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Stereocontrolled Synthesis of Kelsoene by the Homo-Favorskii Rearrangement

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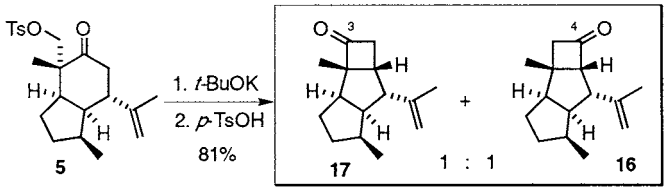
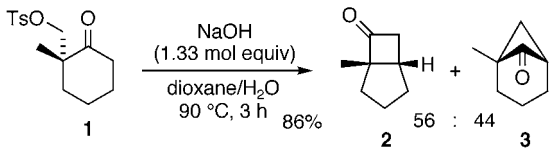
ABSTRACT



(±)-Kelsoene (4) has been synthesized from 2,5-dihydroanisole in 16 steps in 12.5% overall yield. The key step involves a base-catalyzed reaction of γ-keto tosylate (5), which effects a homo-Favorskii rearrangement to 16 as well as the corresponding intramolecular S_N2 product 15 from the enolate of 5. Ketone 15 can efficiently be isomerized to cyclobutanone 17 having the kelsoene carbon skeleton upon acid treatment.

Upon treatment with base, certain γ-keto *p*-toluenesulfonates undergo a stereospecific homoallyl rearrangement, commonly referred to as a homo-Favorskii rearrangement.[1] For example, 2-methyl-2-tosyloxymethyl-cyclohexanone (**1**) provides bicyclo[3.2.0]heptanone **2** in 48% yield together with bicyclo[3.1.1]heptanone **3** (34%) (Scheme 1).[2] While the

Scheme 1



former ketone represents the product of the homo-Favorskii rearrangement, the latter corresponds to that of the direct displacement of the tosylate group by the ketone enolate. However, it is of considerable interest to note that, in general, the bicyclo[3.1.1]heptanone products readily rearrange to bicyclo[3.2.0]heptanones upon treatment with mild acid (vide infra),[3] presumably a manifestation of their relative strain energies.[4] Despite detailed mechanistic understanding and the potential access to synthetically versatile ring structures,[5] this reaction has been scarecely exploited by practicing synthetic chemists. In connection with our interest in the synthesis of cyclobutane-containing natural products, it was envisaged that the use of a homo-Favorskii rearrangement reaction could be ideally suited for the construction of the bicyclo[3.2.0]heptane carbon framework present in the sesquiterpene kelsoene, i.e., C-1∼C-7 (see **4**).

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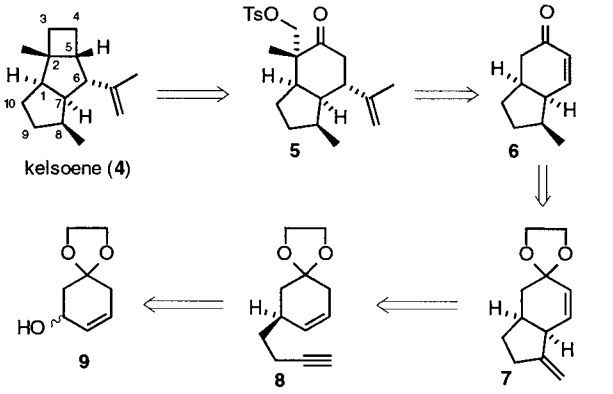
Kelsoene (**4**), isolated in 1997 from the topical marine sponge *Cymbastela hooperi* collected from Kelso reef in Australia,[6] possesses a unique 5−5−4 ring-fused tricarbocyclic structure, which has now been found in several other natural products.[7] This compound has recently been synthesized by Mehta,[8] Schultz,[9] and Piers'[10] groups, all of which employed a photochemical [2 + 2] cycloaddition reaction to introduce the four-membered carbocyclic unit. Interestingly, the absolute configuration postulated by the use of an empirical NMR method[11] has been revised as the result of the synthesis of optically active kelsoene commencing with compounds of known absolute stereochemistry.[8b,9] In the following, we present a highly efficient synthesis of (±)-kelsoene (**4**) by the use of a homo-Favorskii reaction as a salient feature toward the elaboration of the 4−5 ring-fused portion of the molecule.

