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Unexpected Cleavage of 2-Azido-2-(hydroxymethyl)oxetanes: Conformation Determines Reaction Pathway?

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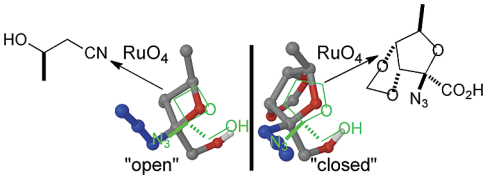

An unanticipated cleavage of 2-azido-2-(hydroxymethyl)oxetanes is reported. In attempts to oxidize the title oxetanyl alcohols to the corresponding carboxylic acids with RuO_4, cleaved nitriles were formed as the sole isolable products, while a closely related tetrahydrofuran gave solely the expected carboxylic acid. Quantum chemical calculations suggest that the divergent outcomes are governed by conformational differences in the azidoalcohols.

Introduction

We have been interested in the synthesis of oxetane containing natural product derivatives. As part of this focus we targeted oxetane analogs of hydantocidin, a natural product which has shown potent herbicidal activity[1] (Figure 1). In an attempt to oxidize a model system to the corresponding carboxylic acid, 2-azido-2-(hydroxymethyl)oxetane **1a** was treated with RuO_4, generated *in situ* from $RuCl_3 \cdot 3H_2O$ and $NaIO_4$; only nitrile **2a** was isolated. This was a surprising outcome since Sano and co-workers previously reported that azidoalcohol **3** was oxidized to carboxylic acid **4** in good yield.[2] No mention was made of nitrile formation (Figure 1).

To our knowledge, there are only three examples of β-hydroxyazide oxidative cleavage described in the literature (Figure 2). In 2004, Suarez and co-workers reported a radical fragmentation with the use of a hypervalent iodine reagent.[3] Then, in 2006, Ye and co-workers noted that oxidative cleavage to nitriles resulted when β-azidoalcohols were treated with PCC.[4] This outcome was attributed to the lability of β-azidoaldehydes under the conditions. The third, by Chiba et al., demonstrated that Pd(II) could promote a ring expansion involving an oxidative cleavage of cyclic 2-azidoalcohols to azaheterocycles.[5]

Ruthenium tetroxide is well-known for oxidizing primary alcohols to carboxylic acids, as well as for cleaving double bonds to carbonyl products.[6] A limited number of other C−C cleavage reactions mediated by RuO_4 have been described. In 1994, Ranganathan and co-workers reported the C−C cleavage of a β-hydroxyamide from a protein backbone using RuO_4.[7] Also, cleavage of β-hydroxyethers under similar oxidative conditions was noted by Ferraz and co-workers.[8] However, C−C scission of β-hydroxyazides with RuO_4 has not been previously reported. Due to the unexpected result when **1a** was treated with RuO_4, we decided to investigate the reactivity of other 2-azido-2-(hydroxymethyl)oxetanes under these conditions.

Results and Discussion

2-Azido-2-(hydroxymethyl)oxetanes **1** were synthesized from the corresponding β-lactones in four steps (Table 1). β-Lactones **6a**−**6c** and **6e** were prepared following the Mukaiyama aldol-lactonization protocol developed by Yang and Romo.[9] Compound **6d** was synthesized under Mitsunobu conditions as

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(2) Sano, H.; Mio, S.; Kitagawa, J.; Shindou, M.; Honma, T.; Sugai, S. *Tetrahedron* **1995**, *51*, 12563.
(3) Hernandez, R.; Leon, E. I.; Moreno., P.; Concepcion, R. F.; Suarez, E. *J. Org. Chem.* **2004**, *69*, 8437.
(4) Fan, Q.; Ni, N.; Li, Q.; Zhang, L.; Ye, X. *Org. Lett.* **2006**, *8*, 1007.
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(6) (a) Plietker, B. *Synthesis* **2005**, 2453. (b) Arends, I. W. C. E.; Kodama, T.; Sheldon, R. A. *Top. Organomet. Chem.* **2004**, *11*, 277.
(7) Ranganathan, D.; Vaish, N. K.; Shah, K. *J. Am. Chem. Soc.* **1994**, *116*, 6545.
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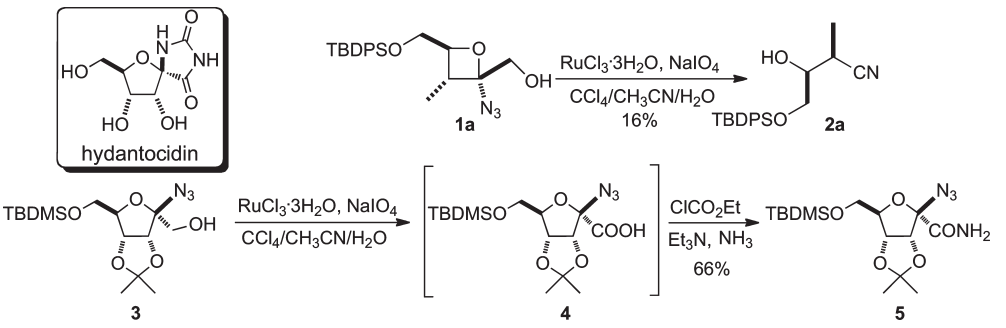
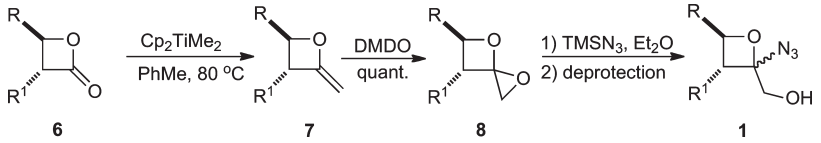


FIGURE 1. Outcome of reaction of oxetane **1a** and *psico*-furanose **3** with RuO_4.

