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Studies directed toward the synthesis of FS-2: observations on the fragmentation of cyclobutylcarbinyl radicals†

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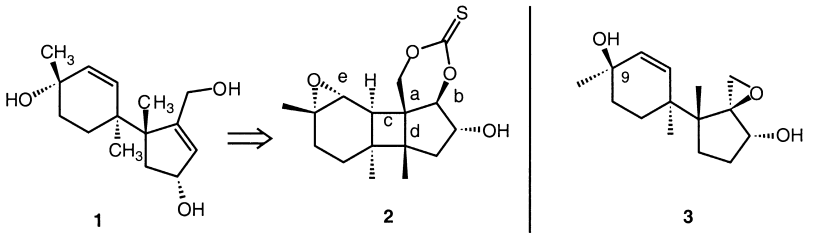
Abstract

Studies directed toward a synthesis of the sesquiterpene FS-2 have permitted an investigation of the fragmentation of a cyclobutylcarbinyl radical that preferentially cleaves to give the more stable of two possible radicals. This observation is contrasted with the results obtained in an analogous cyclobutyloxy radical fragmentation.

In 1987, Tempesta isolated and characterized FS-2 (**1**), a secondary metabolite from the fermentation of *Fusarium sporotrichioides*. The structure was elucidated by spectroscopic means and the absolute configuration was assigned in analogy with other known trichothecenes.[1] Subsequently, the relative configurational assignment of the tertiary hydroxyl group of **1** was questioned by Gilbert.[2] These NMR studies on trichodiol (**3**) led to a change in the C_9 configurational assignment of members of this series of compounds.



Our interest in this compound was stimulated by the opportunity to explore the sequential radical fragmentation of cyclic thiocarbonate **2** with the expectation of resolving the stereochemical issue.

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† In memory of Professor Paul Dowd.

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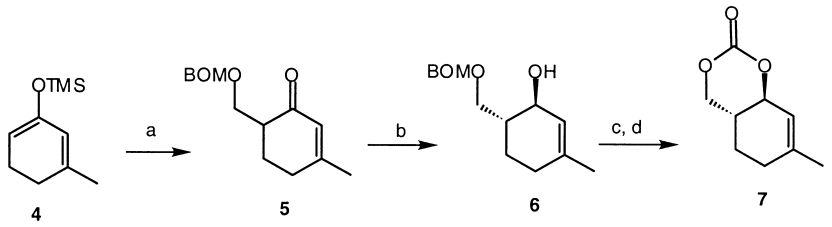
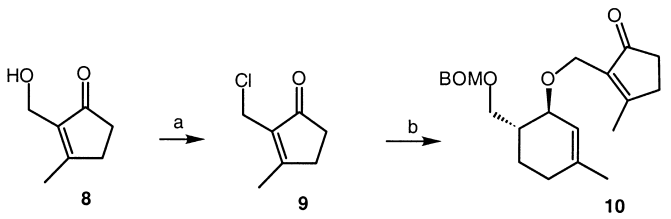
The anticipated sequence of events was initial cleavage of bond b,[3] followed by bond c[4] and bond e[5]. This letter details the preparation of the carbon nucleus of **2** and presents results on the fragmentation of a cyclobutylcarbinyl radical in this series.

Direct kinetic enolate alkylation of 3-methyl cyclohex-2-en-1-one with BOMCl was unsuccessful (Scheme 1). However, electrophilic alkylation of **4**, prepared from the enone as described by Rubottom,[6] was successful on a small scale (< 500 mg, 49%) when freshly sublimed $ZnBr_2$ was used or, on a multigram scale, when the Simmons–Smith reagent was employed as the catalyst.[7,8] Because enone **5** was not very stable, it was reduced after purification to a chromatographically stable, readily separable 7:1 mixture (*trans*:*cis*; 85%) of alcohols. *trans* Alcohol **6** had J = 8.4 Hz (C_1H–C_6H) while the *cis* isomer displayed J = 4.0 Hz in their respective ^1H NMR spectra. These data were supported by the C_1–C_6 coupling constants in the respective *trans* (J = 9.5 Hz) **7** and *cis* (J = 4.3 Hz) cyclic carbonates.