As summarized in the retrosynthetic analysis of kelsoene (Scheme 2), the last few steps, i.e., **5** → **4**, feature the ring-

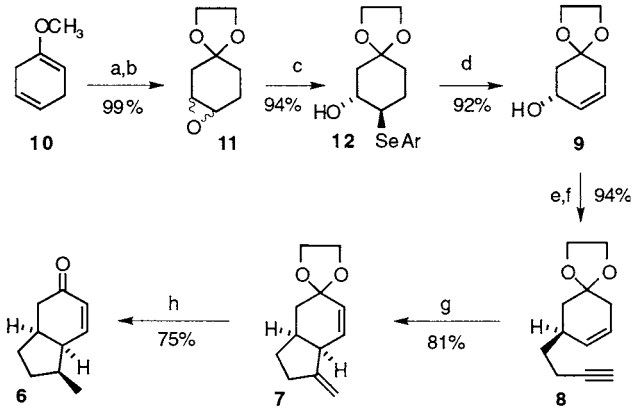
Scheme 2. Retrosynthetic Analysis of Kelsoene (**4**)



contracting homo-Favorskii rearrangement. We considered that the stereocontrolled synthesis of the requisite γ-keto tosylate **5** in turn should be achievable from enone **6** by taking advantage of its conformationally well-definable bicyclic cis 5−6-fused ring system.

On the basis of the approach outlined in Scheme 2, enone **6** was synthesized from commercially available 2,5-dihydroanisole (**10**) (Scheme 3). The treatment of epoxide **11**[12] with LDA provided, upon aqueous workup, exclusively the allylic alcohol **13** (see Figure 1) (80% yield), presumably a consequence of the initial complexation of the Li^+ with the

Scheme 3. Synthesis of Enone **6**[a]



[a] Reagents and conditions: (a) $(HOCH_2)_2$, CH_2Cl_2, *p*-TsOH (cat.) (99%); (b) MCPBA (1.5 mol equiv)/CH_2Cl_2, rt, 10 h (quantitative); (c) di(*p*-chlorophenyl) diselenide (2.0 mol equiv), NaH (1.0 mol equiv)/THF, rt, 10h; (d) 30% aq H_2O_2 (5.0 mol equiv)/EtOH, rt, 0.5 h, then dilution with EtOH and $NaHCO_3$, and reflux, 12 h; (e) pivaloyl chloride (2.0 mol equiv), DMAP (4.2 mol equiv)/CH_2Cl_2, rt, 4 h (quantitative); (f) TMS−C≡CCH_2CH_2MgBr (3.0 mol equiv), CuCN (0.5 mol equiv)/THF, rt, 12 h then MeOH, K_2CO_3, rt, 4 h (94%); (g) $Pd(OAc)_2$ (5 mol %), $AsPh_3$ (15 mol %), AcOH (3 mol equiv)/benzene, 60 °C, 18 min; (h) $CoCl_2 \cdot 2H_2O$ (2.0 mol equiv), $LiBH_4$ (2.4 mol equiv)/2:1 THF/MeOH, −78 °C, 2 h, workup with TFA (10 mol equiv)/hexanes, rt, 14 h.

ketal oxygen atom. In contrast, the use of $ArSe^-$, generated from $(ArSe)_2$/NaH[13] (Ar = *p*-chlorophenyl), resulted in its exclusive attack at the oxirane carbon further away from the ketal. Oxidation of the resulting selenide to the selenoxide at room temperature followed by refluxing in ethanol afforded the desired allylic alcohol **9**. This regioselectivity in the epoxide ring opening of **11** may be explainable in terms of the axial attack by the $ArSe^-$ going through transition state **A** (see Figure 1). The epoxide-ring opening through transition state **B** is likely to encounter severe steric as well as repulsive electrostatic interactions between the ArSe anion and the ketal oxygen, which is 1,3-diaxially juxtaposed against the incoming selenide anion.

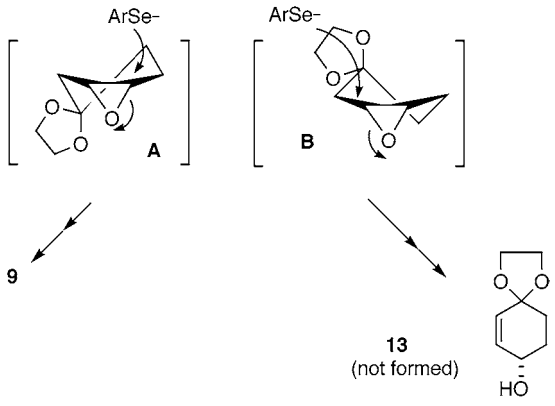


Figure 1. Epoxide-ring opening of **11** by $ArSe^-$.

