Synthesis of a 2,7-Dioxatricyclo[4.2.1.0^{3,8}]nonane: A Model Study for Possible Application in a Synthesis of Dictyoxetane

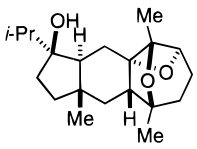
Kelly A. Marshall, Anna K. Mapp, and Clayton H. Heathcock*

Department of Chemistry, University of California—Berkeley, Berkeley, California 94720

Received August 30, 1996[⊗]

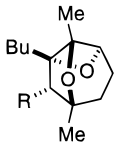
A method for the synthesis of the 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system characteristic of the marine diterpene dictyoxetane has been developed. This method utilizes a dipolar cycloaddition of a 3-oxidopyrylium salt to create the carbon skeleton (Scheme 1) and employs an intramolecular S_N2 displacement to form the oxetane ring (Schemes 9, 10, 13). The route described could easily be adapted to incorporate additional functionality, making it potentially useful in a total synthesis of dictyoxetane.

Dictyoxetane (**1**), a diterpene from the brown alga *Dictyota dichotoma* (Hudson) Lamouroux, was isolated in 1985 by Pullaiah and co-workers from a sample collected in the Indian Ocean.[1] This unusual diterpene embodies within its pentacyclic structure the highly strained and structurally novel 2,7-dioxatricyclo[4.2.1.0^{3,8}]-nonane ring system. At the outset of the current project, a search of the CAS ONLINE structure database showed that dictyoxetane was the only known compound having this particular heterocyclic system. Recently, Reinecke and Hoffmann reported the first synthesis of a 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane, namely the dimethyl derivative **2**.[2] In this Article, we report a synthesis of the related heterocycles **3** and **4**.



1

2



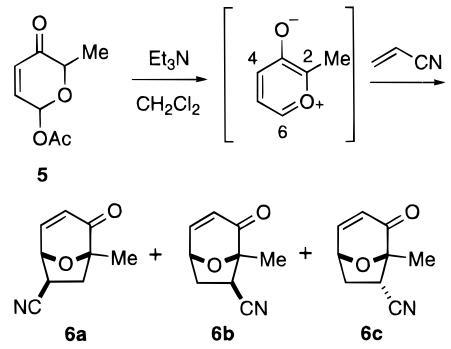
3: R = H
4: R = Me

The method that we chose to construct the basic carbon skeleton of our target compound was a dipolar cycloaddition of a 3-oxidopyrylium salt[3] with an alkene, a well-precedented transformation.[3,4] For example, reaction of acetate **5** with triethylamine and acrylonitrile produces three adducts, **6a**, **6b**, and **6c** in a 1:1:1 ratio (Scheme 1).[3] Even though the precedent reaction illustrated in Scheme 1 gives a complex mixture of products, we thought additional substitution on the 1,3-dipole would bias the regiochemical outcome of the addition. Thus, we set about to prepare an analog of **5** having an additional methyl group at C6.

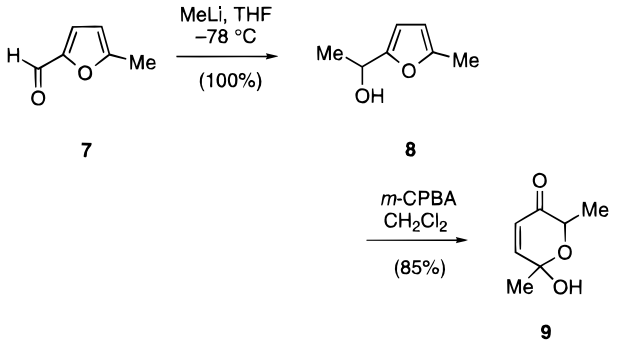
Treatment of commercially available 5-methylfurfural (**7**) with methyllithium produced 2-furylcarbinol **8** in quantitative yield (Scheme 2). It is known that 2-furylcarbinols can be oxidatively rearranged to enones by a variety of reagents, such as bromine in methanol, *tert*-butyl hydroperoxide, NBS, and PCC.[5] In fact, PCC was reported by Piancatelli to oxidize furylcarbinol **8** to the desired enone **9** in greater than 90% yield.[6] However, in our hands yields were consistently around 50%. Other conditions, such as bromine in methanol, NBS, and photooxidation, did produce enone **9**, but again the yields were 50% or less. Eventually we discovered that *m*-CPBA[7] efficiently brings about oxidative rearrangement of alcohol **8** to enone **9** in yields of 85−90%.

With hemiketal **9** in hand, we attempted to acetylate the tertiary alcohol in order to form the pyrylium ylide precursor. However, when **9** was exposed to acetic anhydride in pyridine for 24 h, no reaction occurred. Since acetylation of the tertiary alcohol appeared im-

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) Pullaiah, K. C.; Surapaneni, R. K.; Rao, C. B.; Albizati, K. F.; Sullivan, B. W.; Faulkner, D. J.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 3665.

(2) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, 368.

(3) Sammes, P. G.; Street, L. J. *J. Chem. Res. (S)* **1984**, 196.

(4) (a) Sammes, P. G. *Gazz. Chim. Ital.* **1986**, *119*, 109. For related work, see: (b) Wender, P. A.; Mascarenas, J. L. *Tetrahedron Lett.* **1992**, *33*, 2115. (c) Williams, D. R.; Benbow, J. W.; McNutt, J. G.; Allen, E. E. *J. Org. Chem.* **1995**, *60*, 833.

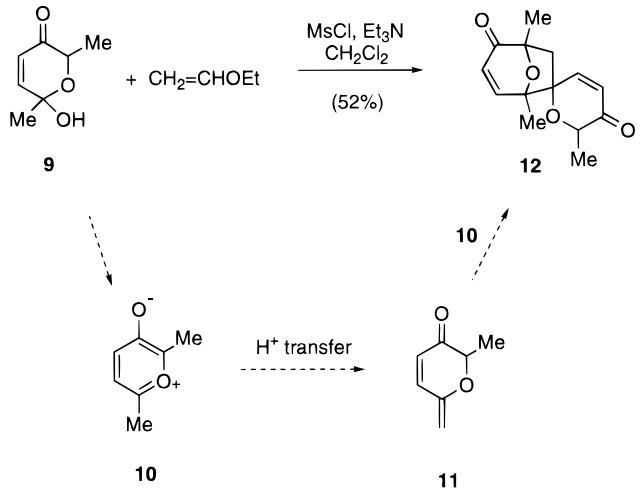
(5) (a) Achmatowicz, O.; Bukowski, R.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. (b) Antonioletti, R.; Arista, L.; Bonadies, F.; Locati, L.; Scettri, A. *Tetrahedron Lett.* **1993**, *44*, 7089. (c) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.

(6) Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* **1977**, *25*, 2199.

(7) Lefebvre, Y. *Tetrahedron Lett.* **1972**, 133.

S0022-3263(96)01680-5 CCC: $12.00

Scheme 3

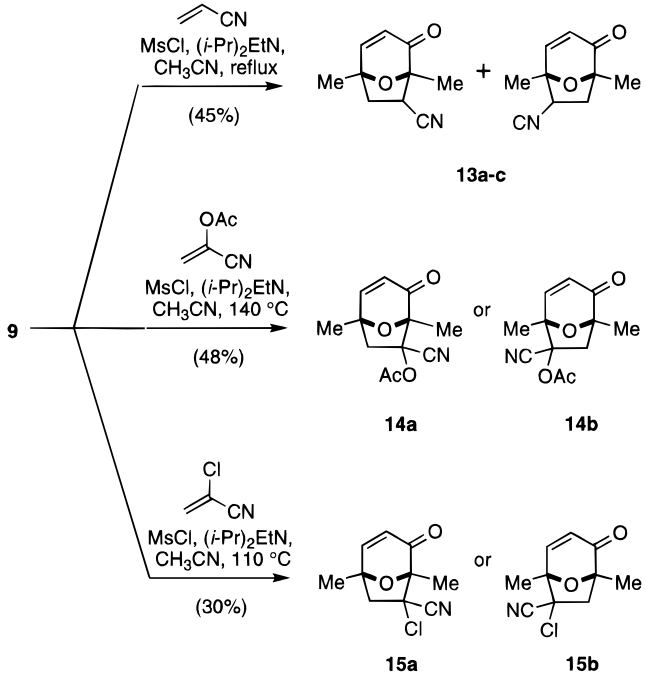


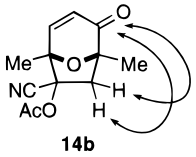
practical, an attempt was made to mesylate the hydroxyl group of **9**. When methanesulfonyl chloride and triethylamine were added to alcohol **9** in methylene chloride, the reaction solution instantly turned red. This color change suggested the presence of dipole **10**, since a color change is indicative of pyrylium formation in similiar systems.[8] Ethyl vinyl ether was added as a dipolarophile, and the reaction mixture was allowed to stand for 36 h. However, the only product isolated showed no ethyl group incorporation by ^{1}H NMR spectroscopy. Mass spectrometry of this product gave a molecular weight of 248, elemental analysis was consistent with the formula $C_{14}H_{16}O_4$, and integration of the ^{1}H NMR spectrum showed the presence of 16 protons. The presence of three methyl singlets and two different α,β-unsaturated enone systems led us to the conclusion that the unexpected product is a dimer of structure **12**, possibly arising from reaction of pyrylium ylide **10** with dienone **11**, the product of internal proton transfer (Scheme 3).