TABLE 1. Synthesis of 2-Azido-2-(hydroxymethyl)oxetanes



entry	reactant	yield (%) of **7**	yield (%) of **1**[a]
1	(**a**) R = $CH_2OTBDPS$; R^1 = CH_3	55	67
2	(**b**) R = $(CH_2)_6CH_3$; R^1 = CH_3	67	30
3	(**c**) R = $(CH_2)_2Ph$; R^1 = CH_3	74[11]	34
4	(**d**) R = H; R^1 = Ph	76[11]	56[14]
5	(**e**) R = *c*-Hexyl; R^1 = H	33[b]	32

[a]Percent yield over 3 steps. [b]This compound is somewhat volatile.

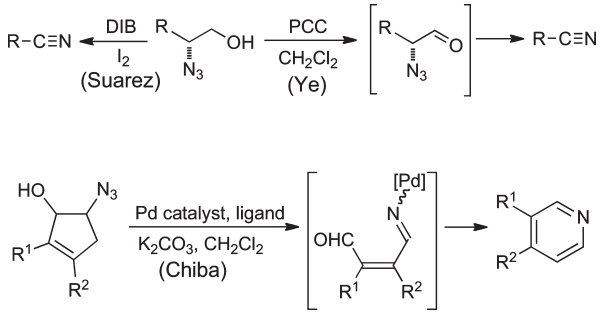


FIGURE 2. β-Hydroxyazide oxidative cleavages described in the literature.

previously described.[10] β-Lactones **6** were then subjected to methylenation with the Petasis reagent.[11] Subsequent epoxidation with acetone-free dimethyldioxirane,[12] produced 1,5-dioxaspiro[3.2]hexanes **8** in quantitative yields.[13] Dioxaspirohexanes **8** were then treated with azidotrimethylsilane,[14] followed by deprotection of the primary alcohol with tetra-*n*-butylammonium fluoride or potassium carbonate. The latter deprotection method was utilized only for *t*-butyldiphenylsilyl-containing oxetane **1a**. The diastereomers of **1** were separable. The relative stereochemistries of the diastereomers of **1a**−**c** were deduced from NOESY experiments.[15] Compound **1d** was known.[14]

Initially, the conditions to oxidize oxetane **1a** were based on Kumaraswamy and co-workers' report for the oxidation of a 2-hydroxymethyloxetane.[16] First, RuO_4 was generated from $RuCl_3 \cdot 3H_2O$ (0.06 equiv) and $NaIO_4$ (4 equiv) in a biphasic solvent system ($CCl_4/CH_3CN/H_2O$). Then, the supernatant was added to a solution of 2-azido-2-(hydroxymethyl)oxetane **1a** in CH_3CN, followed by additional $NaIO_4$ (2 equiv). The resulting mixture was stirred for 3 h at rt. NMR spectra (^1H and ^{13}C) of the crude product showed only nitrile **2a** and no carboxylic acid. However, the mass balance was low, and the yield of isolated nitrile was only 16%. To ascertain if other products were forming and being degraded, the reaction was repeated and monitored by NMR. After 15 min, starting material was still present; however, after 30 min, no starting material remained. The NMR spectra (^1H and ^{13}C) of the crude product (after workup) showed the nitrile as the major component. In addition, there were minor peaks which could not be assigned to any specific, isolable byproduct. The NMR spectra (^1H and ^{13}C) of the crude product after 3 h of reaction was cleaner than the corresponding 30 min reaction. To better understand this result, two reactions, one for 1 h and one for 2 h, were run. Again, the NMR spectra after workup were not as clean as the 3 h reaction, and in both reactions the nitrile was the only isolated product. This suggested that byproducts formed were further degraded at longer reaction times and became either water-soluble or volatile. Then, to clarify if the nitrile was stable under these conditions, nitrile **2b** was subjected to the same conditions. After stirring the reaction

(10) Hmamouchi, M.; Prud'homme, R. E. *J. Polym. Sci. Part A: Polym. Chemistry* **1991**, *29*, 1281.
(11) Dollinger, L. M.; Ndakala, A. J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R.; Rheingold, A. L.; Figuero, J. S. *J. Org. Chem.* **1999**, *64*, 7074.
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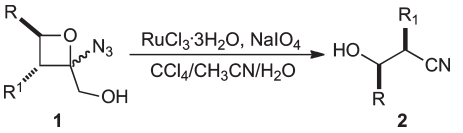
(16) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem.* **2006**, *71*, 337.

TABLE 2. Synthesis of Nitriles



1 2

entry	reactant	diastereomer	yield (%) of **2**	(%) of recovered **1**
1	(**a**) R = $CH_2OTBDPS$; $R^1 = CH_3$	anti[a]	20	33
2	(**b**) R = $(CH_2)_6CH_3$; $R^1 = CH_3$	syn/anti[a]	26	47
3	(**b**) R = $(CH_2)_6CH_3$; $R^1 = CH_3$	syn[a]	23	26
4	(**b**) R = $(CH_2)_6CH_3$; $R^1 = CH_3$	anti[a]	13	25
5	(**c**) R = $(CH_2)_2Ph$; $R^1 = CH_3$	anti[a]	15	24
6	(**d**) R = H; R^1 = Ph	anti[b]	22	0[c]
7	(**e**) R = *c*-Hexyl; R^1 = H	[d]	16	0[c]

[a]Syn/anti defined by relative stereochemistry of N_3 and R. [b]Syn/anti defined by relative stereochemistry of N_3 and R^1. [c]See text for discussion. [d]Reaction done on minor diastereomer; relative stereochemistry not determined.

mixture at rt for 2 h, only nitrile (>90%) was recovered. Thus, any loss of material balance could not be associated with degradation of the nitrile under the reaction conditions.

Next, in an attempt to minimize side reactions, no $NaIO_4$ was added after the RuO_4 supernatant was transferred to the azidoalcohol solution. After 25 min at rt, the NMR spectra (^1H and ^{13}C) of the crude product showed mostly starting material and nitrile, and it was considerably cleaner than the previous reactions. On the basis of this result, these conditions were utilized to study the behavior of other 2-azido-2-(hydroxymethyl)oxetanes **1**.