(6) König, G. M.; Wright, A. D. *J. Org. Chem.* **1997**, *62*, 3837.
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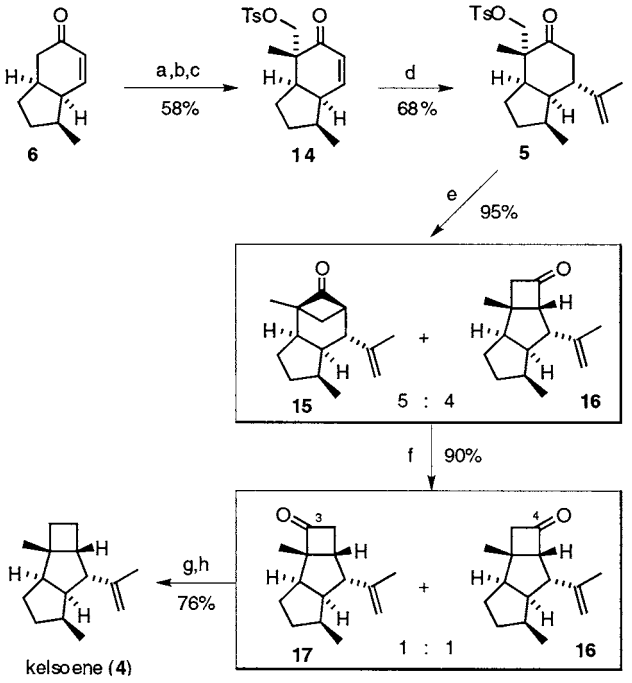
Scheme 4. Completion of the Synthesis of Kelsoene (**4**)[a]



[a] Reagents and conditions: (a) LDA (2.0 equiv)/THF, −78 °C, then MeI (excess)/HMPA (1.0 equiv), −78 → −20 °C (73%); (b) LDA (1.5 equiv)/THF, −78 °C, then CH_2O (gas) (excess), −78 → 0 °C (85%); (c) TsCl (3 mol equiv), DMAP (6.3 equiv)/CH_2Cl_2, 0 °C (93%); (d) isopropenyl-magnesium bromide (5 mol equiv), CuI (2 mol equiv), LiCl (4 mol equiv), TMS−Cl (10 mol equiv)/THF, 0 °C, 12 h; (e) *t*-BuOK (8 mol equiv)/*t*-BuOH, rt, 2 min; (f) *p*-TsOH (1 mol equiv to **15**)/CF_3CH_2OH, 0 °C, 4 h; (g) $TsNHNH_2$ (4 mol equiv)/benzene, 60 °C, 12 h (98%); (h) $NaBH_3CN$ (24.7 mol equiv), *p*-TsOH (1.64 mol equiv)/1:1:2 sulfolane/DMF/hexanes, 110 °C, 6 h (78%).

The cyanocuprate reaction in THF[14] of the pivaloate derivative from **9** proceeded smoothly to give the butynyl group-appended product **8**, which underwent a smooth, Pd(0)-mediated enyne cyclization[15] to afford bicyclic diene **7**. Somewhat surprisingly, the selective reduction of the exo-methylene C=C bond of the diene **7** proved to be highly problematic. Diimide reduction and catalytic hydrogenation were not highly regioselective. The use of Wilkinson's catalyst[16] or $RuCl_2(PPh_3)_3$[17] in H_2 led to extensive C=C bond migration. This unexpected problem was circumvented by the use of $CoCl_2/LiBH_4$ in 2/1 THF/MeOH at −78 °C,[18] regio- and stereoselectively providing enone **6** in 75% yield.

The stereocontrolled elaboration of enone **6** into γ-keto tosylate **5** was achieved in four steps (Scheme 4). Thus, sequential methylation and hydroxymethylation followed by tosylation afforded the enone-tosylate **14**. The introduction of the isopropenyl group to the enone β-carbon proved to be sluggish by the use of standard cuprate reaction conditions. It was found that the use of the CuX_3Li_2-catalyzed Kharasch reaction[19] was necessary in order to effect the conjugate addition of the isopropenyl group to the enone **14**.