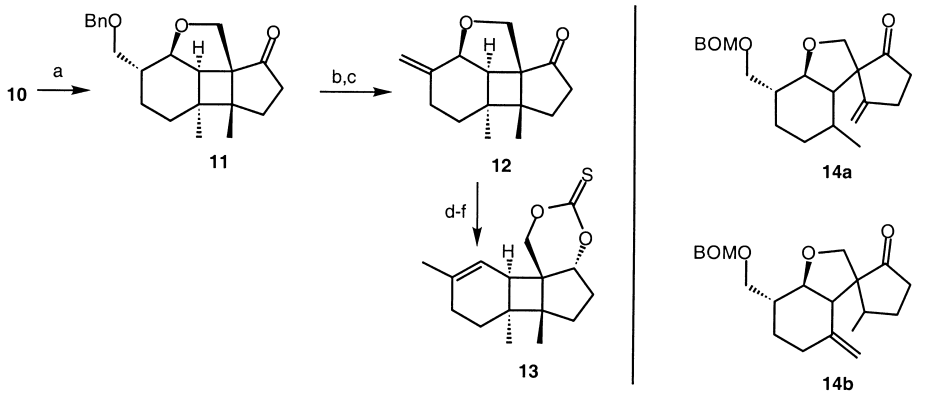
Scheme 1. (a) Zn, Cu_2Cl_2, CH_2I_2, CH_2Cl_2; $PhCH_2OCH_2Cl$, 0°C, (58%). (b) $LiAlH_4$, Et_2O, 0°C, (85%). (c) Li, Et_2NH/THF, –78°C, (97%). (d) triphosgene, DMAP, pyr./THF, 0°C, (93%)

The formation of bis-allyl ether **10** proved to be problematic. The optimal reaction conditions required the slow addition of chloride **9**, readily prepared from the alcohol **8**,[9] to a solution of alcohol **6** in the presence of Ag^+ and non-nucleophilic base, and under scrupulously dry conditions (Scheme 2). When this protocol was followed, yields of **10** were reproducible but the scale of the reaction was limited to ~300 mg.



Scheme 2. (a) $SOCl_2$, neat; 0°C (96%). (b) Compound **6**, AgOTf, 2,6-di-*tert*-butylpyridine, 4 Å MS, CH_2Cl_2, rt, 8h, (57%)

Photolysis of cyclopentenone **10** produced a single product of [2+2]-cycloaddition whose structure was assigned as cyclopentanone **11** (Scheme 3). Presumably cycloaddition occurs *anti* to the benzyloxymethyl group leading to photoadduct **11** having the *cis–anti–cis* stereochemistry about the cyclobutane ring.[10] The *cis* relationship between the ether methine hydrogen and the vicinal cyclobutane proton was confirmed by a coupling constant of J = 6.0 Hz (calcd J = 6.9 Hz), and the presence of the quaternary methyl groups was indicated by singlets at δ 1.09 and 1.11. The ^{13}C NMR spectrum of tetracycle **11** revealed 19 of the 20 unique carbons.



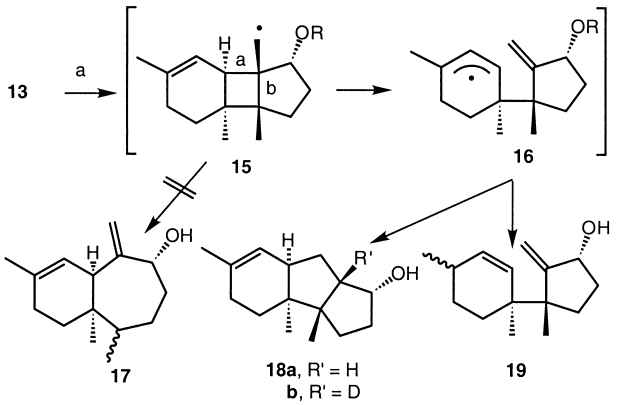
Scheme 3. (a) hν, 450 W Hanovia lamp, rt, 8.75 mM benzene (78%). (b) H_2, Pd/C, 40 psi (98%). (c) *n*-Bu_3P, *o*-$NO_2C_6H_4SeCN$, 0°, THF; O_3, *i*-Pr_2NH, CH_2Cl_2, –78°C (75%). (d) $LiAlH_4$, Et_2O, 0°C (89%). (e) Li/$EtNH_2$, –78°C, (91%). (f) Im_2CS, toluene, reflux, 10 h (85%)

Owing to the photolability of ketone **11**, the photolysis was run to 50% conversion; separation of **10** from **11** was effected and **10** was recycled twice. A minor amount of the two disproportionation products **14a** and **b**, formed from the diradical intermediate (10% yield after three cycles), was isolated and characterized by the appearance in the ^{1}H NMR spectrum of two high field methyl doublets and four low field methylene vinylic signals in the 1:1 mixture of the two compounds.

