-one (**8**). Alkyl bromide **7** was prepared from



5 6 8 9 10

2-allyl-1,3-propanediol (**9**)[7] by formation of acetonide **10** (81%), then treatment with ozone followed by lithium aluminum hydride reduction to afford **11** (91%), and

Scheme I



3 4

conversion to **7** with *N*-bromosuccinimide and triphenylphosphine (86%).[8] Unfortunately, in our hands **7** proved to be too unstable for further use,[9] so attention was turned to alkyl chloride **12**, which was prepared from **11** in 89% yield by treatment with triphenylphosphine and carbon tetrachloride. Although quite reactive (e.g., upon chromatography), **12** proved sufficiently stable for purification and further use. The unusual lability of **12** did not extend to facile formation of its organomagnesium derivative, and several conditions had to be explored for preparation of the Grignard reagent. The best procedure found was that of Helquist,[11] employing magnesium turnings and 1,2-dibromoethane initiation.

Grignard reagent thus generated from **12** reacted with **8** in the presence of cuprous bromide–dimethyl sulfide complex[12] to afford 65% of conjugate addition product **13** when the reaction was quenched with ammonium chloride. When the reaction was quenched instead with chlorotrimethylsilane, the desired reactant **3** was obtained pure in 55% yield. It was found that use of an excess of Grignard reagent relative to enone **8** is necessary in this conjugate addition reaction to prevent formation of some of the trimethylsilyl ether of the alternate enol of **13**, presumably via proton exchange with unreacted enone.

With **3** in hand, the proposed novel cyclization reaction could be attempted. A wide variety of Lewis acids was tried under a wide variety of conditions in efforts to effect ring closure to decalin derivative **4**, but none of this desired product was ever detected.[13] In the midst of these extensive studies, Kocienski and co-workers[15] reported results which tended to confirm that the hoped-for conversion of **3** to **4** was unlikely to be successful. They found, for example, that upon treatment with titanium tetrachloride compound **14** yielded the eight-membered ring **15**, but none of the six-membered ring **16**, the product analogous to **4**. Reluctantly, the efforts to cyclize **3** were abandoned, and utilization of the Grignard conjugate addition product in a more conventional approach to β-eudesmol via an intramolecular alkylation reaction was undertaken.

To this end, ketal **13** was hydrolyzed in acid to afford 88% of diol **17**. Monotosylation of **17** was effected by

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(8) Hanessian, S.; Ducharme, D.; Masse, R.; Capman, M. L. *Carbohydr. Res.* **1978**, *63*, 265.
(9) The instability of **7** is probably due to heightened solvolytic reactivity of the bromide by anchimeric assistance from the ketal oxygens. It should be noted, however, that after our efforts to work with **7** were abandoned, a report[10] appeared describing the preparation of this compound, indicating that it could be stored without decomposition at −20 °C.
(10) Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1985**, *26*, 4265.
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(13) Reaction products were analyzed for the presence of **4** by integration of peaks in the ^{1}H NMR spectra of chromatographic fractions, since **4** would have far fewer protons on carbons bonded to oxygen relative to other protons than would uncyclized compounds such as **3** or **13**. In addition to titanium tetrachloride, Lewis acids such as stannic chloride, boron trifluoride, zinc chloride, zinc bromide, ethylaluminum dichloride, dimethylaluminum chloride, and trimethylsilyl triflate were all tried with equal lack of success.[14] The lithium enolate was prepared from **3** with methyllithium and then treated with a variety of Lewis acids, but again no evidence of formation of **4** was obtained.[14]
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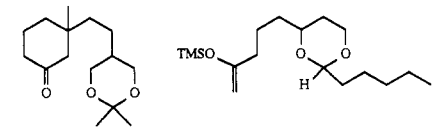
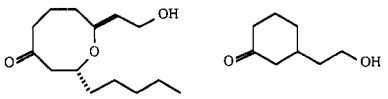


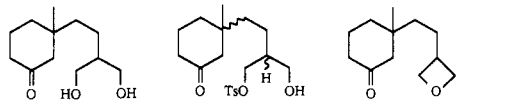
13 14



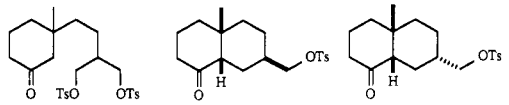
15 16

treatment with 1 equiv of *n*-butyllithium followed by 1 equiv of *p*-toluenesulfonyl chloride[16] to afford **18**. Cyclization of the presumably diastereomeric mixture **18** with sodium *tert*-pentoxide in THF produced some cyclization product **4** but also yielded an equal amount of oxetane **19**.[16] In view of this result, it was decided to modify the intramolecular alkylation approach so as to restore the potential for diastereoselectivity in the cyclization process.