Treatment of γ-keto tosylate **5** with excess *t*-BuOK at room temperature resulted in the rapid (<2 min) formation of a 5:4 mixture of two cyclobutanones, **15** (IR 1773 cm^{-1}; ^{13}C NMR 213.8 ppm) and **16** (IR 1774 cm^{-1}; ^{13}C NMR 210.4 ppm), in a combined yield of 95%. The latter cyclobutanone corresponds to the product of the homo-Favorskii reaction (Figure 2). In a formal sense, the direct intramolecular S_N2 reaction of the keto enolate **C** from **5** leads to **15**. However, this transformation **5** → **15** may be more likely to go through a nonclassical ion form such as **D**. Although both **15** and **16** can easily be isolated to purity, a mixture of the two ketones was subjected to acidic conditions in an effort to isomerize the more strained bicyclo[3.1.1]heptane **15** to its bicyclo-[3.2.0]heptane isomer. Thus, exposure of the mixture to *p*-TsOH (1 mol equiv to **15** in the mixture) in trifluoroethanol at 0 °C for 4 h induced the clean isomerization into a roughly 1:1, separable mixture (90%) of two cyclobutanones, **17** (IR 1776 cm^{-1}; ^{13}C NMR 217.7 ppm) and **16**, indicating that virtually all of **16** remained unchanged during this mild acid treatment. This rearrangement appears to go through a cation species such as **F** or its nonclassical cation equivalent (Figure 3), and the overall stereochemistry of the quaternary methyl group is maintained. The results of the AM1 calculations of

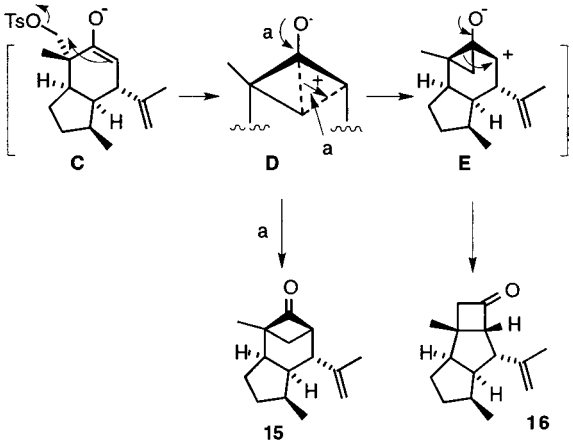


Figure 2. Base-catalyzed reactions of γ-keto tosylate **5**.

(14) This reaction has been shown to be highly solvent-dependent. See: (a) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615−6621. For the reaction in diethyl ether, see: (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884−2891.

(15) Interestingly, the use of $AsPh_3$ as the catalyst was found to be crucial for this Pd(0)-mediated efficient enyne cyclization. Other ligands such as PPh_3 and tris(2-furyl)phosphine proved to be less efficient as the catalyst for this reaction. Reviews: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34−42. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (c) Link, J. T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1523−1559. (d) de Meijere, A.; Reiser, O. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1647−1650.

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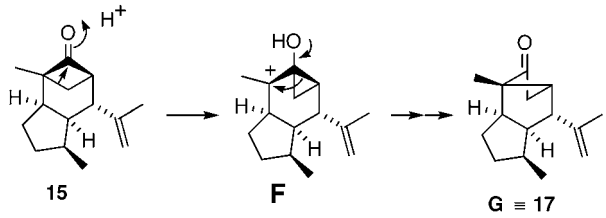

Figure 3. Acid-catalyzed rearrangement of **15** to **17**.

heats of formation for the two ketones **15** and **17** are consistent with observed results. Thus, heats of formation of ketone **17** have been shown to be over 17 kcal/mol lower than that of **15**.[20]

The mixture of ketones **16** and **17** was next converted to their tosylhydrazone derivatives. These tosylhydrazones were subsequently reduced to the hydrocarbon kelsoene (**4**) by the use of Hutchins' two-phase procedure[21] with $NaB(CN)H_3$ in the presence of anhydrous *p*-TsOH in overall 76% yield. The kelsoene thus obtained exhibited IR and ^1H and ^{13}C NMR spectroscopic properties identical to those reported.[6]

(20) Heats of formation calculated for cyclobutanones **15** and **17** by the AM1 method are, respectively, −14.578 and −31.925 kcal/mol.

(21) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc*. **1973**, *95*, 3662−3668.

In summary, we have achieved a highly efficient total synthesis of (±)-kelsoene (**4**) from commercially available 2,5-dihydroanisole (**10**) in 16 steps in overall 12.5% yield. The salient feature of the synthesis lies in the use of a base-catalyzed reaction of γ-keto tosylate **5**, which afforded products of an intramolecular S_N2 reaction of the enolate and a homo-Favorskii reaction, **15** and **16**, respectively, in excellent yield. A mixture of cyclobutanones **15** and **16** has been treated with *p*-TsOH to effect a clean conversion of the former to **17**, whereas the latter remains unchanged. This isomerized cyclobutanone **17** has the same carbon skeleton as kelsoene. This combination of the acid-catalyzed isomerization and a homo-Favorskii reaction of γ-keto tosylates seems to hold excellent potential for the synthesis of a variety of natural products having the bicyclo[3.2.0]heptane carbon framework.

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Supporting Information Available: Experimental details as well as analytical and spectroscopic data for new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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