Oxidation of the *o*-nitrophenylselenide[11] in the sequence of reactions **11**→**12** could not be accomplished with peracid in the conventional way owing to Baeyer–Villiger oxidation of ketone **12**.[12] The use of ozone as an oxidant circumvented this problem. Interestingly, the cyanohydrin of the seemingly hindered ketone **12** was also isolated during selenide formation.[13] The cyanohydrin readily formed ketone **12** upon exposure to base. Reduction of ketone **12** occurred exclusively from the *exo*-face leading to a diol whose *trans*-fused cyclic thiocarbonate **13** had to be formed under forcing conditions.

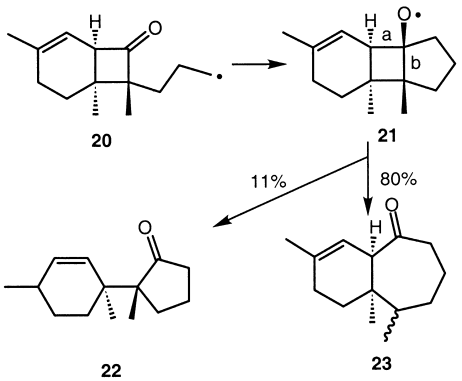
Although not germane to the synthesis of FS-2, cyclic thiocarbonate **13** was, nonetheless, an intriguing substrate upon which to explore cyclobutane fragmentation. Not surprisingly, reduction of **13** with *n*-Bu_3SnH under high dilution conditions ($< 10^{-3}$ M, syringe pump) led to formation of the less stable primary cyclobutylcarbinyl radical **15** owing to ring strain in the thiocarbonate ring (Scheme 4).[3] Cyclobutane fragmentation led only to isolable products from bond a cleavage to produce the stabilized allylic radical **16** as opposed to fragmentation of bond b leading, ultimately, to diene **17**. Allylic radical **16** underwent 5-*endo–trig* cyclization to provide tricycle **18a** (47%) and a mixture of allylic alcohols **19**. When *n*-Bu_3SnD was employed in the radical fragmentation, the deuterium atom was located in **18b** vicinal to the hydrogen on the carbinol carbon. This hydrogen showed reduced coupling in the ^{1}H NMR spectrum. No products leading to ring expansion were isolated. Minimally, 65% of the fragmentation proceeded in the direction of the more stabilized allyl radical.[14–16] In the absence of the unsaturation in **13**, ring expansion, i.e., internal bond cleavage, is observed.[3,17]

This result was the expected course of fragmentation of cyclobutylcarbinyl radical **15**, a result that contrasts sharply with the mode of fragmentation of cyclobutyloxy radical **21** (Scheme 5).[18] Radical **20**, generated from the bromide with *n*-Bu_3SnH/AIBN, in addition to forming 9% of



Scheme 4. R = $COSSnBu_3$; (a) degassed 0.05 M *n*-Bu_3SnH, AIBN/toluene, slow addition to **13**, reflux, 6 h

direct reduction product, gave the alkoxy radical **21**, which, surprisingly, underwent fragmentation to afford preferentially the product of ring expansion **23** (80%) and a minor amount of material (**22**, 11%) from fragmentation to form an allyl radical. Molecular mechanics calculations have supported the argument that the transition state for bond b cleavage in alkoxy radical **21** is higher in energy than for cleavage of bond a.[19] The early transition state for bond a cleavage does not afford the opportunity for allylic radical stabilization. The faster rate ($\sim 10^4$) of fragmentation of cyclobutyloxy radicals[20] over cyclobutylcarbinyl radicals[4] at 80°C implies a late transition state for the latter process and a larger contribution of allyl radical stabilization in the bond-breaking process.



Scheme 5.

Acknowledgements

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