If diol **17** were converted instead to ditosylate **20**, there would be prochirality in the side chain, as there is in **3**, and cyclization via the enolate anion of **20**, which will lead initially to a product with a cis ring fusion,[6] could produce **21** or **22** stereoselectively. Evans has provided a confor-



17 18 19

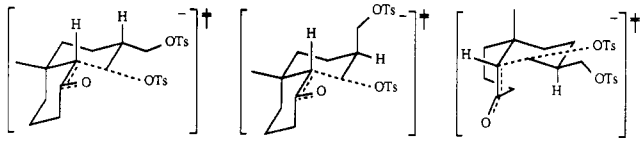


20 21 22

mational analysis of the various possible transition states for such intramolecular alkylation reactions,[17] but the situation is quite complex and often ambiguous even when the experimental results are known. Such an analysis was performed for the cyclization of the enolate anion of **20** and is presented in detail elsewhere.[14] A clear-cut prediction of diastereoselectivity was not possible, but it was hoped that alkylation would occur through a chair-like conformation and that transition state **23** (Scheme II), leading to the 7α-substituted **22**, would be favored over transition state **24**, because the latter has an unfavorable 1,3-diaxial interaction. Selective formation of 7α substitution product would require epimerization at that carbon in order to prepare **5** and complete a β-eudesmol synthesis, but would augur well for a stereoselective synthesis of valeranone, as discussed in the following paper.[18]

Ditosylate **20** was readily prepared from diol **17** in 80% yield by treatment with *p*-toluenesulfonyl chloride in dichloromethane–triethylamine.[19] Cyclization of **20** was carried out with sodium *tert*-pentoxide in benzene[6] to afford 56% (79% based on unrecovered **20**) of a 5:1 mixture of bicyclic products. The major product had the ^1H NMR signal for its angular methyl group at δ 0.73, a value indicating that it was a trans-fused 1-decalone,[20] and the

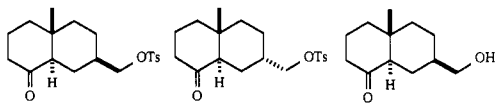
Scheme II



23 24 28

minor isomer had the signal for its angular methyl group at δ 1.12, indicating that it was a *cis*-1-decalone.[20] These assignments were confirmed when it was found that the minor product was converted completely to the major product upon treatment with base or prolonged standing, establishing that the cyclization had afforded exclusively initially either **21** or **22**, which had then undergone epimerization to either **25** or **26**.

Identification of the major product as the 7β-substituted **25** was readily accomplished by its conversion to target keto acid **5**. Treatment of **25** successively with sodium acetate in dimethyl formamide and potassium carbonate in aqueous methanol yielded 79% of keto alcohol **27**, one



25 26 27

of the stereoisomers of the long-sought **4**. Oxidation of **27** with pyridinium dichromate, under conditions known[21] not to cause enolization and thereby epimerization, then gave 72% of **5** which was identical in all respects with an authentic sample[3] kindly provided by Professor C. H. Heathcock.

The exclusive formation of a 7β-substituted product, **21** → **25**, from the cyclization of **20** means that transition state **23** is decidedly not the most favorable one. The cyclization leading to **25** could occur through transition state **28** involving equatorial alkylation of a boat-like conformer, or it could be that transition state **23** is disfavored relative to **24** because there is in **23** an eclipsing interaction between the prospective 7α (tosyloxy)methyl group and the leaving group which outweighs the 1,3-diaxial interaction in **24**. In any case, the exclusive formation of 7β-substituted bicyclic product has led to a stereoselective formal total synthesis of (±)-β-eudesmol, since, as noted earlier, keto acid **5** has previously been converted to that natural product.

Experimental Section

Melting points are uncorrected. Infrared (IR) spectra were referenced to the 1601 cm^{-1} band of polystyrene; liquid samples were analyzed as thin films and solid samples were analyzed as KBr disks. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. Analytical gas chromatography (GC) was performed on a dimethylsilicone capillary column. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM Reagents and visualized by iodine, ultraviolet (UV) light, or ceric sulfate–ammonium molybdate–sulfuric acid spray. Flash chromatography was performed in the manner of Still[22] with EM Reagents silica gel 60 (230–400 mesh). Radial chromatography was performed with EM Reagents silica gel 60 PF_{254} containing gypsum.