We thought that dimerization could be suppressed by choosing a more reactive dipolarophile and varying the concentration of the reactants. Indeed, when the reaction was performed in refluxing acetonitrile with acrylonitrile as the dipolarophile, cycloadduct **13** was produced in 45% yield as a 10:1:1 mixture of diastereomers and regioisomers with no observable dimer formation (Scheme 4). At temperatures above 100 °C, α-acetoxyacrylonitrile and α-chloroacrylonitrile were also reactive dipolarophiles, each providing a single cycloadduct in 48% and 30% yield, respectively. However, more electron-rich dipolarophiles such as ethyl vinyl ether, vinyl acetate, and ketenethioacetals were all unreactive with ylide **10**. When cycloadditions were attempted with these dipolarophiles, only dimerization and/or decomposition was observed, even at high temperatures. Nevertheless, we were satisfied with the dipolarophiles that were successful, since they were all "ketene equivalents"[9] and could provide the necessary oxygen functionality for creation of the oxetane ring.

At this stage, we did not have enough information to assign the regio- or stereochemistry of cycloadducts **13**–**15**. Knowledge of the stereochemistry was unnecessary, since the unknown stereocenter would be destroyed upon conversion to a carbonyl. Knowledge of the regiochemistry, however, was essential. To form the oxetane ring, we would prefer that the carbonyl be proximal (**14a** or **15a**) rather than distal (**14b** or **15b**) to the latent carbonyl group. However, PM3 calculations[10] performed on dipole **10** strongly suggested that regioisomers **14b** and **15b** should be the major products. This theoretical indication was confirmed by an HMBC NMR experiment,[11] which showed three-bond coupling between both methylene protons and the carbonyl carbon, thus verifying structure **14b**:

Scheme 4





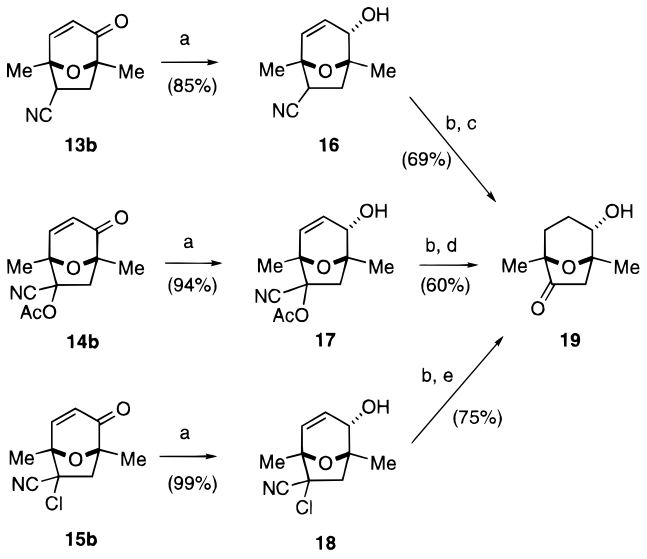
14b

The three cycloadducts were correlated as shown in Scheme 5. Treatment of each cycloadduct with sodium borohydride and cerium trichloride in methanol[12] provided the unsaturated alcohols **16**–**18**. Catalytic hydrogenation, followed by oxidative decyanation[13] of nitrile **16** provided hydroxy ketone **19**. The same compound was obtained when **17** was hydrogenated and treated with sodium methoxide in methanol and when chloronitrile **18** was hydrogenated and treated with KOH in wet DMSO.[14] Thus, all three dipolarophiles react with **10** to produce largely or completely the cycloadduct in which the carbonyl is distal to the nitrile function.

Although the regiochemistry obtained in the cycloaddition does not deliver a product in which the two functions are directly situated for formation of the

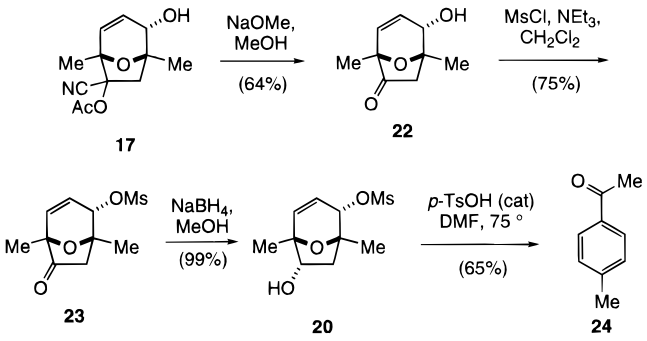
(8) Ullman, E. F.; Milks, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 1315.
(9) (a) Depuy, C. H.; Story, P. R. *J. Am. Chem. Soc.* **1960**, *82*, 627. (b) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211. (c) Watt, D. S.; Kyler, S. K.; Freerksen, R. W.; Selikson, S. J.; Wroble, R. R. *J. Org. Chem.* **1983**, *48*, 4087.
(10) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
(11) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
(12) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(13) Watt, D. S.; Kyler, S. K.; Freerksen, R. W.; Selikson, S. J.; Wroble, R. R. *J. Org. Chem.* **1983**, *48*, 4087.
(14) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211.

Scheme 5

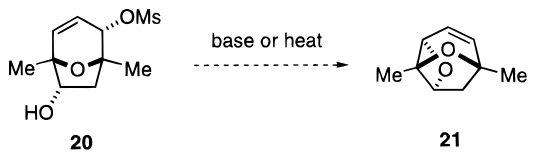


a. $NaBH_4$, $CeCl_3$, MeOH . b. H_2, Pd/C, THF. c. i. LDA, THF, -78 °C. ii. O_2. iii. $SnCl_2$. d. NaOMe, MeOH. e. KOH, wet DMSO.

Scheme 6

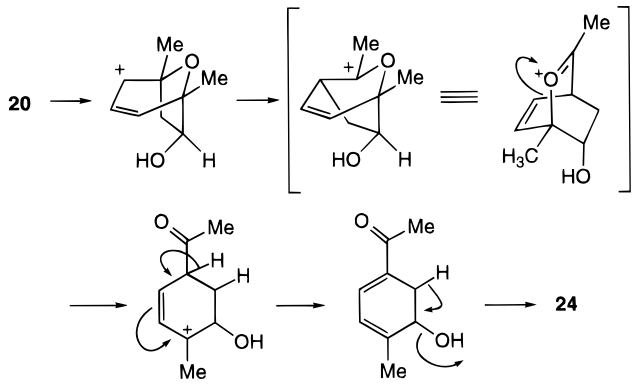


oxetane ring, there are several ways in which these intermediates might be employed to prepare the target compound. The first possibility we considered was formation of the oxetane by an intramolecular allylic displacement reaction:[15]

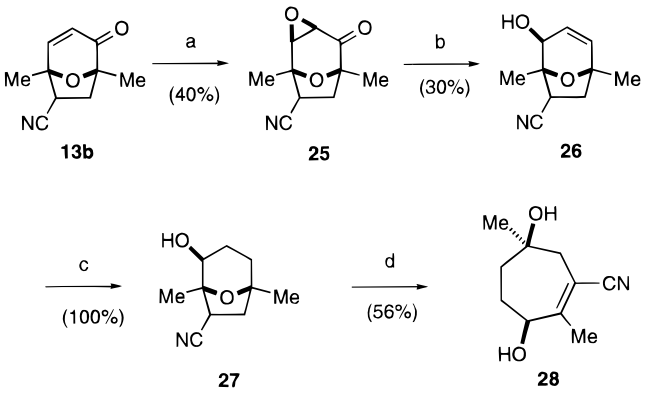


There is precedent for forming five-membered ether rings by allylic nucleophilic displacement,[16] but to our knowledge no four-membered ether rings have been formed by this method. To explore this option, unsaturated alcohol **17** was treated with sodium methoxide in methanol to give hydroxy ketone **22**, which was transformed into mesylate **23** (Scheme 6). Reduction of **23** with sodium borohydride occurs from the less hindered face to provide **20** in almost quantitative yield. Exposure of alcohol **20** to basic conditions resulted in no reaction; we could not isolate even a trace of S_N' product. Although

Scheme 7



Scheme 8



a. *t*-BuOOH, Na_2CO_3, MeOH, H_2O. b. i. N_2H_4. ii. AcOH. c. H_2, Pd/C, THF. d. i. LDA, THF. ii. O_2. iii. $SnCl_2$.

