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Synthesis of the Reported Structure of Pogostol and a Total Synthesis of (±)-Kessane without the Use of Protecting Groups

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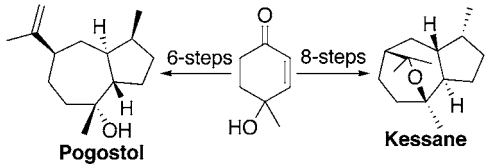
ABSTRACT



A short racemic synthesis of kessane from 4-hydroxy-4-methyl-2-cyclohexenone is described using a route that also resulted in the synthesis of the reported structure of pogostol. The key step involves an Fe(III)-mediated tandem radical ring-expansion/cyclization of the cyclopropylsilyl ether 9. No protecting groups are used in the entire sequence. Comparison of the NMR data of synthetic pogostol to that in the literature indicates that the structure originally proposed is incorrect.

Previously, we reported that cyclopropyl silyl ethers undergo tandem radical ring-expansion/cyclization on treatment with Fe(III) salts.[1] For example, treatment of the cyclopropylsilyl ether **1** with ferric chloride in DMF leads to the [5.3.0] bicyclic chloro-ketone **3** by way of the ring-expanded β-keto radical **2**. At the same time, independent studies by Narasaka[2] and co-workers showed that treatment of cyclopropanols with $Mn(pic)_3$, in conjunction with a variety of trapping agents, could be used to effect similar transformations and add functionality to the resulting bicyclic products.[3] Since then, Simpkins[4] and Cha[5] have reported applications of this Fe(III)/Mn(III) chemistry in synthesis as well as development of related methodology. As this strategy allows rapid diastereoselective access to bicyclic ketones from simple enones, it can be envisioned that this would be particularly useful as a key step in the synthesis of [5.3.0] terpene-based natural products. To that end, Narasaka et al. were able to apply their Mn(III) methodolgy to a total synthesis of 10-isothiocyanatoguaia-6-ene.[3] Recently, we described the use of our Fe(III) methodology in an approach to the terpenoids dictyol-C and α-eudesmol.[6] Herein, we describe the application of the Fe(III)-mediated ring expansion−cyclization

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sequence to a short total synthesis of the reported structures of pogostol **4**, pogostol *O*-methyl ether **5**, and the tricyclic sesquiterpene kessane **6**. Pogostol is one of the constituents of the musky oil isolated from the patchouli plant, which has been used in traditional Chinese medicine and has antiemetic properties.[7] A full structural assignment of pogostol by NMR was described by Weyerstahl in 2000.[8] In 1998, Waterman described the isolation and NMR structural assignment of pogostol *O*-methyl ether **5** from the stem bark of *Artabotrys stenopetalus (Annonaceae)*.[9] Kessane, conceivably related to **4** by cyclization, was isolated[10] from *Valeriana officinalis* in 1967, and a detailed structural assignment was made by van Beek et al.[11] in 1993.

Initially we set out to synthesize pogostol *O*-methyl ether **5** from 4-methoxy-4-methyl-2-cyclohexenone **7** (R = Me). Conjugate addition of 3-butenylmagnesium bromide to **7** (R = Me) using our previously developed conditions[1b] produced the corresponding TMS enol-ether as a single diastereoisomer, but unfortunately the butenyl group was delivered to the enone from the *opposite* side of the methoxy group.