Purification of solvents was done as follows: benzene, dimethylformamide (DMF), pyridine, and triethylamine were distilled from CaH_2; CCl_4 was distilled from $CaCl_2$; diethyl ether was distilled from lithium aluminum hydride (LAH); ethanol and *tert*-butyl alcohol were allowed to react with sodium metal and

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then distilled; hexamethylphosphoramide (HMPA) was distilled from BaO; acetic acid and CH_2Cl_2 were distilled from P_4O_{10}; tetrahydrofuran (THF) was distilled from potassium metal with benzophenone indicator. Dimethyl sulfide was dried over 4-Å molecular sieves. Chlorotrimethylsilane (TMSCl) and reagent-grade hexane were distilled prior to use. *p*-Toluenesulfonyl chloride was purified in the manner of Perrin.[23]

Brine refers to a saturated aqueous NaCl solution. Unless otherwise stated, $NaHCO_3$ refers to a saturated aqueous solution of sodium bicarbonate. HCl refers to an aqueous solution of hydrogen chloride. Anhydrous reactions were performed in glassware that had been flame-dried or heated in an oven overnight at 140 °C and then cooled in a desiccator containing anhydrous Ca_2SO_4. The term "under N_2" refers to maintainence of a positive pressure of nitrogen gas that had been passed through a column of anhydrous Ca_2SO_4. Anhydrous ether refers to the commercially available solvent while dry ether refers to the solvent obtained by distillation from LAH. Alkyllithium reagents were titrated with diphenylacetic acid[24] or 2,5-dimethoxybenzyl alcohol.[25]

2-(2-Propenyl)-1,3-propanediol (9). Diethyl allylmalonate was prepared by the procedure of Arnold, DeMoura Campos, and Lindsay[26] in 61% yield: bp 118–120 °C (20 mm) [lit.[26] bp 103–107 °C (17 mm)]. In a modification of the procedure of Wasson,[7] diethyl allylmalonate was reduced with LAH to afford 89% of **9**: bp 95–98 °C (1.0 mm) [lit.[7] bp 110–112 °C (5 mm)].

5-(2-Propenyl)-2,2-dimethyl-1,3-dioxane (10). A solution of 30.00 g (258.3 mmol) of **9** in 500 mL of benzene was treated with 60 mL of acetone and a catalytic amount of *p*-toluenesulfonic acid monohydrate. The solution was heated at reflux for 11 h with azeotropic removal of water. The solution was cooled to room temperature and washed with $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 42 g of liquid that was distilled at atmospheric pressure to afford 35.83 g (89%) of **10** that was 98% pure by GC: bp 180–182 °C; IR 3080, 1650, 1375, 1260, 1200, 1160, 1065, 920, 830 cm^{-1}; ^1H NMR δ 1.38 (6 H, s), 1.70–2.20 (3 H, m), 3.30–4.23 (4 H, m), 4.80–5.20 (2 H, m), 5.36–6.11 (1 H, m); ^{13}C NMR δ 21.1, 26.8, 33.2, 33.8, 64.4, 97.8, 116.7, 135.2; MS, *m/e* 141 ($M^+ - CH_3$), 81 (base), 67, 59. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.30; H, 10.30.

2,2-Dimethyl-5-(2-hydroxyethyl)-1,3-dioxane (11). In the manner of Sousa and Bluhm,[27] a solution of 12.00 g (76.81 mmol) of **10** in 150 mL of anhydrous ether was ozonized by using a Welsbach ozonator (8 psi, 0.8 slpm, 110 V) for 2 h at −78 °C until a faint blue color persisted and an IR spectrum of an aliquot showed no band at 1650 cm^{-1}. The solution was purged with N_2 and added dropwise over 45 min to a suspension of 9.0 g (230 mmol) of LAH in 150 mL of anhydrous ether at 0 °C under N_2. Proper venting was maintained since the addition caused a vigorous reaction. The mixture was stirred for 2 h at room temperature and was then quenched with sodium sulfate decahydrate. The solid was removed by suction filtration and washed with CH_2Cl_2. The solvents were evaporated and 13.06 g of cloudy liquid was obtained. Distillation yielded 11.33 g (92%) of **11** as a clear oil: bp 81–83 °C (0.20 mm); IR 3410, 1370, 1255, 1195, 1150, 1070, 825 cm^{-1}; ^1H NMR δ ($CDCl_3$, D_2O) 1.38 (6 H, s), 1.50–2.20 (3 H, m), 3.35–4.12 (6 H, m); ^{13}C NMR δ 21.8, 25.9, 31.4, 32.0, 60.1, 64.5, 97.9; MS, *m/e* 145 ($M^+ - CH_3$), 85, 59 (base), 55. In order to provide a sample for analysis, a trace impurity was removed from a small sample of the alcohol by means of flash chromatography (ethyl acetate) followed by distillation. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.82; H, 10.10.