S_N' reactions are reported to be more favorable when the nucleophilic and electrophilic partners are syn-oriented, as is the case in compound **20**,[17] there are examples of S_N' reactions in which a syn arrangement of nucleophile and leaving group failed to cyclize under anionic conditions, but did cyclize thermally.[16] Therefore, we attempted the ether formation under solvolytic conditions. However, heating mesylate **20** and catalytic *p*-toluenesulfonic acid in DMF at 75 °C for 24 h resulted only in the formation of 4-methyl-2-acetophenone (**24**). A reasonable mechanism for this unexpected transformation is depicted in Scheme 7.

Since the allylic displacement route proved not to be feasible, we explored the possibility of a Wharton enone transposition (Scheme 8).[18] Unfortunately, both epoxidation of enone **13b** to epoxy ketone **25** and the elimination reaction of **25** to **26** were low yielding (40% and 30%, respectively). Although the low yields were discouraging, we continued forward since our main goal was to determine if an intramolecular S_N2 displacement would produce the oxetane in ring system **2**. Therefore, we set about transforming allylic alcohol **26** into an oxetane precursor. Hydrogenation of **26** to the saturated alcohol **27** proceeded without incident. However, oxidative decyanantion of **27**,[11] which had been successful with hydroxy nitrile **16** (Scheme 5), led only to cycloheptenol **28**, presumably as a result of simple β elimination of the intermediate nitrile-stabilized anion.

The facile fragmentation of the anion derived from nitrile **27** is surprising, in light of the successful oxidative

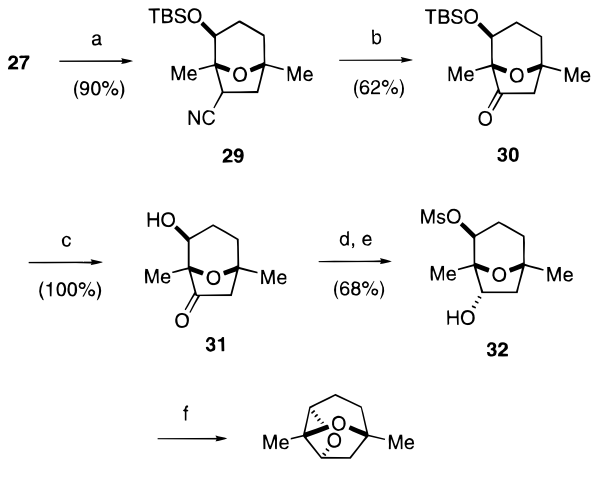
(15) General references for S_N2' reactions: (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Bordwell, F. G. *Acc. Chem. Res.* **1970**, *3*, 281. (c) Kepner, R. D.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 115. (d) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1953**, *75*, 4119. (e) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4609.

(16) LaClair, J. J.; Lansbury, P. T.; Zhi, B.; Hoogsteen, K. *J. Org. Chem.* **1995**, *60*, 4822.

(17) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

(18) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.

Scheme 9



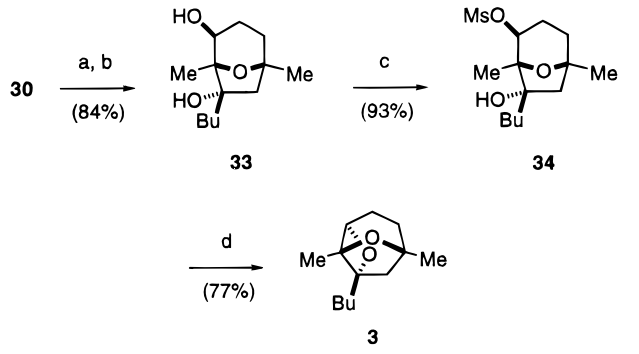
a. TBSCl, imidazole, DMF. b. i. LDA, THF, -78 °C. ii. O_2. iii. $SnCl_2$. c. 2% HF in CH_3CN. d. MsCl, NEt_3, CH_2Cl_2. e. $NaBH_4$, MeOH. f. NaH, THF

decyanation of nitrile **16** (Scheme 5). It is possible that the proximity of the charges in the dianion derived from **27** destabilizes this system enough that β elimination occurs faster than reaction with oxygen. If this is the problem, then protection of the alcohol might suppress the β elimination pathway. To test this proposition, alcohol **27** was treated with *tert*-butyldimethylsilyl chloride and imidazole in DMF[19] to obtain silyl ether **29**, which was treated with 1 equiv of LDA and excess oxygen to obtain the desired ketone **30** in 62% yield (Scheme 9). However, 20% of the protected cycloheptene elimination product was also obtained in this reaction. The remaining steps to the oxetane precursor proceeded smoothly, with the deprotection of the TBS group accomplished by HF/CH_3CN in quantitative yield. The β-hydroxy ketone **31** isolated from this deprotection was then converted to the mesylate, and sodium borohydride reduction of the crude ketomesylate afforded oxetane precursor **32**. Treatment of alcohol **32** with NaH in refluxing THF resulted in the consumption of the starting material and the formation of a less polar material. Although this reaction was not very clean, the ^{1}H NMR spectrum of the major product strongly suggested the formation of tricyclic diether **2**. However, this compound proved to be quite volatile, and we were not able to isolate the small amount of material synthesized completely free of residual solvents. Repeated trials simply resulted in the complete evaporation of the diether. Because of the volatile nature of this tricycle, we decided to alter our model system slightly by adding more molecular weight. This alteration would then allow us to confirm rigorously that we had synthesized the highly strained tricyclic diether.

We decided that the simplest adjustment to our model system would be to add an alkyl chain instead of a hydride to ketone **30**. In fact, this addition would create a more accurate model system (**3**), since the natural product also possesses an alkyl substituent at that position. Transformation of ketone **30** into the tertiary alcohol was accomplished by treatment with butyllithium (Scheme 10). To drive the reaction to completion it was necessary to use an inverse addition method, wherein ketone **30** was added as a THF solution to an excess of

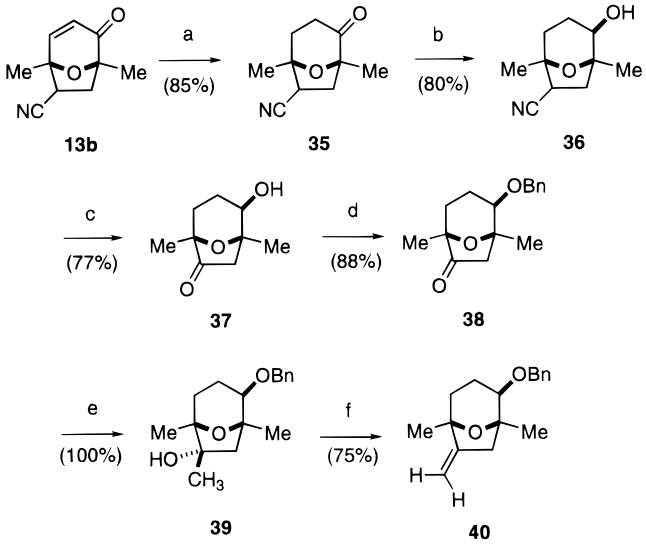
(19) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Scheme 10



a. BuLi, THF, –78 °C. b. 2% HF, CH_3CN. c. MsCl, Et_3N, CH_2Cl_2, 0 °C. d. NaH, THF, reflux.

Scheme 11



a. H_2, Pd/C. b. L-Selectride, THF, -78 °C. c. i. LDA, THF, -78 °C. ii. O_2. iii. $SnCl_2$. d. BnBr, NaH, THF. e. MeMgBr, ether. f. Burgess' reagent, benzene.

butyllithium in THF at −78 °C. Under standard addition conditions, starting material was always recovered in varying amounts. With the butyl chain in place, we proceeded with silyl deprotection to provide diol **33**, followed by selective mesylation of the secondary alcohol to obtain mesylate **34**. Treatment of this material with NaH in refluxing THF cleanly afforded oxetane **3** as a colorless liquid in 77% yield. Even with the additional molecular weight this diether was still slightly volatile, but it proved to be much more manageable than oxetane **2**.

