ORGANIC LETTERS

2008
Vol. 10, No. 11
2255−2258

Rearrangement of a Cyclohexyl Radical to a Cyclopentylmethyl Radical on the Avermectin Skeleton

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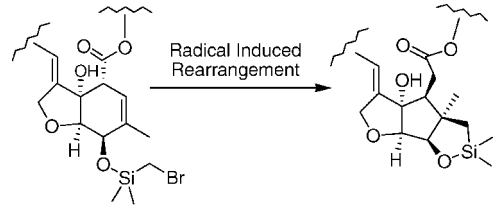
Received March 25, 2008

ABSTRACT



The rearrangement of a substituted cyclohexyl radical to a cyclopentylmethyl radical on the skeleton of avermectin B_1 was observed experimentally and explored computationally. The Stork−Nishiyama methodology was applied to the macrocycle of interest followed by a Tamao oxidation. The expected 5−6 fused ring product was observed in minor amounts. The major product was a 5−5 fused ring resulting from apparent conversion of the initially formed cyclohexyl radical to a cyclopentylmethyl radical. Preliminary computational results indicate that substituents in the macrocycle induce the rearrangement.

The highly potent avermectin macrolides, discovered more than two decades ago at Merck,[1,2] continue to elicit considerable interest for the treatment of parasitic diseases. Synthetic derivatives of avermectins have also been found to be effective against parasitic infections,[3] and many total syntheses of avermectin and its derivatives have been reported.[4] Our interest in this family resides in particular in avermectin B_1 (Figure 1). In order to explore the structure−activity relationships that could govern the efficacy of avermectin B_1 derivatives within this domain, novel structural modifications of the macrolide framework were investigated. We report an unexpected rearrangement that was discovered during our efforts directed toward the preparation of the C-4-hydroxymethylated derivative **1** shown in Figure 1.

The Stork−Nishiyama methodology[5] was selected for the preparation of the desired 1,3-diol, **1**. As shown in Scheme 1,

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10.1021/ol8001283 CCC: $40.75
Published on Web 05/08/2008

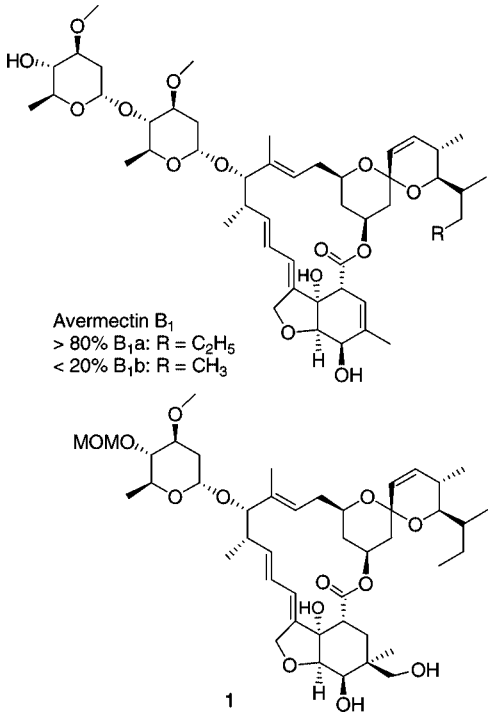
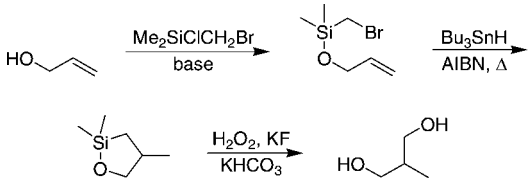


Figure 1. Avermectin B_1 and hydroxymethylated derivative.

this approach involves a radical cyclization process and generally gives high yields of the 5-membered siloxy cycle[6]or the 1,3-diol produced after oxidation.[7] The intermediate silicon-tethered radical typically undergoes cyclization in a 5-*exo* fashion.[7] Literature examples of the Stork−Nishiyama methodology indicate that the silaoxacyclopentylmethyl radical is typically trapped by tributyltin hydride as shown in Scheme 1 or is involved in further radical cyclization.[6,7] Rearrangements of the silaoxa-cyclopentylmethyl radical have not been reported in conjunction with the Stork−Nishiyama methodology.