5-(2-Chloroethyl)-2,2-dimethyl-1,3-dioxane (12). To a solution of 10.0 g (62.4 mmol) of **11** in 125 mL of CCl_4 was added 19.6 g (74.9 mmol) of triphenylphosphine.[28] The resulting solution was heated at reflux for 22 h, cooled to 0 °C, and diluted with 125 mL of cold hexane. The precipitate of triphenylphosphine oxide was removed by suction filtration and rinsed with 125 mL of cold hexane. Evaporation of the solvents gave 15.9 g of crude **12**. Flash chromatography (ether) with rapid elution gave 9.89 g (89%) of **12** as a pale yellow liquid. An analytical sample was prepared by distillation: bp 80 °C (1.25 mm); IR 3000, 2940, 2870, 1370, 1250, 1200, 1155, 1135, 1020, 835 cm^{-1}; ^1H NMR δ 1.40 (6 H, s), 1.60–2.25 (3 H, m), 3.20–4.20 (6 H, m); ^{13}C NMR δ 22.9, 24.9, 31.7, 31.8, 42.4, 63.8, 98.0; MS, *m/e* 163 ($M^+ - CH_3$), 143 ($M^+ - Cl$), 85, 67, 59 (base), 55; TLC R_f 0.37 (2:1 hexane–ether, visualized with $AgNO_3$–bromphenol blue in ethanol[29]). Anal. Calcd for $C_8H_{15}ClO_2$: C, 53.78; H, 8.46; Cl, 19.84. Found: C, 53.84, H, 8.50; Cl, 19.91.

3-Methylcyclohex-2-en-1-one (8). The procedure of Cronyn and Riesser[30] was used to prepare 57% of **8**: bp 90–93 °C (20 mm) [lit.[30] bp 88–90 °C (18 mm)].

3-[2-(2,2-Dimethyl-1,3-dioxan-5-yl)ethyl]-3-methylcyclohexanone (13). In a procedure based on that of Helquist,[11] a solution of 5.05 g (28.3 mmol) of **12** in 6 mL of dry THF was added to 2.10 g (84.9 mmol) of magnesium turnings under N_2. 1,2-Dibromoethane (0.1 mL) was added and gentle heating was applied to initiate Grignard reagent formation. The mixture was stirred at room temperature for 0.5 h after which time TLC showed no **12**. The reaction mixture was diluted with 22 mL of dry THF and the stirring was continued for 0.5 h. The mixture was cooled to −78 °C in a dry ice–isopropyl alcohol bath and a solution of 1.95 g (9.5 mmol) of cuprous bromide–dimethyl sulfide complex in 10 mL of dry dimethyl sulfide was added. The mixture was stirred for 1.5 h and a solution of 2.08 g (18.9 mmol) of **8** in 27 mL of dry ether was added over 45 min via syringe. The mixture was stirred for 18 h at −78 °C and allowed to warm to 0 °C over 4 h. The reaction mixture was quenched with 45 mL of saturated aqueous NH_4Cl (adjusted to pH 8 with aqueous NH_4OH) and stirred for 0.5 h. The organic layer was separated, washed with water (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$, and evaporated to give 4.72 g of colorless liquid which was distilled to afford 3.12 g (65%) of **13**: bp 160–163 °C (1.5 mm); IR 1710, 1455, 1365, 1250, 1195, 1150, 1065, 830 cm^{-1}; ^1H NMR δ 0.87 (3 H, s), 1.10–1.30 (4 H, m), 1.38 (6 H, s), 1.40–2.40 (9 H, m), 3.33–4.10 (4 H, m); ^{13}C NMR δ 20.9, 22.0, 22.4, 24.7, 26.8, 34.6, 35.6, 38.3, 38.4, 40.9, 53.4, 64.6, 64.7, 97.7, 211.8; MS, *m/e* 239 ($M^+ - CH_3$), 111 (base), 55, 43; TLC R_f 0.50 (5:1 ethyl acetate–hexane). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.75; H, 10.34.

3-[2-(2,2-Dimethyl-1,3-dioxan-5-yl)ethyl]-3-methyl-1-(trimethylsiloxy)-1-cyclohexene (3). A solution of 5.40 g (30.2 mmol) of **12** in 6 mL of dry THF was added to 2.22 g (90.7 mmol) of magnesium turnings under N_2. Grignard reagent formation was initiated by the addition of 0.10 mL of 1,2-dibromoethane followed by gentle heating. The reaction mixture began to boil and continued to do so for several minutes without further heating. When the initial exothermic reaction had subsided, an additional 0.05 mL of 1,2-dibromoethane was added to ensure complete formation of the Grignard reagent. The reaction mixture was diluted with 25 mL of dry THF and stirred for 1 h at room temperature. The mixture was then cooled to −78 °C and a solution of 1.55 g (7.56 mmol) of cuprous bromide–dimethyl sulfide complex in 8 mL of dry dimethyl sulfide was introduced over several minutes via syringe. After 1 h, 1.71 mL (15.1 mmol) of **8** in 30 mL of dry ether was added over 0.5 h. The mixture was stirred for 16 h at −78 °C and then allowed to warm to −25 °C over 2 h. A mixture of 12 mL of TMSCl, 16 mL of dry triethylamine, and 8 mL of dry HMPA was added over a few minutes. The resulting mixture was stirred for 15 min at −20 °C and then for 20 min at 0 °C. The reaction contents were poured into 125 mL of cold hexane and washed in rapid succession with 125 mL each of cold 0.1 M HCl, $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated to give 4.46 g of clear liquid. Short-path distillation afforded 2.69 g (55%) of **3**. An analytical sample was obtained by redistillation: bp 157–159 °C (1.75 mm); IR 1670, 1460, 1260, 1375, 1205, 1150, 1080, 970, 890, 840 cm^{-1}; ^1H NMR δ 0.20 (6 H, s), 0.91 (3 H, s), 1.02–2.05 (17 H,