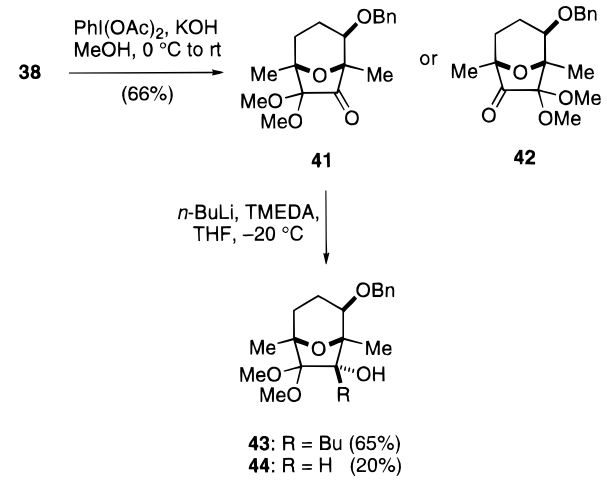
At this point, we had successfully synthesized the diether ring system **3**, but our synthesis still had several drawbacks. The low yields of the epoxidation and Wharton rearrangement and the competing β elimination in the oxidative decyanation were troublesome. It occurred to us that we might circumvent these troublesome steps if we could accomplish a carbonyl transposition in the two-carbon bridge instead of rearranging oxygen functionality in the three-carbon bridge. To this end, adduct **13b** was converted by three straightforward steps into hydroxy ketone **37**, which was benzylated to obtain **38** (Scheme 11). Addition of methylmagnesium bromide proceeded in good yield (100%) to provide alcohol **39**. We had anticipated that elimination of this tertiary alcohol would occur readily under acidic conditions to provide

the endocyclic alkene, which would be suitable for hydroboration and oxidative workup. However, all attempts to perform an acid-catalyzed elimination resulted in decomposition of the substrate. Because of our lack of success with acid-catalyzed elimination, we turned our attention to E2-type eliminations. Our first choice was Burgess's reagent ($MeO_2CN^-SO_2N^+Et_3$),[20] which is reported to minimize carbonium ion rearrangements because ionization leads to a tight ion pair that undergoes fast proton transfer to give the alkene. When alcohol **39** and Burgess's reagent were refluxed in benzene, alkene **40** was isolated as the sole product in 75% yield. At this point, we began to suspect that endo-elimination in this bicyclic system is not thermodynamically feasible.

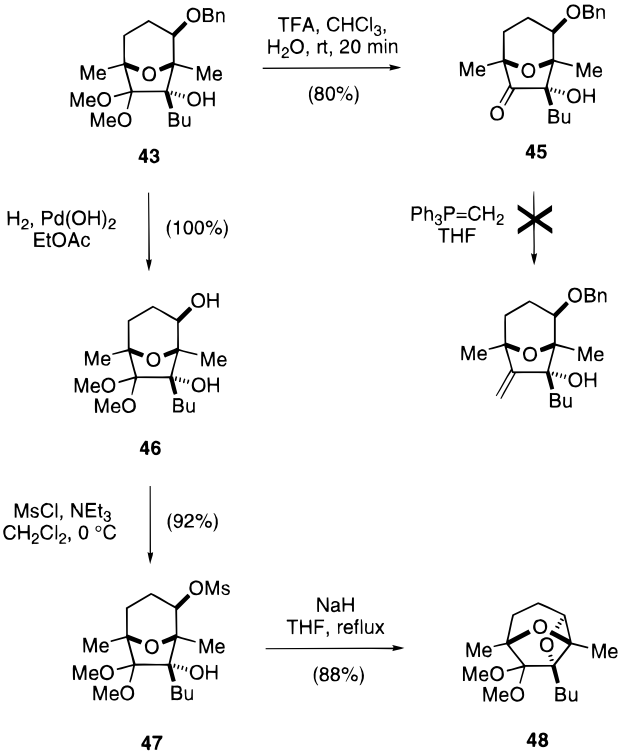
In our second attempt to oxidize ketone **38** at the α position we sought to epoxidize the silyl enol ether.[21] However, all attempts to prepare the silyl enol ether were unsuccessful. Using either thermodynamic or kinetic conditions,[22,23] we only obtained unchanged starting material after standard workup. These results, taken together with the observation that tertiary alcohol **39** undergoes dehydration exclusively to the exocyclic alkene isomer, suggest that an endocyclic double bond is relatively strained in this system. We next investigated selenium dioxide oxidation of **38**, with the idea in mind that the resulting diketone might exhibit some preference in reactivity at one carbonyl relative to the other.[24] However, after refluxing ketone **38** in 95% EtOH with SeO_2 for three days, starting material was recovered in quantitative yield.

We also attempted to hydroxylate **38** by treating its enolate with an oxidizing agent. Several oxidants were considered, including the Davis oxaziridine[25] and MoOPh.[26] However, the oxidant we investigated first was $PhI(OAc)_2$ in methanolic KOH, which has been reported to oxidize cyclic ketones to the corresponding α-hydroxy ketones.[27] In the event, addition of excess oxidant to ketone **38** in methanolic solution led to smooth transformation to a dimethoxy ketone (Scheme 12). The formation of a dimethoxy ketone under these reaction conditions is unprecedented, and without any mechanistic information we were unsure whether the product had structure **41** or **42**. However, an HMBC NMR experiment established that the product was isomer **41**. While this oxidative transformation was unexpected and appears to be unique to our substrate, it was nonetheless a welcome discovery. The previous need for multistep oxidation and selective protection of ketone **38** was now eliminated, since this single step equipped our system with the desired regiochemistry and proper functionality to create the more highly substituted oxetane **4**. With the bicyclic system now functionalized to our specifications, we began to explore the conversion of **41** into oxetane **4**. Treatment of ketone **41** with 2 equiv of butyllithium and 3 equiv of TMEDA in THF solvent at −20 °C produced alcohol **43**

Scheme 12



Scheme 13

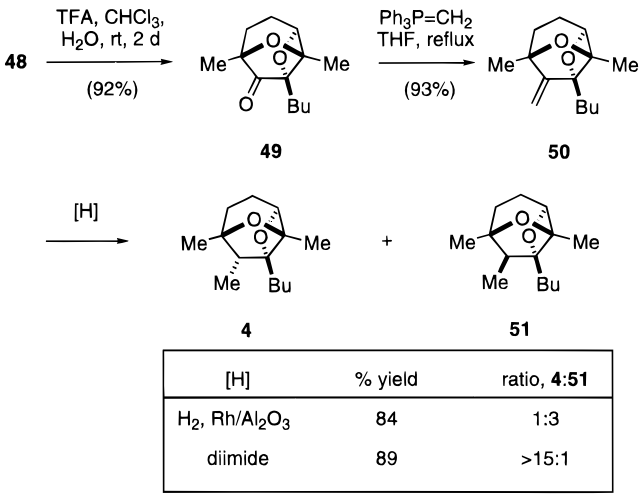


in 65% yield, accompanied by 20% of the reduction product **44**. Although it is uncommon to observe carbonyl reduction with alkyllithiums, this side reaction has been observed with relatively hindered ketones.[28]

Concern over the stability of the strained oxetane system made it desirable to postpone oxetane formation until the final step of the synthesis. Therefore, we decided to hydrolyze the dimethyl acetal and attempt a Wittig reaction and hydrogenation of the resulting exocyclic alkene. Ketone **45** was easily obtained, since removal of the acetal proceeded smoothly and completely within 20 min when **43** was stirred at room temperature with a 1:1:1 mixture of trifluoroacetic acid, water, and chloroform (Scheme 13). We then attempted a Wittig reaction with methylenetriphenylphosphorane on the free hydroxy ketone **45**. Although there is precedent for using α-hydroxy ketones as substrates in Wittig reactions,[29] our

(20) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(21) Lin, J.; Nikado, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745.
(22) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(23) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.
(24) Rabjohn, N. *Org. React.* **1976**, *24*, 261.
(25) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Davis, F. A.; Chattapadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087.
(26) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.
(27) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.
(28) Heathcock, C. H.; Badger, R. A.; Patterson, Jr., J. W. *J. Am. Chem. Soc.* **1967**, *89*, 4133.

Scheme 14



[H]	% yield	ratio, **4**:**51**
H_2, Rh/Al_2O_3	84	1:3
diimide	89	>15:1

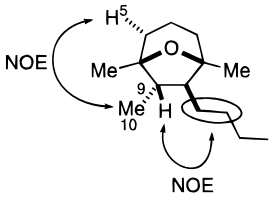
substrate completely decomposed under the reaction conditions, presumably because of the extremely hindered environment of the carbonyl group in **45**. At this point, we realized that the carbonyl group would be less hindered after closure of the oxetane ring, so we removed the benzyl protecting group to obtain diol **46**, which was converted into mesylate **47** and cyclized as before to provide oxetane **48** in 88% yield.

With the oxetane in hand, we faced the worrisome acid-catalyzed hydrolysis of the dimethyl acetal. Our concern was that acid-catalyzed scission of the strained oxetane ring might compete with acetal hydrolysis. However, events proved this concern to be unfounded. With 1:1:1 TFA/$CHCl_3$/H_2O, two full days were required to completely hydrolyze the acetal, and even with this extended exposure to acid, the oxetane ring was left untouched and keto-oxetane **49** was isolated in 92% yield (Scheme 14). It is interesting to compare the acid-catalyzed hydrolysis of acetals **43** and **48**. In the case of **43** hydrolysis was complete in 20 min, whereas the oxetane acetal **48** required two days for complete hydrolysis. This difference in reactivity is probably a consequence of ring strain in the tricyclic system, making it more difficult to form the sp^2-hybridized carbonyl center. With ketone **49** in hand, we carried out the Wittig olefination, and this time the reaction was successful. Conversion of the ketone into the methylene occurred after refluxing with the phosphonium ylide in THF for 12 h, and alkene **50** was isolated in an excellent 93% yield.