Scheme 1. Stork−Nishiyama Radical Cyclization Followed by Tamao Oxidation



Radical generation was carried out using bromomethylsilyl ether **2** (Scheme 2), which was refluxed in *tert*-butyl alcohol in the presence of *n*-Bu_3SnCl, AIBN, and $NaCNBH_3$[5c] for 3 h. The products were then oxidized by a Tamao oxidation.[8] Surprisingly, the 5-*exo* mode of cyclization afforded the expected 5−6 fused ring system **1** only in minor amounts (<5%). The ^1H NMR spectrum of the minor product shows a doublet of doublets at δ 1.84 ppm and δ 1.71 ppm, corresponding to the unsubstituted CH_2 at C-3, coupled to the CH at C-2 (δ 2.96 ppm). The ^1H NMR spectrum of the major product does not contain such doublets. The major product (isolated in 46% yield from the silyl ether) was the novel 17-membered lactone **3** (rather than the expected 16-membered lactone **1**) resulting from contraction of the cyclohexane to a cyclopentane. The ^1H NMR of lactone **3** has a multiplet between δ 2.53 ppm and δ 2.35 ppm corresponding to three hydrogens on C-2 and C-3. Competitive reduction of the bromomethyl silyl tether was also observed (12%). The structure elucidation of the new compounds is described in the Supporting Information (experimental section), wherein the fully assigned ^1H and ^{13}C NMR data are provided.

The formation of **3** may be rationalized by rearrangement of the cyclohexyl radical **5** to a more stable, nucleophilic radical **6**, by an unusual fragmentation of the C-2, C-7 σ bond, as illustrated in Scheme 3. Normally, cyclohexyl radicals are trapped without fragmentation. Subsequent intramolecular addition of this tertiary radical to the α,β-unsaturated ester function could then lead to the highly congested tricycle **7**. The macrocyclic radical **6** is stabilized by the presence of the butadienyl group and the butadiene retains the E,E-geometry. The stereochemistry of the methylene ester in **7** is explained by the conformational preference of the macrocycle.[9] Isolation of **8**, followed by Tamao oxidation led to **3** in good yield.

Experiments conducted on avermectin B_1 similarly led to rearranged diol **9** in 34% yield, Figure 2. The ^1H NMR peaks for C-2 and C-3 hydrogens in **9** are not clean doublets and are similar to the multiplet seen in **3**.

The reactions of 5-hexenyl radicals have been studied thoroughly.[10,11] Both the 5-exo-trig and 6-endo-trig closures

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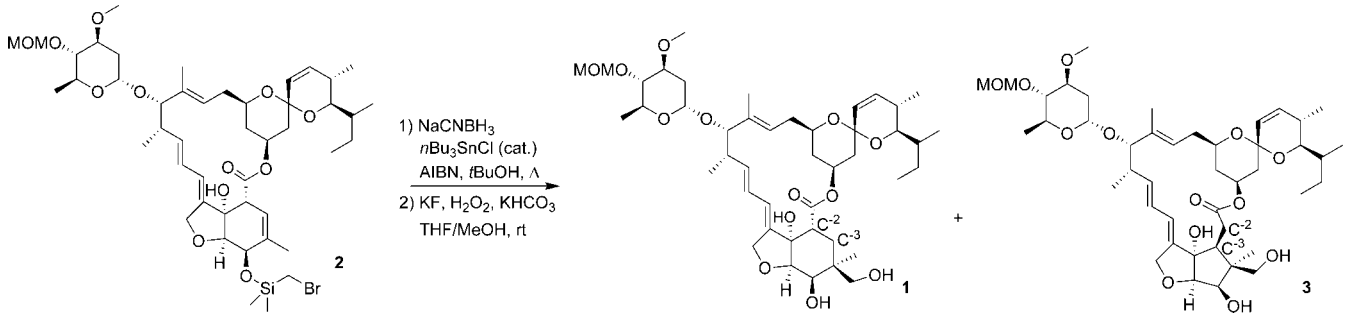
Scheme 2. Formation of **1** (Minor Product) and **3** (Major Product) from **2**