The reactivities of oxetanes **1a**−**1e** were examined. Besides recovered starting material, nitriles were the only isolable compounds (Table 2). This was true for both diastereomers, although the two isomers did not react with equal efficiency (entries 3 and 4). A slower rate of reaction for the isomers where the 2-azido and 3-methyl groups were on the same face of the oxetane was demonstrated by reaction of a mixture of the diastereomers of **1b** (entry 2). The *anti*-diastereomer (with the methyl group on the same side of the ring as the azide) was consumed more slowly, as evidenced by a change in ratio of the diastereomers in the reactants, compared to the recovered starting materials. A more rapid consumption of the *syn*-diastereomer was also observed when a reaction was done with a mixture of **1c**. This outcome will be discussed further in the quantum calculations section. In all cases, even with shorter reaction times and recovery of some of the starting material, the material balance was not accounted for. Since nitrile **2b** was shown to be stable under the reaction conditions, we postulated that the azidooxetanes were not themselves stable and that their byproducts may have been subjected to further oxidative degradation. For β-azidoalcohols **1d** and **1e** the expected nitriles were the major products isolated. However, no starting material was recovered, and based on the NMR spectra prior to purification, many additional products were observed. For substrate **1d** this outcome was attributed to aromatic ring degradation, as previously reported by Sharpless and co-workers.[17] In addition, considering **1e**, tertiary carbons can be oxidized by RuO_4.[18] If this occurs at the cyclohexyl tertiary carbon, along with the cleavage giving the nitrile, a vicinal diol would result. Further oxidative cleavage could lead to water-soluble and/or volatile byproducts.

To ascertain if the cleavage was being effected by RuO_4 or simply by $NaIO_4$, β-hydroxyazide **1b** was treated with 4 equiv of $NaIO_4$ in $CCl_4/CH_3CN/H_2O$, with no addition of RuO_4. After 25 min nitrile **2b** was isolated in 36% yield; no starting material was recovered. The fact that $NaIO_4$ effects nitrile formation is interesting and will be discussed later. However, these conditions were different from the conditions utilized in Table 2, where only the supernatant was transferred. To mimic these conditions the supernatant of a mixture of 4 equiv of $NaIO_4$ in $CCl_4/CH_3CN/H_2O$ was added to a solution of β-hydroxyazide **1b** in acetonitrile. After 25 min, only 6% of nitrile **2b** was isolated. This implies that RuO_4 was the main promoter for the reactions shown in Table 2.

The unexpected nitrile formation resulting from 2-azido-2-(hydroxymethyl)oxetane cleavage with RuO_4 led to three key questions for us: (1) Is this pathway unique to oxetane systems? (2) Which oxidation state--the primary alcohol, the aldehyde or the carboxylic acid--of the α-hydroxymethyl group is the immediate precursor of oxidative cleavage? (3) What is the role of the metal in the reaction?

To address the first question, other β-azidoalcohol systems were treated with RuO_4. First, *psico*-furanose **9**[19] was subjected to our optimized RuO_4 conditions. After 30 min carboxylic acid **10** was observed, and substantial starting material remained (based on ^1H and ^{13}C NMR). When more RuO_4 (0.5 equiv) was added, following the conditions utilized by Sano and co-workers,[2] only amide **11**, derived from carboxylic acid **10**, was ultimately isolated. The oxidation with the increased equivalents of RuO_4 took ∼1.5 h. Next, azidophytosphingosine **12**[20] was treated with 0.06 equiv of RuO_4, and only carboxylic acid **13** was isolated after 3 h (Scheme 1). These results suggested that there is something unique about the β-azidoalcoholoxetanes **1**.

A second issue considered was the oxidation state of the cleaved carbon. Ignoring for now the role of the metal, plausible cleavage pathways can be drawn from each of the possible oxidation states (Figure 3). Each reaction was carefully monitored (^{13}C NMR) for aldehyde and/or carboxylic acid formation; at no point was either observed. Nevertheless, oxidation to either of these states, followed by rapid

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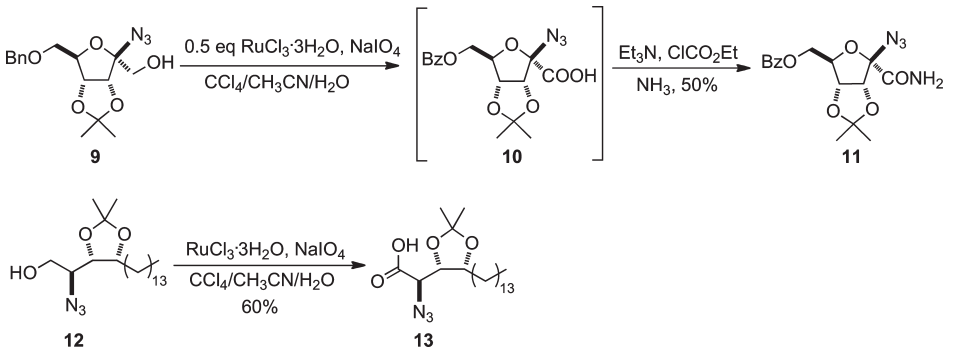
(20) Dere, R. T.; Zhu, X. *Org. Lett.* **2008**, *10*, 4641.

SCHEME 1. Oxidation of *psico*-Furanose 9 and Azidophytosphingosine 12 with RuO_4



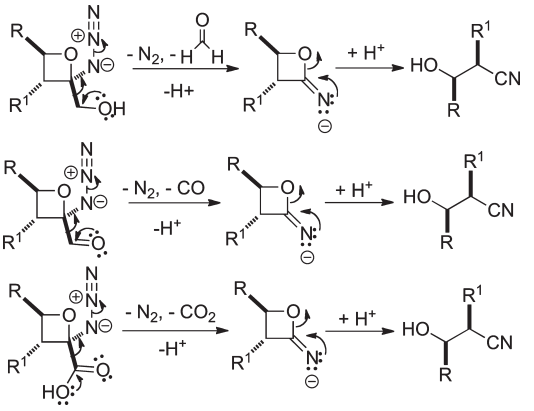


FIGURE 3. Possible states involved in the oxidative cleavage.

cleavage, could not be ruled out. Consequently, one goal was to access an aldehyde and acid by alternative pathways to investigate their behavior under the reaction conditions.