The only remaining step was to hydrogenate the exocyclic methylene to the *endo* methyl group. However, hydrogenation over Pd/C gave a complex mixture of products. With hindsight, we realized that this was a poor choice of conditions, as insertion of palladium into the allylic oxetane would open the four-membered ring.[30] We then searched for a hydrogenation catalyst that was unlikely to form a π-allyl complex with our substrate, and rhodium on alumina powder appeared attractive.[31] When this reduction was performed on oxetane **50**, we isolated what appeared to be a 1:3 mixture of diastereomers in 84% yield. Particularly unusual was the fact that the newly formed methine quartet of the major isomer appeared downfield at 2.0 ppm, while the methyl doublet coupled to it was at 0.8 ppm. In the minor isomer, the methine and methyl signals were at 1.5 and 0.9 ppm, respectively. This data seemed to suggest that the methine proton in the major diastereomer was being deshielded by its proximity to the oxetane oxygen. This effect could only be possible if the methyl group was *exo* to our ring system, as in **51**. We speculated that the rhodium was coordinating to the oxetane oxygen, thereby directing the hydrogenation from underneath the ring system and producing the *exo* methyl.[32]

To test our theory concerning coordination of the rhodium catalyst to the oxetane oxygen, we attempted to hydrogenate exocyclic alkene **50** with diimide, which is incapable of oxygen coordination. Treatment of oxetane **50** with tosyl hydrazide and sodium acetate in refluxing THF/H_2O gave essentially only one isomeric product, identical spectrally with the minor isomer from the rhodium-catalyzed hydrogenation. This reversal of facial preference under the two different reaction conditions is consistent with our hypothesis concerning the substrate-directed hydrogenation. However, at this point we did not have a rigorous proof of structure of the two stereoisomers.

A combination of DQF-COSY,[33] HMBC,[11] and HMQC[34] NMR experiments were used to assign the ^1H and ^{13}C spectra of the two hydrogenation products and to verify that they indeed have the same connectivity. Determination of the stereochemistry at C9 of oxetane **4** was then accomplished with a NOESY experiment.[34a] As indicated below, NOEs were observed between the C10 methyl group and H5 as well as between H9 and protons on the butyl chain:



These results confirmed our hypothesis regarding the stereochemical outcome of the two hydrogenation reactions. The diimide reduction of alkene **50** affords the desired oxetane **4**, and we had now completed an efficient route to the novel ring system possessed by dictyoxetane (**1**). This extremely strained tricyclic skeleton has been shown to be much more stable than previously anticipated, suggesting that oxetane formation need not be the last step in a total synthesis of dictyoxetane.

Experimental Section

General. All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere. Flash chromatography[35] was carried out using Merck 60 230−400 mesh silica gel, and thin layer chromatography was carried out on Merck silica gel 60 F-254 glass plates. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen immediately prior to use. Methylene chloride (CH_2Cl_2), meth-

(29) (a) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2629. (b) Daniewski, A. R.; Kabat, M. M.; Masnyk, M.; Wicha, J.; Wojciechowska, W. *J. Am. Chem. Soc.* **1988**, *53*, 4855.

(30) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969.

(31) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; pp 41−42.

(32) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

(33) (a) Bodenhausen, G.; Kogler, H.; Ernst, R. R. *J. Magn. Res.* **1984**, *58*, 370. (b) Derome, A. E.; Williamson, M. P. *J. Magn. Res.* **1990**, *88*, 177.

(34) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

anesulfonyl chloride, diisopropylamine, and triethylamine were distilled from calcium hydride under nitrogen prior to use. Reagents were used as received from commerical suppliers unless otherwise noted. Organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator. Unless otherwise indicated, IR spectra were obtained as thin films on NaCl plates. All NMR spectra were obtained in $CDCl_3$, except where noted. ^{1}H NMR spectral data are tabulated in the following order: multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants in hertz. ^{13}C NMR spectra were recorded at 100 MHz.

6-Hydroxy-2,6-dimethyl-2*H*-pyran-3(6*H*)-one (9). To a solution of **8**[36] (15.5 g, 124 mmol) in CH_2Cl_2 at 0 °C was added *m*-CPBA (21.5 g, 124 mmol) portionwise over 3 min. After stirring for 5 min, the reaction mixture was filtered through a Buchner funnel and rinsed once with cold CH_2Cl_2. The filtrate was then washed with 20% aqueous KI, 30% aqueous $Na_2S_2O_3$, and aqueous saturated $NaHCO_3$. The combined aqueous layers were then backwashed with CH_2Cl_2. The combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (15% ethyl acetate in hexanes) provided enone **9** (15 g, 85%) as an inseparable 9:1 mixture of diastereomers as a pale yellow oil. IR: 3390, 1695 cm^{-1}. ^{1}H NMR (400 MHz): (major isomer) δ 1.33 (d, 3, J = 6.8), 1.60 (s, 3), 3.52 (s, 1), 4.62 (q, 1, J = 6.8), 5.98 (d, 1, J = 10.0), 6.80 (d, 1, J = 10.0). ^{13}C NMR: δ 15.3, 28.8, 70.7, 92.8, 125.9, 148.3, 197.5. The ^{1}H NMR data agreed with the literature values.[6]

Dimer 12. To a solution of **9** (22 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was added triethylamine (22 μL, 0.16 mmol) and methanesulfonyl chloride (12 μL, 0.16 mmol). The reaction was stirred for 18 h at room temperature. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (30% ethyl acetate in hexanes) to provide dimer **12** (10 mg, 53%) as a white solid, mp 110−111 °C. IR: 1700, 1694 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.32 (d, 1, J = 6.9), 1.46 (s, 3), 1.47 (s, 3), 2.28 (d, 1, J = 17.6), 2.32 (d, 1, J = 17.6), 4.30 (q, 1, J = 6.9), 6.17 (d, 1, J = 9.8), 6.19 (d, 1, J = 10.5), 6.98 (d, 1, J = 10.5), 7.03 (d, 1, J = 9.8). ^{13}C NMR: δ 17.9, 20.0, 20.7, 48.0, 74.8, 83.5, 83.7, 84.2, 124.5, 126.3, 150.9, 154.2, 195.4, 196.9. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.58; H, 6.37.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-one (13). To a solution of **9** (1.6 g, 11.0 mmol) in acrylonitrile (60 mL) was added diisopropylethylamine (2.3 mL, 13 mmol), followed by methanesulfonyl chloride (1.0 mL, 13 mmol). The resulting solution was heated to a reflux and stirred for 12 h. After cooling to room temperature, the reaction mixture was filtered through a plug of Celite, and the filtrate was concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided the cycloadduct **13** (880 mg, 45%) as an inseparable 10:1:1 mixture of regio- and stereoisomers. IR: 2260, 1710 cm^{-1}. ^{1}H NMR (400 MHz): (major isomer) δ 1.55 (s, 3), 1.76 (s, 3), 2.33 (dd, 1, J = 14.0, 3.6), 2.42 (dd, 1, J = 14.0, 9.1), 3.10 (dd, 1, J = 9.1, 3.6), 6.06 (d, 1, J = 9.7), 6.99 (d, 1, J = 9.7). ^{13}C NMR: δ 19.4, 21.5, 37.6, 39.2, 80.7, 85.5, 118.7, 126.9, 152.7, 196.1. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.41; H, 6.34; N, 8.01.

6-Acetoxy-6-cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-one (14b). To a solution of **9** (25 mg, 0.18 mmol) in α-acetoxyacrylonitrile[37] (1.7 mL) was added diisopropylethylamine (37 μL, 0.21 mmol), followed by methanesulfonyl chloride (16 μL, 0.21 mmol). The reaction was heated to 140 °C for 15 h. After cooling to room temperature, the dark red reaction mixture was concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided the cycloadduct **14b** (20 mg, 48%) as a white solid; mp 143−144 °C. IR: 2300, 1765, 1710 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.51 (s, 3), 1.79 (s, 3), 2.11 (s, 3), 2.25 (d, 1, J = 15.2), 3.07 (d, 1, J = 15.2), 6.15 (d, 1, J = 9.8), 6.92 (d, 1, J = 9.8). ^{13}C NMR: δ 19.5, 20.4, 20.5, 47.2, 79.5, 82.3, 84.1, 116.6, 127.5, 150.1, 168.5, 195.6. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.13; H, 5.71; N, 5.82.