are favored by Baldwin's rules.[12] The 5-exo product is generally the kinetic product, whereas the 6-endo analogue is the thermodynamic product. The cyclohexyl radical is stable, when formed, since the cyclohexyl radical is 14 kcal/mol more stable than the 5-hexenyl radical and 6 kcal/mol more stable than the cyclopentylmethyl radical. The energies of activation for the 6-endo and 5-exo ring closures of 5-hexenyl radical have been established theoretically and experimentally (8−9 kcal/mol and 6−7 kcal/mol, respectively).[10b,e,11a,b]

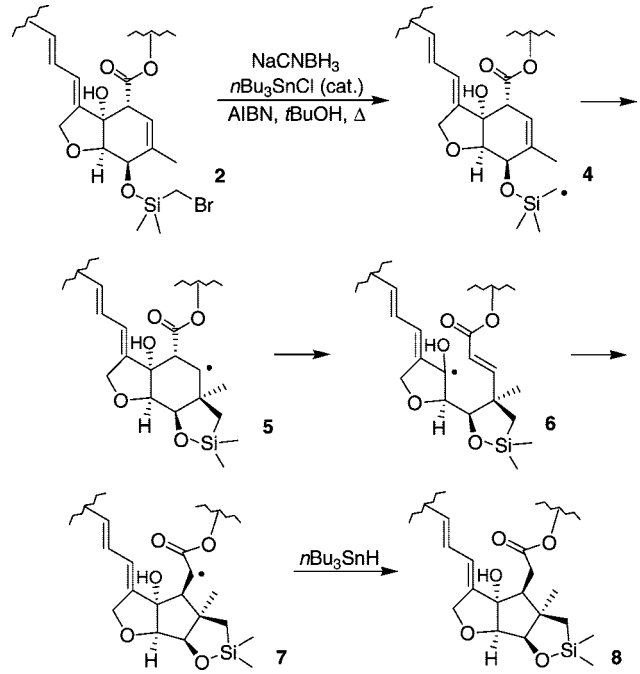
DFT calculations have been carried out on simplified model systems to understand how the unprecedented conversion of the normally stable cyclohexyl radical to the less stable cyclopentylmethyl radical occurs. Gas phase optimizations and frequency calculations were carried out using UB3LYP/6-31G(d)[13] as implemented in Gaussian 03.[14] Previous investigations have shown that UB3LYP geometries and energies are reasonably accurate for evaluation of the energies of radical reactions.[11,15]

The energies for ring closures of an unsubstituted 5-hexenyl radical were investigated at this level of theory. Table 1 compares these energies to those previously calculated and energetics obtained experimentally.

Simplified 5−6−5 model systems with varying substituents were investigated, Table 2. Without substituents at R^1 and R^2, the enthalpy for ring-cleavage is prohibitively high and the rearrangement is endothermic ($\Delta H_1 + \Delta H_2 = 9$ kcal/mol). With a vinyl group at R^2, the enthalpy of ring-cleavage is lowered by 10 kcal/mol, but the overall rearrangement remains endothermic. The proposed rearrangement is exothermic with a formyl group at R,[1] but this substituent only minimally affects the energetics of ring-cleavage, so the rearrangement would proceed slowly.