All attempts to synthesize α-azidoaldehydes from azidohydroxyoxetanes were unsuccessful. 2-Azido-2-(hydroxymethyl)oxetanes **1a** and **1b** were treated with a variety of oxidants, including IBX, Dess-Martin periodinane, Swern conditions, TEMPO/NMO and PCC/NaOAc. In all cases, the starting material was consumed, but no isolable product resulted. Similarly, when **1c** was treated with PDC in DMF no carboxylic acid was observed. Thus, the ability to more directly probe the nature of the intermediate that undergoes the cleavage has to this point been precluded because of the sensitivity of the 2-azido-2-(hydroxymethyl)oxetanes. Nevertheless, there are a number of observations that suggest that it is the hydroxymethyloxetanes that are cleaved.

Our conviction that the azidoalcohol is cleaved is based both on a comparison of our results to those reported for the PCC mediated cleavage of *β*-azidoalcohols and on the fact that both RuO_4 and IO_4^- effect the cleavage. The mechanism of oxidative cleavage proposed by Ye and co-workers[4] invoked an intramolecular reaction between the distal nitrogen of the azide and the carbonyl of the presumed aldehyde intermediate, followed by proton transfer, oxidation, and loss of CO and N_2 (Figure 4). Considering that α-azidoaldehydes are readily isolated, stable

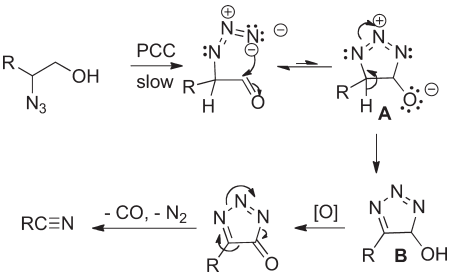
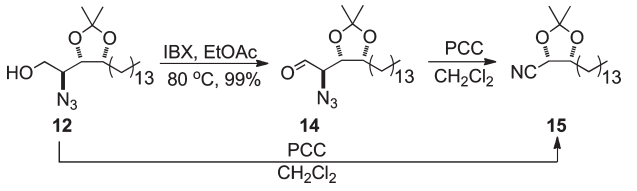


FIGURE 4. Oxidative cleavage mechanism proposed by Ye and co-workers.

SCHEME 2. Oxidation of Protected Azidophytosphingosine



species,[21] it is logical to assume that, if the proposed mechanism is correct, the equilibrium for the intramolecular addition favors the aldehyde with ultimate irreversible conversion to the nitrile driving the reaction to completion over time. We examined one of the Ye examples, azidophytosphingosine **12**, in more detail (Scheme 2). Compound **12**, as well as its corresponding α-azidoaldehyde **14** (prepared in 99% yield by oxidation of **12** with IBX), required more than two days in the presence of PCC for complete conversion to nitrile **15**. The conversion of **12** to **15** using PCC was slower than that of **14** to **15**. Both reactions were checked intermittently by NMR. Over the course of reaction of alcohol **12**, starting material, aldehyde and the nitrile could be seen for almost the entire time of monitoring. As expected, the reaction of aldehyde **14** showed starting material and nitrile. In neither case was any carboxylic acid observed. These results are consistent with the mechanism proposed by Ye. However, for 2-azido-2-(hydroxymethyl)oxetane cleavage there are several key differences. The reaction is much more rapid, with complete consumption of the starting material occurring in less than an hour. Also, with the oxetanes there is no hydrogen on the carbon attached to the azide, precluding the type of rearrangement shown in going from A to B (Figure 4). Thus, the cleavage observed with the 2-azido-2-(hydroxymethyl)oxetanes could not proceed by the same pathway as the PCC mediated oxidative cleavage.

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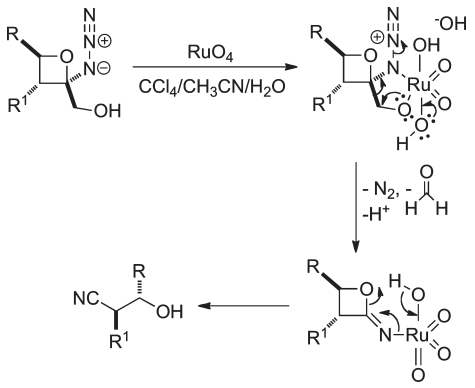

FIGURE 5. Proposed mechanism of 2-azido-2-(hydroxymethyl)-oxetane oxidative cleavage.

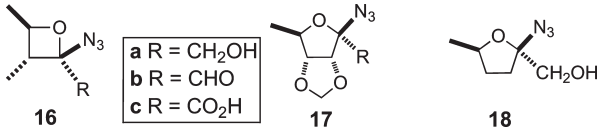

FIGURE 6. Model oxetanes and tetrahydrofurans for quantum chemical analysis.

On the basis of observations thus far, we think that the RuO_4 (or $NaIO_4$) plays an integral role and that the cleavage is most likely occurring from the alcohol oxidation state. We propose that the azido nitrogen directly bound to C-2 and the oxygen from the primary alcohol react with RuO_4 forming a five-membered intermediate (Figure 5). Subsequent loss of N_2 occurs with the regeneration of the double bond between oxygen and ruthenium and the loss of formaldehyde. Finally, nitrile formation and oxetane ring-opening result from the regeneration of RuO_4. It is important to note that we have observed no aldehyde or carboxylic acid in any of our reactions. Further support for the alcohol being the species cleaved comes from the outcome with $NaIO_4$ (*vide supra*). Nitrile formation was observed from the reaction of $NaIO_4$ and oxetane **1b**. Periodate is not used to oxidize primary alcohols without an appropriate catalytic oxidant, while it is widely used for oxidative cleavages. However, even if the alcohol is the precursor and RuO_4 or $NaIO_4$ is integral to the cleavage process, a question remains: why do the 2-azido-2-(hydroxymethyl)oxetanes, but not the corresponding tetrahydrofurans, undergo cleavage to nitriles?