6-Chloro-6-cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-one (15b). To a solution of **9** (200 mg, 1.4 mmol) and α-chloroacrylonitrile (5 mL) in acetonitrile (7 mL) was added diisopropylethylamine (0.37 mL, 2.1 mmol), followed by methanesulfonyl chloride (0.16 mL, 2.1 mmol). The reaction mixture was heated to 110 °C for 12 h. After cooling to room temperature, the dark red reaction mixture was concentrated *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexanes) provided the cycloadduct **15b** (90 mg, 30%) as a white solid; mp 64 °C. IR: 2243, 1711 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.51 (s, 3), 1.80 (s, 3), 2.56 (d, 1, J = 14.8), 3.00 (d, 1, J = 14.8), 6.19 (d, 1, J = 9.8), 6.98 (d, 1, J = 9.8). ^{13}C NMR: δ 19.2, 19.6, 50.2, 59.9, 83.9, 84.1, 117.5, 127.5, 150.1, 194.6. Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.76; H, 4.76; N, 6.62. Found: C, 56.81; H, 4.91; N, 6.43.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-*endo*-ol (16). To a solution of **13** (50 mg, 0.28 mmol) in methanol (3 mL) at room temperature was added $CeCl_3 \cdot 7H_2O$ (105 mg, 0.28 mmol). When the solution was homogeneous, sodium borohydride (11 mg, 0.28 mmol) was added. When the bubbling had ceased (5 min), the reaction was quenched with H_2O and diluted with ethyl acetate. The biphasic mixture was stirred for 10 min, and then the layers were separated. The aqueous layer was extracted once with ethyl acetate, and the combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (30% ethyl acetate in hexanes) provided alcohol **16** (41 mg, 81%) as a colorless, thick oil. IR: 3450, 2241, 1641 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.49 (s, 3), 1.55 (s, 3), 1.88−1.91 (m, 2), 2.89 (dd, 1, J = 13.3, 9.3), 2.95 (dd, 1, J = 9.3, 1.5), 4.35 (d, 1, J = 0.9), 5.61 (dd, 1, J = 9.6, 1.9), 5.77 (dd, 1, J = 9.6, 1.6). ^{13}C NMR: δ 21.3, 23.9, 36.2, 39.9, 72.6, 80.0, 82.7, 120.1, 129.7, 134.0. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.95; H, 7.53; N, 7.70.

6-Acetoxy-6-cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-*endo*-ol (17). To a solution of **14b** (90 mg, 0.38 mmol) in methanol (4 mL) at room temperature was added $CeCl_3 \cdot 7H_2O$ (140 mg, 0.38 mmol). When the solution was homogeneous, sodium borohydride (14 mg, 0.38 mmol) was added. When the bubbling had ceased (5 min), the reaction was quenched with H_2O and diluted with ethyl acetate. This biphasic mixture was stirred for 5 min, and then the layers were separated. The aqueous layer was extracted once with ethyl acetate, and the combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided the allylic alcohol **17** (85 mg, 94%) as a colorless oil. IR: 3481, 2246, 1754 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.47 (s, 3), 1.56 (s, 3), 1.79 (br d, 1, J = 5.4), 2.11 (s, 3), 2.17 (d, 1, J = 14.8), 2.61 (d, 1, J = 14.8), 4.38 (br d, 1, J = 4.9), 5.70 (dd, 1, J = 9.7, 1.8), 5.77 (dd, 1, J = 9.7, 1.6). ^{13}C NMR: δ 19.9, 20.5, 23.9, 43.3, 72.5, 80.5, 81.0, 81.2, 117.5, 130.3, 132.1, 168.8. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.60; H, 6.34; N, 5.83.

6-Chloro-6-cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-*endo*-ol (18). To a solution of **15b** (80 mg, 0.38 mmol) in methanol (4 mL) at room temperature was added $CeCl_3 \cdot 7H_2O$ (140 mg, 0.38 mmol). When the solution was homogeneous, sodium borohydride (14 mg, 0.38 mmol) was added. When the bubbling had ceased (5 min), the reaction was quenched with H_2O and diluted with ethyl acetate. This biphasic mixture was stirred for 5 min, and then the layers were separated. The aqueous layer was extracted once with ethyl acetate, and the combined organics were dried and concentrated *in vacuo* to provide the allylic alcohol **18** (80 mg, 99%) as a white solid; mp 75−76 °C. IR: 3480, 2246 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.48 (s, 3), 1.58 (s, 3), 1.95 (br d, 1, J = 5.3), 2.55 (d, 1, J = 14.3), 2.94 (d, 1, J = 14.3), 4.36 (br d, 1, J = 5.0), 5.76 (dd, 1, J = 9.7, 1.8), 5.84 (dd, 1, J = 9.7, 1.4). ^{13}C NMR: δ 19.1, 23.6, 46.9, 61.9, 72.4, 81.6, 83.0, 118.6, 131.0, 131.8. Anal. Calcd for $C_{10}H_{12}NO_2$: C, 56.20; H, 5.66; N, 6.55. Found: C, 56.57; H, 5.81; N, 6.36.

2-*endo*-Hydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-6-one (19). A suspension of **16** (12 mg, 0.07 mmol) and Pd/C (10%) in ethanol (0.5 mL) was stirred under an atmosphere of

(36) Noyce, D. S.; Kaiser, G. V. *J. Org. Chem.* **1969**, *34*, 1008.
(37) Nowak, R. M. *J. Org. Chem.* **1963**, *28*, 1182.

H_2 for 2 h. Then the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the crude saturated alcohol. To a solution of diisopropylethylamine (20 μL, 0.14 mmol) in THF (0.3 mL) at −78 °C was added butyllithium in hexanes (0.10 mL, 0.14 mmol). The solution was warmed to 0 °C and stirred for 30 min. Then the solution was recooled to −78 °C, and a solution of the crude alcohol (12 mg, 0.07 mmol) in THF (0.1 mL) was added via cannula. After stirring for 2 min, dry oxygen gas was bubbled into the solution for 30 min. The reaction was quenched with 2 mL of 1 M stannous chloride in 2 M HCL solution and stirred for 30 min at 0 °C. Then the reaction mixture was diluted with ethyl acetate and washed with water, 1 M NaOH, and brine. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided the hydroxy ketone **19** (7 mg, 62%) as a clear oil. IR: 3463, 1756 cm $^{-1}$. ^{1}H NMR (400 MHz): δ 1.25 (s, 3), 1.32−1.43 (m, 1), 1.48 (s, 3), 1.64−1.70 (m, 3), 1.99−2.03 (m, 1), 2.18 (d, 1, J = 18.5), 2.63 (d, 1, J = 18.5), 3.70 (br t, 1, J = 5.1). ^{13}C NMR: δ 19.6, 23.4, 27.6, 32.9, 43.0, 71.4, 79.3, 82.0, 217.5. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.78; H, 8.47.

From 17: A suspension of **17** (20 mg, 0.12 mmol) and Pd/C (10%) in ethanol (1 mL) was stirred under an atmosphere of H_2 for 2 h. Then the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the saturated hydroxy ketone. This crude material was then dissolved in methanol (1 mL), and sodium methoxide in methanol (0.05 mL 0.18 mmol) was added. After stirring for 25 min, the reaction was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography (20% ethyl acetate in hexanes) provided hydroxy ketone **19** (12 mg, 60%).

From 18: A suspension of **18** (40 mg, 0.19 mmol) and Pd/C (10%) in ethanol (2 mL) was stirred under an atmosphere of H_2 for 2 h. Then the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the saturated hydroxy ketone. This crude material was then dissolved in wet DMSO (3 mL), and KOH (80 mg, 1.4 mmol) was added. The reaction solution was then heated to 70 °C and stirred for 1 h. After cooling to room temperature, the reaction was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided hydroxy ketone **19** (24 mg, 75%).

2-*endo*-Hydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6-one (22). To a solution of **17** (90 mg, 0.38 mmol) in methanol (2 mL) was added sodium methoxide in methanol (0.15 mL, 0.56 mmol). After stirring for 30 min, the reaction was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography (25% ethyl acetate in hexanes) provided the ketone **22** (41 mg, 64%) as a colorless, somewhat volatile oil. IR: 3444, 1754 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.36 (s, 3), 1.55 (s, 3), 2.13 (d, 1, J = 18.6), 3.19 (d, 1, J = 18.6), 4.35 (br s, 1), 5.73 (dd, 1, J = 9.6, 1.8), 5.83 (dd, 1, J = 9.7, 2.0). ^{13}C NMR: δ 17.2, 24.3, 41.0, 70.4, 78.7, 80.6, 131.0, 132.8, 209.3. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.44; H, 7.22.

2-*endo*-[(Methanesulfonyl)oxy]-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6-one (23). To a solution of **22** (30 mg, 0.18 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added triethylamine (27 μL, 0.20 mmol), followed by methanesulfonyl chloride (15 μL, 0.20 mmol). After stirring for 30 min, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted once with CH_2Cl_2, and the combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided the keto mesylate **23** (33 mg, 75%) as a white solid. IR: 1760 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.38 (s, 3), 1.59 (s, 3), 2.24 (d, 1, J = 18.7), 3.09 (s, 3), 3.11 (d, 1, J = 18.6), 5.23 (d, 1, J = 1.6), 5.89 (dd, 1, J = 9.7, 1.5), 5.95 (dd, 1, J = 9.7, 2.0). ^{13}C NMR: δ 17.1, 24.3, 38.8, 41.5, 77.2, 77.3, 81.0, 128.1, 134.0, 207.3. Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73. Found: C, 48.93; H, 5.88.