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m), 3.25–4.04 (4 H, m), 4.50 (1 H, s); ^{13}C NMR δ 0.3, 19.6, 20.3, 23.4, 27.6, 28.0, 29.8, 34.3, 34.4, 34.9, 40.1, 65.0, 65.0, 97.7, 114.2, 149.6; TLC R_f 0.68 (5:1 ethyl acetate–hexane). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 66.34; H, 10.49.

3-Methyl-3-[3,3-bis(hydroxymethyl)propyl]cyclohexanone (17). To a solution of 1.01 g (3.97 mmol) of **13** in 10 mL of THF which was cooled to 0 °C in an ice–water bath was added 5 mL of 3 M HCl. The resulting mixture was stirred for 4.5 h at room temperature. Solid $NaHCO_3$ was added until the resulting aqueous layer became saturated. The THF was evaporated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to afford 0.767 g of clear oil. Flash chromatography (5% methanol–ether) gave 0.734 (86%) of **17** which was homogeneous by TLC. An analytical sample was obtained by bulb-to-bulb distillation: bp 190–195 °C (0.9 mm); IR 3400, 1710, 1035 cm^{-1}; ^{1}H NMR δ 0.90 (3 H, s), 1.00–2.50 (13 H, m), 3.10 (2 H, s), 3.40–4.40 (4 H, m); ^{13}C NMR δ 21.2, 22.0, 25.0, 35.7, 38.4, 38.6, 40.9, 42.4, 53.4, 65.1, 65.3, 213.1; MS, *m/e* 215 (M^+ + 1), 199 (M^+ – CH_3), 111 (base), 55; TLC R_f 0.15 (5:1 ethyl acetate–hexane). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.40; H, 10.39.

3-Methyl-3-[3-(hydroxymethyl)-3-[(tosyloxy)methyl]propyl]cyclohexanone (18). Following a procedure by Moulines,[16] 734 mg (3.42 mmol) of **17** was dissolved in 8.5 mL of dry THF under N_2. The solution was cooled to 0 °C in an ice–water bath and treated with 2.5 mL (3.4 mmol; 1.35 M in hexane) of *n*-butyllithium. A white precipitate formed that dissolved when the mixture was warmed to room temperature. The ice–water bath cooling was resumed and a solution of 662 mg (3.42 mmol) of *p*-toluenesulfonyl chloride in 2 mL of dry THF was added over 15 min via syringe. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 0.5 h. The mixture was poured into 100 mL of ether and washed with brine (2 × 20 mL). The organic layers were dried over $MgSO_4$ and evaporated to give 1.22 g of yellow oil. Flash chromatography (hexane, 1:4 ethyl acetate–hexane, 1:1 ethyl acetate–hexane) afforded 262 mg (15%) of ditosylate **20** and 825 mg (65%) of **18** as a pale yellow oil that was homogeneous by TLC: IR 3450, 1710, 1650, 1465, 1360, 1195, 1180, 1045, 965, 820 cm^{-1}; ^{1}H NMR δ 0.90 (3 H, s), 1.07–2.40 (14 H, m), 2.50 (3 H, s), 3.65 (2 H, d), 4.14 (2 H, d), 7.53 (4 H, q); MS, *m/e* 368 (M^+), 179, 173, 155, 111 (base), 55; TLC R_f 0.20 (1:1 ethyl acetate–hexane). Anal. Calcd for $C_{19}H_{28}O_5S$: C, 61.93; H, 7.66; S, 8.70. Found: C, 61.89; H, 7.67; S, 8.61.