Quantum Chemical Analysis. To answer the question presented above, a series of density functional theory (DFT) calculations (see Experimental section for details on the level of theory) for model oxetanes **16** and tetrahydrofurans **17** (Figure 6) was undertaken.

DFT calculations reveal an important structural difference between **16a** and **17a**. Oxetane **16a** exhibits what we refer to as an "*open*" conformation, characterized by a dihedral angle between atoms $C_1-C_2-N_1-N_2$ of $\phi = 171°$. On the other hand, the minimum energy structure of **17a** has a "*closed*" conformation with $\phi = 70°$ (Figure 7). The possibility for **16a** to present a stable *closed* conformation was explored, as was the potential for **17a** to present an *open* conformation. In the case of **16a**, a *closed* conformation is stable, but it is 0.7 kcal/mol higher in energy. For **17a**, the *open* conformation is also stable, but 5.0 kcal/mol in energy above the *closed* one. Thus, these higher

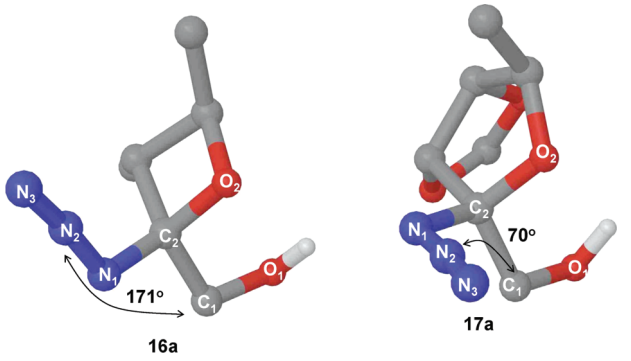

FIGURE 7. Computed minimum energy configurations of model complexes of oxetane (**16a**) and tetrahydrofuran (**17a**) obtained at DFT level.

energy conformers will be essentially unpopulated at room temperature ($k_BT \approx 0.5$ kcal/mol). The structural differences between **16a** and **17a** therefore suggest that the most stable *open* conformations of the azidooxetanyl alcohols may allow them to accommodate the RuO_4 (or IO_4^-) in a manner that leads to cleavage. In contrast, the *closed* conformation of the tetrahydrofuran precludes this, and standard oxidation of the alcohol to the carboxylic acid occurs. Conformational influences on oxidation reaction pathways are known for proteins,[5] but reports for simple organic molecules are hard to find. Nevertheless, the complexity of many oxidation pathways and the difficulty of reliably oxidizing alcohols with α-oxidation suggest that conformation may play a greater role than has been recognized.

We further explored whether these structural differences persist in the aldehyde and acid oxidation states. Figure 8 shows the computed minimum energy structures for the aldehydes (denoted as **16b** and **17b**) and the acids (denoted as **16c** and **17c**).

The lowest energy structure for both the oxetanyl aldehyde **16b** and acid **16c** is an *open* conformation. Compound **16b** also presents a stable *closed* conformation with energies 0.8 kcal/mol higher than the *open* one. In the acid state (**16c**), however, the *open* conformation is isoenergetic with the *closed* one. For the aldehyde (**17b**) oxidation state in the tetrahydrofuran model, the *open* conformation is unstable. In the acid state, it becomes stable but 4.6 kcal/mol higher in energy than the *closed* conformation. Thus, we conclude that this fundamental structural difference between the model oxetane and tetrahydrofuran (*open* versus *closed*) persists up to the aldehyde oxidation state.

Analysis of the molecular electrostatic potential (MEP) surface reveals a potential explanation for why the oxetane prefers the *open* conformation, while the tetrahydrofuran favors the *closed*. Figure 9 shows a crucial difference in the electrostatic interaction between the azide and the rest of the molecule in **16a** *open* and **17a** *open*. More precisely, the unfavorable electrostatic repulsion between the distal azide nitrogen and one of the oxygens in the formal group is not present in the lowest energy conformation of **17a**.

To test whether the formal group is entirely responsible for this conformational difference a tetrahydrofuran **18** in which this group was removed from **17a** was evaluated. This change gave rise to an *open* conformation 1.5 kcal/mol higher than the *closed* one, thus reducing the energy difference by 3.5 kcal/mol. Although this is consistent with the electrostatic argument above, it is apparent that the formal is not entirely responsible

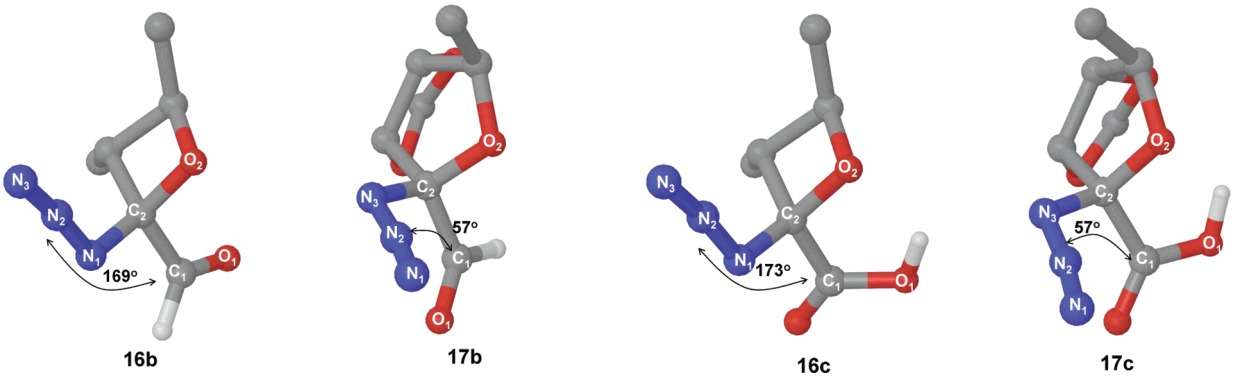

FIGURE 8. DFT computed minimum energy configurations of model oxetane and tetrahydrofuran in their aldehyde (**16b** and **17b**, respectively) and acid (**16c** and **17c**, respectively) oxidation states.