About this time, Csaky et al.[12] reported that Grignard reagents could be added in a syn manner to 4-hydroxy-2-cyclopentenones without the need for copper(I) catalysis. With this in mind, 4-hydroxy-4-methyl-2-cyclohexenone **7** (R = H) was treated with 3 equiv of 3-butenylmagnesium bromide and an excess of TMSCl followed by the addition of Et_3N to afford the enol-ether **8** as a single diastereoisomer. It is interesting to note that if Et_3N was omitted, then the intermediate magnesium enolate was inert to reaction with TMSCl and only the corresponding ketone could be isolated on workup. As soon as Et_3N was added, an instantaneous reaction was triggered and TLC indicated the formation of the enol-ether. Furthermore, the tertiary hydroxyl group in **8** proved to be so inert to reaction with TMSCl under these conditions that it was carried on through subsequent steps without protection. Cyclopropanation with Et_2Zn/CH_2I_2 gave an excellent yield of the hydroxy-cyclopropane **9**. It should be noted that the use of PhMe as a solvent, instead of the usual Et_2O, resulted in greatly enhanced rates and yields of this and related cyclopropanations. With quantities of **9** in hand, we then investigated the key Fe(III)-mediated ring expansion−cyclization reaction. With $Fe(NO_3)_3$ and 1,4-cyclohexadiene as a hydrogen atom donor, it was found that the bicyclic ketone **10** could be formed in 57% yield as a single diastereoisomer and without elimination of the tertiary hydroxyl group. Introduction of the 2-propenyl moiety was achieved by first treating **10** with ethyl triphenyl phosphorane to generate the corresponding alkene **11** as a 1:1 *E*/*Z* mixture. Hydroboration of this followed by in situ oxidation[13] with PCC generated the ketone **12** in good yield as a 2:1 mixture of epimers.[14] Tebbe methylenation[15] of these yielded a partially separable 2.5:1 mixture of the reported structure for (±)-pogostol **4** and *epi*-pogostol **13** in quantitative overall yield.

However, at this point we were dismayed to find that detailed comparison of the literature ^1H and ^{13}C NMR data of pogostol with both synthetic (±)-**4** and the epimer (±)-**13** unequivocally demonstrated that *neither* of them were consistent with the data reported for the natural product.

Fearing that an earlier step in our synthesis had proceeded to give an incorrect stereocenter, we sought to resolve the issue by X-ray crystallography. Reduction of **10** with $NaBH_4$ produced a 1:1 mixture of the corresponding epimeric alcohols. Both these alcohols were then converted to separable epimeric *p*-nitrobenzoates. Careful crystallization of one of the esters **14** gave suitable crystals for X-ray crystallography, which proved that both the conjugate addition and the ring expansion−cyclization sequence had proceeded as anticipated to give the same relative stereochemistry reported for pogostol (Figure 1).[16] We can only

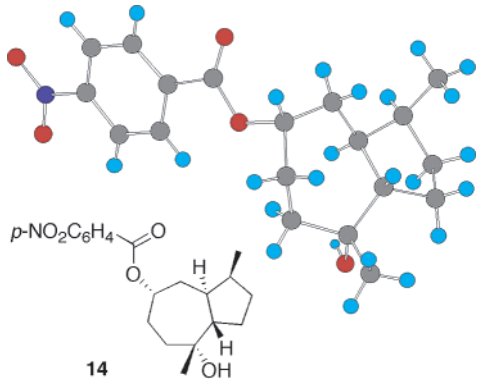

Figure 1. X-ray of *p*-nitrobenzoate **14**.

conclude, therefore, that the structure originally proposed for the natural product is now untenable and that structural revision will be necessary.

Initial attempts to form (±)-pogostol *O*-methyl ether by methylation of both (±)-**4** and (±)-**13** under standard conditions with MeI and base were unsuccessful presumably due to the extremely hindered nature of the tertiary hydroxyl group. However, methylation under more forcing conditions yielded the reported structure for pogostol *O*-methyl ether