2-*endo*-[(Methanesulfonyl)oxy]-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6-*endo*-ol (20). To a solution of **23** (10 mg, 0.04 mmol) in methanol (1 mL) at 0 °C was added sodium borohydride (3 mg, 0.08 mmol). After stirring for 10 min, the reaction was quenched with H_2O and diluted with ethyl acetate. The aqueous layer was extracted once with ethyl acetate, and the combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (40% ethyl acetate in hexanes) provided the hydroxy mesylate **20** (10 mg, 99%) as a colorless oil that decomposed upon standing to 4-methylacetophenone. IR: 3441, 1643 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.37 (s, 3), 1.40 (s, 3), 1.66 (s, 1), 2.12−2.15 (m, 2), 3.06 (s, 3), 4.06 (dd, 1, J = 8.7, 7.0), 5.25 (s, 1), 5.86 (dd, 1, J = 9.9, 2.0), 6.01 (dd, 1, J = 9.9, 1.4). ^{13}C NMR: δ 21.0, 24.4, 38.7, 40.2, 78.8, 80.3, 80.4, 81.6, 125.4, 137.4.

6-Cyano-3,4-epoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]-octan-2-one (25). To a solution of enone **13** (6.0 g, 33.7 mmol) in 200 mL of 3:1 methanol/water at 0 °C was added *tert*-butyl hydroperoxide (6.7 mL, 67.4 mmol), followed by 15 mL of aqueous saturated Na_2CO_3 solution. This mixture was stirred at 0 °C until all the starting material had been consumed by TLC. The reaction was then quenched with aqueous saturated sodium bisulfite and extracted twice with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue provided the epoxy ketone **25** (2.6 g, 40%) as a white solid; mp 90−91 °C. IR: 2245, 1728 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.48 (s, 3), 1.79 (s, 3), 2.24 (dd, 1, J = 14.3, 5.0), 2.39 (dd, 1, J = 14.3, 9.6), 3.17 (dd, 1, J = 9.6, 5.0), 3.32 (d, 1, J = 3.5), 3.34 (d, 1, J = 3.5). ^{13}C NMR: δ 19.0, 20.5, 36.0, 42.0, 52.1, 54.9, 79.7, 86.3, 118.5, 200.5. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.96; H, 5.64; N, 7.15.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-4-*exo*-ol (26). A solution of epoxide **25** (1.3 g, 6.7 mmol) in methanol (20 mL) was added *via* a dropping funnel to a solution of hydrazine (1.1 mL, 33.5 mmol) in methanol (50 mL) at 0 °C over 10 min. The resulting solution was warmed to room temperature over 1 h, and then glacial acetic acid (80 μL, 1.3 mmol) was added. After stirring the yellow solution at room temperature for 18 h, the reaction was diluted with brine and ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (40% ethyl acetate in hexanes) provided the allylic alcohol **26** (320 mg, 27%) as a thick, foamy oil that solidified on high vacuum; mp 121−122 °C. IR: 3455, 2240, 1642 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.44 (s, 3), 1.62 (s, 3), 1.87 (d, 1, J = 11.0), 1.98 (dd, 1, J = 11.8, 8.6), 2.31 (dd, 1, J = 11.8, 8.6), 2.80 (t, 1, J = 8.6), 3.40 (dd, 1, J = 11.0, 4.4), 5.82 (dd, 1, J = 9.7, 4.4), 5.94 (dd, 1, J = 9.7, 0.6). ^{13}C NMR: δ 20.4, 22.4, 35.2, 44.6, 69.6, 79.4, 83.3, 119.7, 125.7, 136.9. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.03; H, 7.31; N, 7.82. Found: C, 67.18; H, 7.67; N, 7.89.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-4-*exo*-ol (27). A suspension of **26** (320 mg, 1.8 mmol) and Pd/C (10%) in ethanol (20 mL) was stirred under an atmosphere of hydrogen for 90 min. Then the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to provide the saturated alcohol **27** (323 mg, 100%) as a white solid; mp 130−131 °C. IR: 3438, 2238 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.35−1.38 (m, 4), 1.54 (s, 3), 1.70−1.81 (m, 3), 2.03 (dd, 1, J = 13.1, 5.9), 2.27 (br d, 1, J = 10.1), 2.35 (dd, 1, J = 13.1, 9.8), 2.93 (dd, 1, J = 9.8, 5.9), 3.32 (br d, 1, J = 9.2). ^{13}C NMR: δ 20.6, 25.7, 26.1, 31.0, 36.8, 41.5, 69.1, 81.5, 83.8, 120.4. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.04; H, 8.47; N, 7.52.

3-Cyano-2,5-dimethylcyclohept-2-ene-1,5-diol (28). To a solution of diisopropylethylamine (0.05 mL, 0.33 mmol) in THF (0.75 mL) at −78 °C was added butyllithium in hexanes (0.18 mL, 0.33 mmol). The solution was warmed to 0 °C and stirred for 30 min. Then the solution was recooled to −78 °C, and a solution of **27** (27 mg, 0.15 mmol) in THF (0.3 mL) was

added via cannula. Immediately following the addition, dry oxygen gas was bubbled into the solution for 30 min. The reaction was quenched with 0.5 mL of 1 M stannous chloride in 2 M HCL solution and stirred for 30 min at 0 °C. Then the reaction mixture was diluted with ethyl acetate and washed with water, 1 M NaOH, and brine. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (50% ethyl acetate in hexanes) provided diol **28** (15 mg, 56%) as a white solid. IR: 3406, 2212, 1633 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.30 (s, 3), 1.70−1.76 (m, 2), 1.91−1.99 (m, 2), 2.19 (s, 3), 2.49 (d, 1, J = 15.6), 2.57 (d, 1, J = 15.6). ^{13}C NMR: δ 20.3, 30.2, 31.6, 39.3, 42.5, 69.3, 72.6, 104.6, 109.4, 161.9. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34, N, 7.73. Found: C, 66.08; H, 8.34, N, 7.58.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-4-*exo*-yl *tert*-Butyldimethylsilyl Ether (29). To a solution of alcohol **27** (275 mg, 1.5 mmol) in DMF (3 mL) was added imidazole (410 mg, 6.0 mmol) and *tert*-butyldimethylsilyl chloride (450 mg, 3.0 mmol). The resulting solution was stirred at room temperature for 48 h. The reaction was quenched with aqueous saturated NH_4Cl and diluted with ethyl ether. The layers were separated, and the organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (7% ethyl acetate in hexanes) provided silyl ether **29** (400 mg, 90%) as a pale yellow oil. IR: 2239 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.06 (s, 3), 0.07 (s, 3), 0.91 (s, 9), 1.26 (ddd, 1, J = 13.0, 5.7, 1.4), 1.35 (s, 3), 1.47 (s, 3), 1.64−1.85 (m, 3), 1.96 (ddd, 1, J = 13.0, 5.8, 2.0), 2.31 (dd, 1, J = 13.0, 9.7), 2.83 (dd, 1, J = 9.7, 5.8), 3.30 (app t, 1, J = 2.5). ^{13}C NMR: δ −4.9, −4.7, 18.0, 21.0, 25.7, 26.1, 26.4, 31.0, 36.7, 41.4, 69.5, 80.5, 83.9, 120.8. Anal. Calcd for $C_{16}H_{29}NO_2Si$: C, 65.03; H, 9.89; N, 4.74. Found: C, 64.88; H, 10.14; N, 4.80.

4-*exo*-[(*tert*-Butyldimethylsilyl)oxy]-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-6-one (30). To a solution of diisopropylethylamine (0.16 mL, 1.15 mmol) in THF (5 mL) at −78 °C was added butyllithium in hexanes (0.63 mL, 1.15 mmol). The solution was warmed to 0 °C and stirred for 30 min. Then the solution was recooled to −78 °C, and a solution of **29** (295 mg, 1.00 mmol) in THF (0.5 mL) was added via cannula. Immediately following the addition, dry oxygen gas was bubbled into the solution for 30 min. The reaction was quenched with 2 mL of 1 M stannous chloride in 2 M HCL solution and stirred for 30 min at 0 °C. Then the reaction mixture was diluted with ethyl acetate and washed with water, 1 M NaOH, and brine. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (10% ethyl acetate in hexanes) provided ketone **30** (175 mg, 62%) as a colorless oil. IR: 1754 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.06 (s, 3), 0.07 (s, 3), 0.92 (s, 9), 1.20 (s, 3), 1.34−1.41 (m, 1), 1.47 (s, 3), 1.66−1.72 (m, 2), 1.95−2.05 (m, 1), 2.30 (d, 1, J = 17.9), 2.41 (d, 1, J = 17.9), 3.45 (app t, 1, J = 2.7). ^{13}C NMR: δ −4.7, −4.6, 17.3, 18.2, 25.8, 26.7, 27.8, 30.4, 47.0, 67.1, 77.3, 85.9, 217.8. Anal. Calcd for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 62.96; H, 9.99.