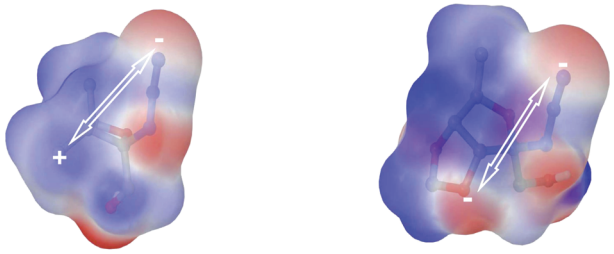

FIGURE 9. Molecular electrostatic potential obtained from the DFT electron density. Negative and positive potentials are represented by red and blue, respectively. The double arrows mark the crucial interaction that makes the open conformation in **17a** less stable relative to the same conformation in **16a**.

for the differential preference of the *closed* versus the *open* conformation.

Another question that might be addressed by a quantum mechanical analysis is the observed difference in reactivity between the *syn* and *anti* stereoisomers of azidooxetanes **1a**−**c** (see Table 2 for how *syn* and *anti* are defined). The *anti*-isomer (which has the 2-azido and 3-methyl groups on the same face) gave a lower yield of nitrile (see entries 3 and 4, Table 2) and reacted at a slower rate (see discussion of Table 2) than the *syn*. The corresponding energies of the *open* and *closed* conformations for the *anti* isomer of **16a**, as well as the transition state between the two, were computed. For the anti-isomer the *open* and *closed* conformations have the same energy, and they are separated by a 0.5 kcal/mol barrier. Considering that *only* cleavage was observed, the result suggests that, for the *anti*-isomer case, RuO_4 promoted cleavage competes with the interconversion between the *open* and *closed* forms. Furthermore, the oxidation to the carboxylic acid of azidotetrahydrofuran **9** is somewhat slower than the cleavage/degradation of the azidooxetanes **1**. By transitivity, this last observation suggests that the back and forth equilibration between the *open* and *closed* forms in the oxetane *anti*-isomers will also compete with the oxidation to the carboxylic acid. That is: although we have argued that oxidation to the carboxylic acid occurs from the *closed* form, it is possible that the fact that *no* carboxylic acid was observed for the *anti* isomers of **1a**−**c** could be due to rapid cleavage depleting the *open* azidoalcohols and conversion between the forms being faster than oxidation to the carboxylic acid.

In conclusion, an unexpected cleavage of 2-azido-2-(hydroxymethyl)oxetanes appears to be a result of a conformational preference that allows RuO_4 or IO_4^- to interact with both the alcohol and azido moieties, leading to cleavage. The lowest energy conformation for a closely related tetrahydrofuran blocks similar access of the oxidant, and this is consistent with the observed conversion of the alcohol to the corresponding carboxylic acid.

Experimental Section

Typical Procedure for the Synthesis of Methyleneoxetanes (7). *trans*-4-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methyl-2-methyleneoxetane (7a). Dimethyltitanocene (2.54 mmol, 5.00 mL, 0.50 M in toluene)[11] and *trans*-4-(*tert*-butyldiphenylsilanyloxymethyl)-3-methyloxetan-2-one (**6a**) (0.36 g, 1.05 mmol) were stirred at 80 °C under N_2 in the dark. After 2 h, TLC (petroleum ether/EtOAc, 98:2) showed the presence of starting material; so more dimethyltitanocene (1.0 mL, 0.50 mmol) was added. After 40 min, TLC indicated reaction completion. The solution was then cooled to rt, and petroleum ether (10 mL) was added, at which point a yellow precipitate formed. The resulting mixture was stirred for 18 h at rt. The solid residue was filtered through a pad of Celite, rinsing with petroleum ether. The solvent was removed under reduced pressure to 5 mL (total volume), and the residue was purified by flash chromatography on silica gel, packing the column with petroleum ether/triethylamine (96:4) and eluting with petroleum ether/EtOAc/triethylamine (97.5:2.0:0.5) to afford methyleneoxetane **7a** as white crystals (196 mg, 55%): mp 52−54 °C; IR (neat): 3072, 2930, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.39 (m, 6H), 4.42 (ddd, J = 4.3, 4.3, 4.3 Hz, 1H), 4.08 (m, 1H), 3.82 (m, 2H), 3.73 (m, 1H), 3.30 (m, 1H), 1.26 (d, J = 7.1 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 135.9, 135.7, 129.9, 127.9, 127.9, 86.6, 78.0, 65.2, 38.2, 27.0, 19.5, 16.6; HRMS (ESI) calcd for $C_{22}H_{28}NaO_2Si$ (M^+ + Na) m/z 375.1751, found 375.1739.

Typical Procedure for the Synthesis of 1,5-Dioxaspiro[3.2]hexanes (8). (2*S,3*R**,4*S**/*R**)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methyl-1,5-dioxaspiro[3.2]hexanes (8a).** A flask was charged with *trans*-4-(*tert*-butyldiphenylsilanyloxymethyl)-3-methyl-2-methyleneoxetane (**7a**) (0.72 g, 2.0 mmol) in dry CH_2Cl_2 (6 mL), and the resulting solution was cooled to −78 °C (dry ice/acetone bath) under N_2. A solution of dimethyldioxirane[13] (9.50 mL, 4.08 mmol, 0.43 M in CH_2Cl_2) was added dropwise. The reaction solution was stirred for 1 h at −78 °C under N_2. The solvent was removed under reduced pressure, and the resulting clear oil **8a** (3:1 mixture of diastereomers) was used in the next reaction without purification: IR (neat): 3071, 3050, 3014, 2998, 2931, 2857, 1589, 1472, 1462, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) minor diastereomer: δ 7.75 (m, 4H), 7.43 (m, 6H), 4.24 (ddd, J = 4.3,