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(14) Stepwise hydroboration and oxidation of the purified mixture of alcohols with DMP yielded the ketones **12** as a 1:1 mixture.
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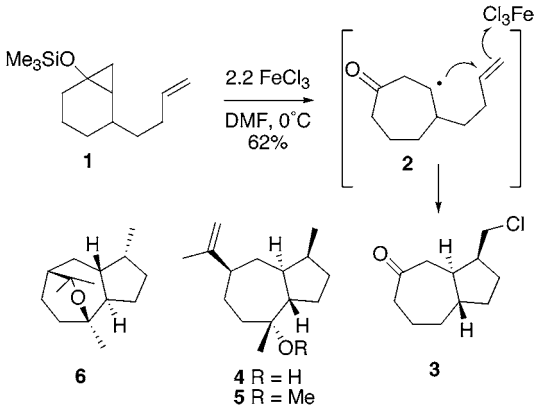
(16) X-ray data were collected on a Bruker APEX single-crystal diffractometer. Crystal data for **14**: $C_{19}H_{25}NO_5$, $M = 347.40$, orthorhombic, $a = 12.774(7)$ Å, $b = 10.955(4)$ Å, $c = 25.097(9)$ Å, $U = 3512(3)$ Å^3, $T = 100$ K, space group *Pbca* (no. 61), $Z = 8$, μ(Mo Kα) = 0.095 mm^{-1}, $R_{int} = 8.0\%$ (for 18382 data), w$R_2 = 10.1\%$ (for all 2922 unique data), $R_1 = 4.7\%$ [for 2161 data with $I > 2s(I)$].

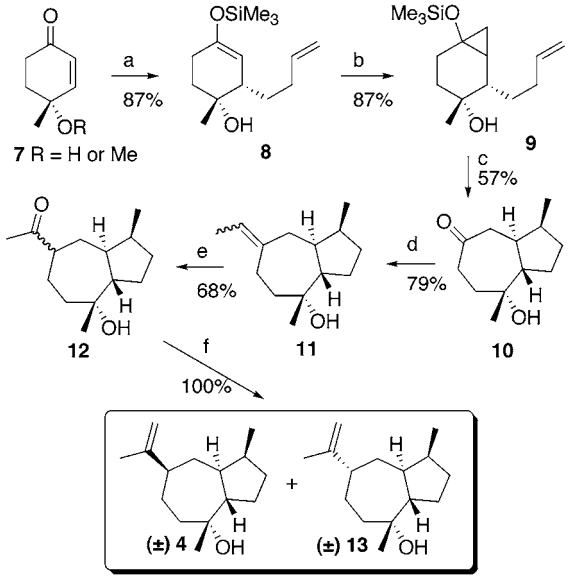
(±)-**5** and the epimer, (±)-**15**. These same two compounds were also synthesized via an alternative strategy involving methylation of **11** to give the ether **16**. This was followed by hydroboration to the alcohols **17** and Dess−Martin oxidation to the ketones **18**. Finally, Tebbe methylenation afforded a mixture of (±)-**5** and (±)-**15**, which were identical to those prepared above (Scheme 3). Unfortunately, NMR

Scheme 1. Fe(III)-Mediated Ring Expansion−Cyclization



analysis showed that neither (±)-**5** or (±)-**15** possessed spectral data consistent with that reported by Waterman et

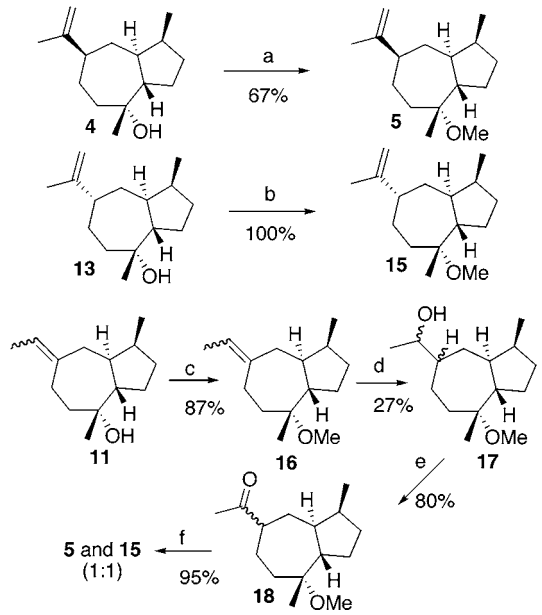
Scheme 2. Total Synthesis of (±)-Pogostol and *epi*-Pogostol[a]