The proposed rearrangement is energetically feasible with a formyl substituent at R^1 and a vinyl substituent at R.[2] The highly stabilizing vinyl substituent lowers the activation enthalpy of ring-cleavage by 8−9 kcal/mol. The presence of a formyl substituent at the R^1 stabilizes the cyclopentylmethyl radical so that formation of the cyclopentylmethyl radical from the cyclohexyl radical is exothermic. With both

Scheme 3. Proposed Mechanism for Rearrangement of Cyclohexyl Radical **5** to Cyclopentylmethyl Radical **7**



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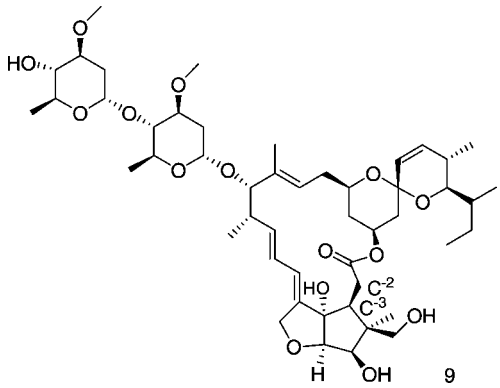


Figure 2. Rearranged product of avermectin B_1.

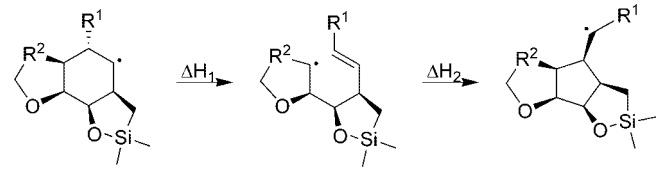
a formyl group at R^1 and a vinyl group at R^2, the overall rearrangement is exothermic and the enthalpies of activation for ring cleavage and ring closure are low enough to compete with radical trapping, especially since the rate of trapping is affected by the dilute concentration of tributyltin hydride.[16] In **2**, the lactone is present at R^1, instead of the formyl group in the model system. The hydroxyl, dienyl groups in **2** are even more potent radical stabilizing groups than the vinyl group of the model system.

Table 1. Activation Energies (kcal/mol) of 5-Hexenyl Radical Ring Closures

	6-endo $E^{\ddagger}$	5-exo $E^{\ddagger}$
this study[a]	9.3	6.9
previous computational work[b]	9.1	6.4
experimental[c]	8.5	6.8

[a] UB3LYP/6-31G(d). [b] UB3LYP/6-31+G(d,p)//UHF/3-21G(d), ref 11b. [c] Reference 10b,e.

Table 2. Enthalpies for Rearrangement of Cyclohexyl Radicals to Cyclopentylmethyl Radicals (in kcal/mol at UB3LYP/6-31G(d))



substituents	$\Delta H_1^{\ddagger}$	ΔH_1	$\Delta H_2^{\ddagger}$	$\Delta H_1 + \Delta H_2$
$R^1 = H$, $R^2 = CH_2$	29.4	15.5	6.3	9.3
$R^1 = H$, $R^2 = C{=}CH_2$	20.1	5.2	13.9	8.5
$R^1 = CHO$, $R^2 = CH_2$	24.0	11.7	2.3	−5.1
$R^1 = CHO$, $R^2 = C{=}CH_2$	15.8	−1.7	8.0	−6.2

We have demonstrated that the normal relative stabilities of the 5-hexenyl radical, cyclohexyl radical, and cyclopentylmethyl radical can be altered by substitution. DFT calculations show that highly radical-stabilizing substituents at R^1 and R^2 enable the rearrangement of a cyclohexyl radical to afford a ring-contracted product.

Acknowledgment. Work at UCLA was supported by the National Institute of General Medical Sciences, National Institutes of Health (GM 36700 to K.N.H.).

Supporting Information Available: Experimental details, characterization of the compounds discussed, Cartesian coordinates, and UB3LYP/6-31G(d) energetics for transition and ground states. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8001283

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