4.3, 4.3 Hz, 1H), 3.93 (m, 2H), 3.26 (qd, J = 6.8, 6.4 Hz, 1H), 2.89 (d, J = 3.2 Hz, 1H), 2.79 (d, J = 3.2 Hz, 1H), 1.27 (d, J = 7.2 Hz, 3H), 1.14 (s, 9H); major diastereomer: δ 7.75 (m, 4H), 7.43 (m, 6H), 4.39 (ddd, J = 3.7, 3.7, 3.7 Hz, 1H), 3.93 (m, 2H), 3.45 (qd, J = 7.0, 6.4 Hz, 1H), 3.00 (d, J = 3.1 Hz, 1H), 2.70 (d, J = 3.2 Hz, 1H), 1.27 (d, J = 7.2 Hz, 3H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) minor diastereomer: δ 135.8, 135.7, 133.5, 133.3, 129.9, 129.9, 127.9, 127.9, 92.1, 80.6, 65.4, 49.1, 38.3, 26.9, 19.4, 14.1; major diastereomer: δ 135.8, 135.7, 133.5, 133.3, 129.9, 129.9, 127.8, 127.9, 91.5, 83.2, 65.1, 51.1, 36.5, 26.9, 19.4, 12.7; HRMS (ESI) calcd for $C_{22}H_{28}O_3SiNa$ (M^+ + Na) m/z 391.1705, found 391.1743.

Typical Procedure for the Synthesis of 2-Azido-2-(hydroxymethyl)oxetanes (1). (2*R/*S**,3*R**,4*R**)-2-Azido-4-heptyl-2-(hydroxymethyl)-3-methyloxetanes (1b).** (2*S**,3*S**,4*S**/*R**)-2-Heptyl-3-methyl-1,5-dioxaspiro[3.2]hexanes (**8b**) (1.83 mmol) were dissolved in Et_2O (3 mL) at rt under N_2. Trimethylsilyl azide (0.36 mL, 2.74 mmol) was added dropwise, and the resulting solution was stirred overnight at rt. Then, the solvent was removed in vacuo to afford a yellow oil which was dissolved in THF (9.2 mL), and the resulting solution was cooled to 0 °C (ice bath). Tetra-*n*-butylammonium fluoride (2.74 mmol, 2.74 mL, 1 M in THF) was added dropwise, and the solution was stirred for 2 h at 0 °C. Then, the solvent was removed under reduced pressure, and CH_2Cl_2 (10 mL) was added. The resulting solution was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) provided β-azidoalcohols **1b** as a clear oil (diastereomeric ratio 4:1) (132 mg, 30% over 3 steps). The two diastereomers were separated by careful chromatography: Characterization of (2*S**,3*R**,4*R**)-2-azido-4-heptyl-2-(hydroxymethyl)-3-methyloxetane (minor diastereomer): IR (neat) 3447, 2930, 2114, 1458, 1379, 1251 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (ddd, J = 6.7, 6.7, 6.7 Hz, 1H), 3.62 (m, 2H), 2.73 (dq, J = 7.0, 7.0 Hz, 1H), 2.17 (m, 1H), 1.79−1.63 (m, 2H), 1.25−1.21 (m, 13H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.1, 82.2, 64.0, 44.4, 36.8, 31.9, 29.5, 29.3, 24.4, 22.8, 14.2, 12.1; HRMS (ESI) calcd for $C_{12}H_{23}N_3NaO_2$ (M^+ + Na) m/z 264.1682, found 264.1671. Characterization of (2*R**,3*R**,4*R**)-2-azido-4-heptyl-2-(hydroxymethyl)-3-methyloxetane (major diastereomer): IR (neat) 3432, 2924, 2857, 2115, 1456.9, 1260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (ddd, J = 6.8, 6.8, 6.8 Hz, 1H), 3.52 (dd, J = 12.4, 4.8 Hz, 1H), 3.40 (dd, J = 12.4, 8.5 Hz, 1H), 2.82 (dq, J = 7.1, 7.1 Hz, 1H), 2.25 (dd, J = 8.4, 5.2 Hz, 1H), 1.72−1.62 (m, 2H), 1.25 (m, 10H), 1.14 (d, J = 7.1 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.0, 85.8, 66.1, 41.1, 36.3, 31.9, 29.6, 29.4, 24.6, 22.8, 14.2, 13.0; HRMS (ESI) calcd for $C_{12}H_{23}N_3NaO_2$ (M^+ + Na) m/z 264.1682, found 264.1696.

Typical Procedure for the Synthesis of Nitriles (2). (2*S,3*S**)-4-(*tert*-Butyldiphenylsilanyloxy)-3-hydroxy-2-methylbutanenitrile (2a).** A flask was charged with CCl_4:CH_3CN:H_2O (1:1:1, 0.9 mL) and $NaIO_4$ (133 mg, 0.62 mmol). The resulting mixture was cooled to 0 °C (ice bath), and $RuCl_3 \cdot 3H_2O$ (2.0 mg, 0.009 mmol) was added at once. The mixture was stirred for 1 h at 0 °C. Then, the supernatant was added to (2*R**,3*R**,4*S**)-2-azido-4-(*tert*-butyldiphenylsilanyloxymethyl)-2-(hydroxymethyl)-3-methyloxetane (**1a**) (64 mg, 0.16 mmol) in CH_3CN (0.30 mL), and the mixture was stirred at rt for 25 min. It was then diluted with CH_2Cl_2 (5 mL) and H_2O (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic extracts were dried ($MgSO_4$), and the solvents removed under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 85:15) provided recovered starting material, (2*R**,3*R**,4*S**)-2-azido-4-(*tert*-butyldiphenylsilanyloxymethyl)-2-(hydroxymethyl)-3-methyloxetane (**1a**) (20 mg, 33%), and nitrile **2a** as a clear oil (10 mg, 20%): IR (neat) 3462 (br), 3072, 2930, 2857, 2117, 1472, 1428 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.41 (m, 6H), 3.70 (m, 3H), 2.84 (dq, J = 7.2, 4.2 Hz, 1H), 2.49 (d, J = 4.6 Hz, 1H), 1.30 (d, J = 7.1 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.7, 132.8, 132.7, 130.3, 128.2, 120.8, 72.5, 65.4, 29.6, 27.0, 19.5, 14.8; HRMS (ESI) calcd for $C_{21}H_{27}NNaO_2Si$ (M^+ + Na) m/z 376.1703, found 376.1728.