Cyclization of 18. In a modification of Conia's procedure,[6] a solution of 167 mg (0.453 mmol) of **18** in 4 mL of dry THF was cooled to −78 °C and treated with a solution of 105 mg (0.906 mmol) of sodium *tert*-pentoxide (Aldrich) in 1.5 mL of dry THF. The progress of the reaction was monitored by TLC as the mixture was allowed to warm to −10 °C for 1.5 h, then to 0 °C for 1.5 h, and finally to room temperature for 1 h. The mixture was diluted with 10 mL of ether and quenched by the addition of 6 mL of 0.1 M HCl. The organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with 10 mL of 10% aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to give 95 mg of yellow oil. Flash chromatography (hexane, 1:9 ethyl acetate–hexane, 1:3 ethyl acetate–hexane, 1:1 ethyl acetate–hexane) provided 18 mg (11%) of **18**, 18 mg (20%) of oxetane **19** [^{1}H NMR δ 0.93 (3 H, s), 1.00–2.45 (12 H, m), 2.53–3.20, (1 H, m), 4.27–4.53 (2 H, dd), 4.70–5.03 (2 H, dd); MS, *m/e* 196 (M^+), 111 (base), 81, 69, 67, 55; TLC R_f 0.44 (ethyl acetate); HRMS, *m/e* 196.1473 (calcd for $C_{12}H_{20}O_2$ 196.1464)], and 19 mg (21%) of **4** [IR 3440, 1705 cm^{-1}; ^{1}H NMR δ 0.77 (s), 1.13 (s), 0.85–2.45 (m), 3.33–3.63 (d); MS, *m/e* 196 (M^+), 181 (M^+ – CH_3), 163 [(M^+ – CH_3) – H_2O], 153 (base), 107, 98, 95, 93, 91, 81, 79, 67, 55, 53; TLC R_f 0.41 (ethyl acetate); TLC R_f 0.36 (5:1 ethyl acetate–hexane); HRMS, *m/e* 196.1465 (calcd for $C_{12}H_{20}O_2$ 196.1464)].

3-Methyl-3-[3,3-bis[(tosyloxy)methyl]propyl]cyclohexanone (20). As in McAuley's procedure for the bistosylation of 1,3-propanediol,[19] to 0.854 g (3.98 mmol) of **17** under N_2 were added 7 mL of dry CH_2Cl_2 and 7 mL of dry triethylamine. The resulting solution was cooled in an ice–salt bath, and a solution of 1.68 g (8.80 mmol) of *p*-toluenesulfonyl chloride in 6 mL of dry CH_2Cl_2 was added over a few minutes. The reaction mixture was stirred at −20 °C for 18 h and then washed with 1 M HCl (3 × 20 mL). The combined aqueous layers were extracted with 20 mL of CH_2Cl_2. The organic layers were washed with 20 mL of $NaHCO_3$, dried over $MgSO_4$, and evaporated to give 1.93 g of yellow oil. Flash chromatography (hexane, 1:3 ether–hexane, 1:1 ether–hexane, ether) yielded 1.67 g (80%) of **20** as a colorless gum that was homogenous by TLC: IR 1710, 1600, 1355, 1175, 950, 820 cm^{-1}; ^{1}H NMR δ 0.80 (3 H, s), 1.00–2.3 (13 H, m), 2.42 (3 H, s), 3.90 (4 H, d), 7.45 (8 H, q); ^{13}C NMR δ 20.7, 21.6, 21.9, 24.5, 35.3, 38.0, 38.2, 38.4, 40.8, 53.4, 68.4, 68.5, 127.8, 129.9, 132.3, 145.1, 211.5; MS, *m/e* 522 (M^+), 179, 155, 111 (base), 91, 55; TLC R_f 0.36 (1:1 ethyl acetate–hexane). Anal. Calcd for $C_{26}H_{34}O_7S_2$: C, 59.75; H, 6.56; S, 12.27. Found: C, 59.89; H, 6.58; S, 12.16.

2,3,4,5,6,7,8,9-Octahydro-7β-[(tosyloxy)methyl]-10β-methyl-1(10*H*)-naphthalenone (21 and 25). In a modification of Conia's procedure,[6] a solution of 72 mg (0.65 mmol) of sodium *tert*-pentoxide in 1 mL of dry benzene under N_2 was cooled in an ice–water bath and a solution of 269 mg (0.515 mmol) of **20** in 1.5 mL of dry benzene was added. The reaction mixture was stirred for 2 h at room temperature and for 3 h at 50 °C. The mixture was cooled to room temperature and quenched by the addition of 2 mL of saturated aqueous NH_4Cl. The resulting thick white precipitate was dissolved by the addition of 2 mL of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 188 mg of yellow oil. Radial chromatography (2:1 hexane–ether, 1:1 hexane–ether, ethyl acetate) afforded 80.0 mg (30%) of recovered **20**, 16.2 mg (9%) of *cis*-decalone **21** as a colorless oil [^{1}H NMR δ 1.12 (3 H, s), 1.10–2.40 (14 H, m), 2.45 (3 H, s), 3.88 (2 H, d), 7.58 (4 H, q); ^{13}C NMR δ 21.6, 21.8, 23.1, 24.2, 27.5, 32.1, 38.4, 39.4, 41.5, 54.1, 75.1, 128.0, 129.9, 133.2, 144.7, 212.2; MS, *m/e* 350 (M^+), 178, 163 (base), 145, 111, 107, 93, 91, 55; TLC R_f 0.48 (4:1 ether–hexane); HRMS, *m/e* 350.1561 (calcd for $C_{19}H_{26}O_4S$ 350.1551)], and 83.5 mg (46%) of *trans*-decalone **25** as a colorless oil [^{1}H NMR δ 0.73 (3 H, s), 0.85–2.43 (14 H, m), 2.50 (3 H, s), 3.88 (2 H, d), 7.63 (4 H, q); ^{13}C NMR δ 16.7, 21.6, 22.4, 23.0, 23.8, 36.8, 39.3, 39.6, 40.1, 41.1, 56.3, 74.7, 127.8, 129.8, 132.8, 144.7, 211.9; MS, *m/e* 350 (M^+), 179, 178, 163, 135, 107 (base), 93, 91, 81, 79, 67, 55; TLC R_f 0.43 (4:1 ether–hexane). Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48; S, 9.15. Found: C, 65.12; H, 7.53; S, 9.08.].