[a] Reagents: (a) 3-butenylmagnesium bromide, TMSCl, DMPU, THF −78 °C, 1 h then Et_3N; (b) Et_2Zn, CH_2I_2, PhMe, 0 °C; (c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 10 min; (d) 3 equiv $Ph_3P{=}CHCH_3$, THF, rt to 50 °C; (e) BH_3·THF, THF then PCC, THF; (f) Tebbe reagent (Cp_2TiCl_2, $AlMe_3$, PhMe), THF.

al. for pogostol *O*-methyl ether. As with pogostol, there were simply too many differences in key ^{13}C signals for a satisfactory match. As both (±)-**5** and (±)-**15** have been derived,

Scheme 3. Total Synthesis of (±)-Pogostol *O*-Methyl Ether and Epimer[a]

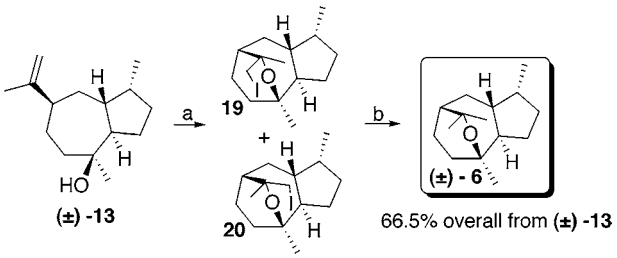


[a] Reagents: (a) Me_3OBF_4, proton sponge, CH_2Cl_2; (b) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; (c) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, heat; (d) BH_3·THF, THF then NaOH, H_2O_2; (e) Dess−Martin periodinane, CH_2Cl_2; (f) Tebbe reagent (Cp_2TiCl_2, $AlMe_3$), CH_2Cl_2.

via two different synthetic routes, from a ketone **10** whose structure is unambiguous, we can only conclude that the reported structure for pogostol *O*-methyl ether is also incorrect.

Although this was disappointing, it occurred to us that "*epi*-pogostol" (±)-**13** may prove to be useful as an intermediate in a racemic synthesis of the sesquiterpene kessane **6**, which was previously synthesized by Gijsen et al.[17] It was envisaged that the pyran ring in **6** could be constructed by an electrophilic cyclofunctionalization reaction of *epi*-pogostol (±)-**13**. Initial attempts using mercuric acetate gave only starting material. Treatment of racemic (±)-**13** (drawn in Scheme 4 with the same relative stereochemistry as **6**)

Scheme 4. Total Synthesis of (±)-Kessane[a]



[a] Reagents: (a) *N*-iodosuccinimide, CH_2Cl_2, rt, 4 h; (b) Pd/C/H_2, EtOAc, 6 h.

with *N*-iodosuccinimide[18] generated the labile diastereomeric iodides **19** and **20** in essentially quantitative yield. Attempts

at reductive deiodination under a number of conditions resulted in either ring opening back to *epi*-pogostol (Zn/AcOH) or no reaction ($LiAlH_4$). Hydrogenation over Pd/C, however, eventually afforded synthetic kessane in 66.5% overall yield from (±)-**13**. Detailed analysis of the ^1H and ^{13}C spectral data of synthetic (±)-**6** showed excellent agreement (±0.2 ppm for all signals in ^{13}C spectra) with that reported for the natural product by van Beek et al.[11]

In summary, a short racemic synthesis of the reported structures of both pogostol and pogostol *O*-methyl ether has been described using our previously developed Fe(III)-mediated tandem radical ring expansion−cyclization chemistry of cyclopropylsilyl ethers. Detailed NMR, X-ray crystallographic, and subsequent synthetic studies, however, have clearly demonstrated that the previously reported structures for both these natural products are incorrect and will require revision. It was possible to convert *epi*-pogostol (±)-**13** into (±)-kessane **6** in an additional two steps, thus completing an eight-step linear synthesis of this tricyclic sesquiterpene in which *no protecting groups* were used.

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Supporting Information Available: Experimental procedures and characterization for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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