1-β-Azido-1-α-carbamoyl-1-dehydro-1-deoxy-5-*O*-benzoyl-2,3-*O*-isopropylidene-D-ribofuranose (11). 2-Azido-2-deoxy-6-*O*-benzyl-2,3-*O*-isopropylidene-β-D-psicofuranose (**9**)[19] (99 mg, 0.30 mmol) and sodium periodate (0.33 g, 1.5 mmol) in CH_3CN (1.6 mL), CCl_4 (1.6 mL) and H_2O (2.4 mL) were stirred vigorously in the presence of $RuCl_3 \cdot 3H_2O$ (32 mg, 0.15 mmol) at rt for 90 min. Then, the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were dried ($MgSO_4$), and the solvents were removed in vacuo to give a mixture of carboxylic acids (diastereomers). The mixture was then dissolved in dry THF (3 mL) and treated with triethylamine (0.09 mL, 0.62 mmol) and ethyl chloroformate (0.08 mL, 0.86 mmol) at 0 °C. After 5 min, NH_3 (gas) was bubbled through the solution for 10 min. Then, H_2O (5 mL) was added, and the two layers were separated. The aqueous layer was washed with MTBE (5 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50) to afford amide **11** (50 mg, 50%) as a white solid: $[\alpha]^{23}_D$ −47 (*c* 0.10, CH_2Cl_2); mp 170−171 °C; IR (mineral oil) 3446, 3162, 2850, 2118, 1721, 1657, 1459 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 6.61 (bs, 1H), 5.81 (bs, 1H), 4.86 (dd, J = 5.7, 1.2 Hz, 1H), 4.76 (d, J = 5.7 Hz, 1H), 4.72 (ddd, J = 6.5, 6.5, 1.0 Hz, 1H), 4.53 (dd, J = 11.8, 6.5 Hz, 1H), 4.47 (dd, J = 11.8, 6.7 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 166.3, 133.7, 130.0, 129.6, 128.8, 114.2, 100.9, 86.3, 86.0, 82.1, 64.1, 26.6, 24.9; HRMS (ESI) calcd for $C_{16}H_{19}N_4O_6$ (M^+ + H) m/z 363.1299, found 363.1296.

(2*R*,3*S*,4*R*)-2-Azido-3,4-*O*-isopropylidene-1-octadecanoic acid (13). Sodium periodate (0.11 g, 0.52 mmol) was added to a flask charged with $CCl_4/CH_3CN/H_2O$ (1:1:1, 0.8 mL), and the resulting mixture was stirred at 0 °C (ice bath). $RuCl_3 \cdot 3H_2O$ (1.60 mg, 0.0078 mmol) was added, and the biphasic orange mixture was vigorously stirred for 1 h. Then, the supernatant was added to (2*S*,3*S*,4*R*)-2-azido-3,4-*O*-isopropylidene-1-octadecanol (**12**) (50 mg, 0.13 mmol) in CH_3CN (0.3 mL) at rt, followed by the addition of more sodium periodate (56 mg, 0.26 mmol). The resulting mixture was vigorously stirred for 3 h at rt and then diluted with CH_2Cl_2 (5 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 80:20) yielded carboxylic acid **13** as a white solid (30 mg, 60%): $[\alpha]^{23}_D$ −8.0 (*c* 0.12, CH_2Cl_2); mp 69−71 °C; IR (neat) 3162, 2919, 2850, 2103, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (m, 2H), 3.84 (d, J = 8.4 Hz, 1H), 1.62 (m, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.24 (m, 24 H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 109.3, 77.9, 76.3, 61.1, 32.2, 29.9, 29.9, 29.9, 29.8, 29.7, 29.6, 28.9, 28.0, 27.0, 25.7, 22.9, 14.3; HRMS (ESI) calcd for $C_{21}H_{39}N_3NaO_4$ (M^+ + Na) m/z 420.2833, found 420.2815.

(2*R*,3*S*,4*R*)-2-Azido-3,4-*O*-isopropylidene-1-octadecanal (14). 2-Iodoxybenzoic acid (0.95 g, 3.4 mmol) was added to (2*S*,3*S*,4*R*)-2-azido-3,4-*O*-isopropylidene-1-octadecanol (**12**) (0.43 g, 1.1 mmol) in EtOAc (17 mL) at rt. The reaction mixture was refluxed at 90 °C for 3.5 h. Then, it was cooled to rt and filtered through a pad of Celite, rinsing with EtOAc. The filtrate was concentrated in vacuo to afford aldehyde **14** (0.43 g, 99%) as a pale yellow oil which solidified overnight: $[\alpha]^{23}_D$ −8.3 (*c* 0.10, CH_2Cl_2); mp 52−54 °C; IR (neat) 2987, 2925, 2114, 1735, 1468, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.19 (m, 2H), 3.90 (d, J = 7.6 Hz, 1H), 1.58 (m, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.24 (m, 23H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 197.1, 109.4, 77.9, 76.8, 66.4, 32.1, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.4, 27.8, 26.9, 25.4, 22.9, 14.3, 1.21; HRMS (ESI) calcd for $C_{21}H_{39}N_3O_3$ (M^+) m/z 381.2986, found 381.2956.

Computational Method and Theory Level. Full geometry optimization at the DFT level were carried out using the hybrid functional B3LYP with basis set 6-31 g(d,p) using the program Gaussian 09.[22] All energies reported were obtained in vacuum. On benchmark calculations of **16a** and **17a**, in which we computed the relative energy between the *open* and *closed* conformation, we found that inclusion of zero point energy effects and thermal corrections only changes the energy differences by a tenth of a kcal/mol. Since all of our conclusions would be unaltered by such correction, we reported energies without the inclusion of zero point energy and thermal effects. Transition state calculations were carried out with the program Jaguar using the quadratic synchronous transit (QST) method. Analysis of the Molecular Electrostatic Potential was performed with the quantum chemical software Jaguar,[23] at the same theory level specified above. Image rendering in Figures 7, 8, and 9 was performed with the program Maestro.[24]

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Supporting Information Available: General experimental methods and procedures, spectroscopy data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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