2,3,4,5,6,7,8,9α-Octahydro-7β-(hydroxymethyl)-10β-methyl-1(10*H*)-naphthalenone (27). In the manner of Meyer zu Reckendorf,[31] 118 mg (0.337 mmol) of **25** was converted to the corresponding acetate by treatment with 55 mg (0.67 mmol) of anhydrous sodium acetate in 1.5 mL of dry DMF at 120 °C for 2 h under N_2. The reaction mixture was cooled to room temperature, diluted with 10 mL of ether, and washed with water (2 × 5 mL). The combined aqueous layers were extracted with ether (2 × 10 mL). The organic layers were dried over $MgSO_4$ and evaporated to give 89 mg of crude acetate: IR 1740, 1710, 1250 cm^{-1}; TLC R_f 0.51 (1:1 ethyl acetate–hexane). Without purification, the acetate was dissolved in 2 mL of 98% aqueous methyl alcohol and stirred with a catalytic amount of K_2CO_3 for 3 h at room temperature. The solvent was evaporated and the residue was taken up in ether and dried over anhydrous K_2CO_3. The ether was evaporated to afford 79 mg of clear oil. Flash chromatography (hexane, 1:3 ether–hexane, 1:1 ether–hexane ether) afforded 5.0 mg of unidentified material and 52.0 mg (79%) of **27** as a colorless oil: IR 3410, 1715, 1080, 1030 cm^{-1}; ^{1}H NMR δ 0.74 (3 H, s), 1.00–2.65 (15 H, m), 3.40–3.55 (2 H, m); ^{13}C NMR δ 17.0, 22.7, 23.6, 24.3, 39.7, 40.0, 40.2, 40.5, 41.3, 56.9, 68.3, 212.6; MS, *m/e* 196 (M^+), 181 (M^+ – CH_3), 163 [(M^+ – CH_3) – H_2O], 153 (base), 125, 107, 98, 93, 81, 79; TLC R_f 0.14 (4:1 ether–hexane); HRMS, *m/e* 196.1455 (calcd for $C_{12}H_{20}O_2$ 196.1464).

2,3,4,5,6,7,8,9α-Octahydro-7β-carboxy-10β-methyl-1-(10*H*)-naphthalenone (5). According to the method of Corey,[32] to a solution of 27 mg (0.14 mmol) of **27** in 1 mL of dry DMF under N_2 was added 180 mg (0.48 mmol) of pyridinium dichromate. The mixture was stirred at room temperature for 12 h and 2 mL of 1 M HCl was added. The liquid phase was decanted, leaving a black tar which was triturated with ether (6 × 2 mL) until a black granular solid resulted. The decanted aqueous DMF layer was extracted with ether (6 × 2 mL). The ether layers were combined,

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dried over $MgSO_4$, and evaporated to afford 32 mg of crude **5**. Purification by flash chromatography (hexane, 1:3 ethyl acetate–hexane, 1:1 ethyl acetate–hexane, ethyl acetate) yielded 21 mg (72%) of **5**. A small sample was recrystallized from ether–petroleum ether to afford **5**: mp 124.5–125.5 °C; mp with authentic **5**[3] 123.5–125.0 °C (lit.[3] mp 124.0–125.8 °C); IR 3500–2100, 1720, 1700, 1465, 1445, 1430, 1395, 1370, 1330, 1315, 1265, 1250, 1240, 1200, 965, 935 cm^{-1} (IR of authentic **5**: 3500–2100, 1720–1690, 1465, 1445, 1430, 1395, 1370, 1330, 1315, 1265, 1250, 1240, 1200, 965, 940 cm^{-1}); ^1H NMR δ 0.79 (3 H, s), 1.1–2.5 (14 H, m) [^1H NMR of authentic **5**: δ 0.79 (3 H, s), 1.1–2.5 (14 H, m)]; ^{13}C NMR δ 16.9, 22.6, 23.1, 23.6, 39.2, 39.8, 40.2, 41.2, 42.6, 56.3, 180.9, 211.3 (^{13}C NMR of authentic **5**: δ 16.9, 22.6, 23.1, 23.6, 39.1, 39.8, 40.2, 41.2, 42.6, 56.3, 181.1, 211.3).

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Registry No. (±)-**3**, 113999-08-9; **4**, 113999-18-1; (±)-**5**, 42246-08-2; (±)-**6**, 3287-59-0; **8**, 1193-18-6; **9**, 42201-43-4; **10**, 113999-09-0; **11**, 102147-75-1; **12**, 113998-32-6; (±)-**13**, 113999-10-3; (±)-**17**, 113999-11-4; (±)-**18** (isomer 1), 113999-12-5; (±)-**18** (isomer 2), 113999-19-2; (±)-**19**, 113999-13-6; (±)-**20**, 113999-14-7; (±)-**21**, 113999-15-8; (±)-**25**, 113999-16-9; (±)-**27**, 113999-17-0; diethyl allylmalonate, 2049-80-1.

Synthesis of (±)-7-Epivaleranone and (±)-Valeranone

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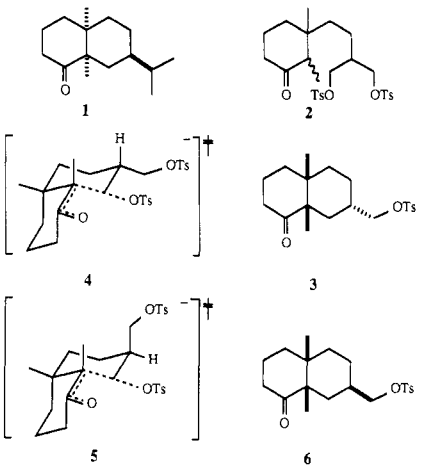
The cyclization of ditosylate **2** was investigated as a possible diastereoselective route to compounds like valeranone (**1**) which possess a C7 substituent trans to the angular methyl groups. However, cyclization of **2** (which was prepared via reaction of **9** with **7** to afford **11**, followed by reaction with lithium dimethylcuprate, hydrolysis, and tosylation) produced exclusively the 7β-substituted **6**, which was identified by its conversion to (±)-7-epivaleranone (**13**). A synthesis of (±)-**1** was achieved via elimination product **20** derived from **6**. This synthesis proceeded analogously to the conversion of **6** to **13**, involving the sequence **20** → **21** → **22** → **23** → **25** → **1**.

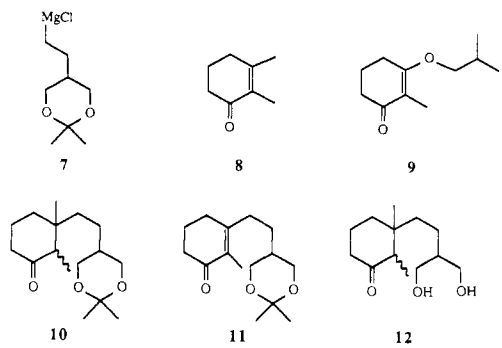
The natural product (−)-valeranone (**1**) is unusual in that its isoprene units are not connected in the "head-to-tail" fashion found in the biogenetic progenitor of sesquiterpenes, farnesyl pyrophosphate. Initial confusion about the structure and stereochemistry of valeranone was corrected in the early 1960s[1] and the structural assignment was confirmed shortly thereafter by a synthesis of (±)-valeranone by Marshall.[2] There have been several subsequent syntheses of the valeranone structure,[3-5] among which Wenkert's short synthesis of (−)-valeranone stands out for its elegant solution to the difficult problem of introducing the second angular methyl group.[6]

Our hope was that a stereoselective synthesis of (±)-valeranone could be achieved via diastereoselective cyclization of ditosylate **2** to form **3** having the C7 (tosyloxy)methyl group trans to the angular methyl groups, as is the isopropyl group in **1**. The opposite stereochemical result had been obtained in the cyclization of the ditosylate lacking the methyl group α to the carbonyl group, as described in the preceding paper.[7] Nonetheless, our predisposition to consider transition states with chair-like conformations encouraged us to predict that the presence of that additional methyl group would favor **4**, leading to **3**, over **5**, which would lead to **6**, owing to the severe 1,3-diaxial interaction in the latter transition state. If **3** were



indeed obtained, subsequent elaboration to valeranone (**1**) would be expected to be straightforward.

The first approach to synthesis of intermediate ditosylate **2** involved conjugate addition of the Grignard reagent **7**, which had been used in the synthesis of (±)-β-eudesmol,[7] to 2,3-dimethylcyclohex-2-en-1-one (**8**), which was readily prepared from **9**[8] by Jung's procedure.[9] However, cop-



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