4-*exo*-Hydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-6-one (31). A solution of **30** (65 mg, 0.23 mmol) in 2% HF/CH_3CN (2.5 mL) was stirred at room temperature for 1 h. Then the reaction was quenched with aqueous saturated $NaHCO_3$ and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (50% ethyl acetate in hexanes) provided the hydroxy ketone **31** (40 mg, 100%) as a clear oil. IR: 3462, 1754 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.26 (s, 3), 1.44−1.49 (m, 4), 1.71 (dddd, 1, J = 15.1, 13.4, 5.7, 3.4), 1.79−1.94 (m, 2), 2.33, (dd, 1, J = 17.9, 1.1), 2.43 (d, 1, J = 17.9), 2.50 (br d, 1, J = 9.1), 3.43 (br s, 1). ^{13}C NMR: δ 16.8, 26.5, 26.8, 30.4, 46.7, 66.9, 78.2, 85.5, 216.2. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.75; H, 8.52.

4-*exo*-[(Methanesulfonyl)oxy]-1,5-dimethyl-8-oxabicyclo-[3.2.1]octan-6-*endo*-ol (32). To a solution of alcohol **31** (85 mg, 0.50 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added triethylamine (0.11 mL, 0.77 mmol), followed by methanesulfonyl chloride (59 μL, 0.77 mmol). After stirring for 30 min, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted once with CH_2Cl_2, and the combined organics were dried and concentrated *in vacuo*. The residue was then dissolved in methanol (2.5 mL), and the resulting solution was cooled to 0 °C with stirring. Sodium borohydride (27 mg, 0.72 mmol) was added, and the reaction mixture was stirred at 0 °C for 10 min. The reaction was quenched with H_2O and diluted with ethyl acetate. The resulting biphasic mixture was stirred at room temperature for 15 min, and then the layers were separated. The aqueous layer was extracted twice with ethyl acetate, and the combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue provided the hydroxy mesylate **32** (85 mg, 68%) as a white solid; mp 104−105 °C. IR: 3431, 2360 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.30 (s, 3), 1.34 (s, 3), 1.43 (ddd, 1, J = 13.5, 6.0, 1.2), 1.76 (dd, 1, J = 13.4, 4.1), 1.85 (ddd, app td, 1, J = 13.5, 13.5, 5.4), 2.08 (dddd, app ddt, 1, J = 15.7, 5.4, 1.6, 1.6), 2.17 (ddd, 1, J = 13.4, 10.9, 1.1), 2.21 (br d, 1, J = 5.0), 2.41 (dddd, 1, J = 15.7, 13.6, 6.1, 3.8), 3.06 (s, 3), 4.23 (ddd, app dt, 1, J = 10.9, 4.2, 4.2), 4.77 (dd, 1, J = 3.6, 1.6). ^{13}C NMR: δ 21.6, 25.2, 26.7, 31.9, 38.7, 43.9, 77.5, 78.7, 79.7, 82.1. Anal. Calcd for $C_{10}H_{18}O_5S$: C, 47.99; H, 7.25. Found: C, 48.31; H, 7.34.

6-Butyl-1,5-dimethyl-8-oxabicyclo[3.2.1]octane-4-*exo*-6-*endo*-diol (33). To a solution of butyllithium in hexanes (0.6 mL, 1.8 mmol) in THF (4 mL) at −78 °C was added dropwise a solution of **30** (100 mg, 0.35 mmol) in THF (0.5 mL). After stirring for 20 min, the dry ice bath was removed, and the reaction was quenched with aqueous saturated NH_4Cl. The reaction mixture was extracted twice with ethyl acetate, and the combined organics were dried and concentrated *in vacuo*. The residue was then dissolved in 3 mL of 2% HF/CH_3CN, and the resulting solution was stirred for 1 h. The reaction was quenched with aqueous saturated $NaHCO_3$ and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (40% ethyl acetate in hexanes) provided the diol **33** (67 mg, 84%) as a white solid; mp 85−86 °C. IR: 3403 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.94 (t, 3, J = 6.9), 1.19 (s, 3), 1.24 (s, 3), 1.33−1.40 (m, 5), 1.48−1.62 (m, 2), 1.67−1.79 (m, 3), 1.85 (d, 1, J = 13.5), 1.89 (d, 1, J = 13.5), 2.22 (d, 1, J = 11.0), 2.39 (dddd, 1, J = 15.7, 11.4, 8.0, 3.4), 3.56 (br d, 1, J = 10.1). ^{13}C NMR: δ 14.1, 16.9, 23.2, 25.2, 26.8, 27.2, 31.9, 40.1, 48.0, 68.0, 79.1, 82.3, 86.0. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.39; H, 10.60. Found: C, 68.42; H, 10.58.

6-Butyl-4-*exo*-[(methanesulfonyl)oxy]-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-6-*endo*-ol (34). To a solution of diol **33** (14 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C was added triethylamine (17 μL, 0.12 mmol), followed by methanesulfonyl chloride (7 mg, 0.06 mmol). After stirring for 30 min, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted once with CH_2Cl_2, and the combined organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (30% ethyl acetate in hexanes) provided hydroxy mesylate **34** (17 mg, 93%) as a white solid; mp 118 °C. IR: 3517 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.95 (t, 3, J = 6.9), 1.21 (s, 3), 1.27 (s, 3), 1.38−1.43 (m, 5), 1.49−1.58 (m, 3), 1.81−1.93 (m, 3), 2.09 (dddd, app ddt, 1, J = 15.7, 5.4, 2.1, 2.1), 2.53 (dddd, 1, J = 15.7, 13.7, 6.2, 3.7), 3.06 (s, 3), 4.81 (dd, 1, J = 3.4, 2.1). ^{13}C NMR: δ 14.1, 17.2, 23.2, 25.1, 25.6, 27.1, 31.7, 38.8, 39.8, 47.9, 78.6, 78.7, 82.6, 84.7. Anal. Calcd for $C_{14}H_{26}O_5S$: C, 54.88; H, 8.55. Found: C, 54.88; H, 8.89.

1-Butyl-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane (3). To a solution of hydroxy mesylate **34** (35 mg, 0.11 mmol) in THF (1.1 mL) was added 60% NaH in oil (13.7 mg, 0.34 mmol), and the resulting suspension was heated to reflux. After stirring for 2 h, the reaction was cooled to 0 °C and was quenched by the dropwise addition of aqueous saturated $NaHCO_3$. The mixture was then extracted with ethyl ether, and the organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexanes) provided the oxetane **3** (18 mg, 77%) as a colorless liquid. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.2), 1.19−1.27 (m, 1), 1.31−1.37 (m, 5), 1.39−1.46 (m, 4), 1.47−1.54 (m, 2), 1.64−1.72 (m, 1), 1.79−1.93 (m, 4), 2.00 (d, 1, J = 13.0), 4.39 (app t, 1, J =

2.5). ^{13}C NMR: δ 14.0, 16.5, 23.2, 23.6, 25.9, 27.7, 30.5, 34.5, 50.7, 79.5, 82.7, 82.8, 97.5. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.04; H, 10.80.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-2-one (35). A suspension of enone **13** (4.0 g, 22.5 mmol) and 10% palladium on carbon (100 mg) in ethanol (45 mL) was shaken under 40 psi of hydrogen for 17 h. The reaction mixture was then filtered through Celite, and the filtrate was concentrated *in vacuo*. Flash chromatography of the residue (20% ethyl acetate in hexanes) provided the saturated ketone **35** (3.5 g, 85%) as a colorless oil that crystallized upon standing; mp 58−60 °C. IR: 2241, 1728 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.40 (s, 3), 1.65 (s, 3), 1.98 (ddd, 1, J = 13.7, 8.0, 2.5), 2.19−2.27 (m, 2), 2.38 (ddd, 1, J = 17.7, 9.7, 8.0), 2.48−2.55 (m, 2), 3.22 (dd, 1, J = 9.7, 6.0). ^{13}C NMR: δ 18.9, 24.3, 32.2, 37.8, 37.9, 42.0, 81.5, 85.6, 120.0, 205.8. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.94; H, 7.34; N, 7.73.

6-Cyano-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-2-*exo*-2-ol (36). To a solution of ketone **35** (3.7 g, 20.7 mmol) in THF (70 mL) at −78 °C was added L-Selectride (25.0 mL, 25.0 mmol) via syringe while maintaining the reaction temperature at −78 °C. After stirring the reaction mixture at this temperature for 10 min, the cooling bath was removed, and the reddish-orange solution was slowly quenched with H_2O (200 mL). To this mixture was added $NaBO_3$·$4H_2O$ (11.5 g, 75.0 mmol), and the resulting suspension was stirred at room temperature for 90 min. Then the mixture was diluted with ethyl acetate (150 mL), and the layers were separated. The aqueous layer was extracted twice with ethyl acetate (50 mL), and the combined organics were then dried and concentrated *in vacuo*. Flash chromatography of the residue (50% ethyl acetate in hexanes) provided the axial alcohol **36** (3.0 g, 80%) as a white solid; mp 84−85 °C. IR: 3468, 2238 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.39−1.44 (m, 4), 1.54 (s, 3), 1.69−1.90 (m, 3), 2.08 (dd, 1, J = 13.7, 5.2), 2.17 (d, 1, J = 10.1), 2.33 (dd, 1, J = 13.7, 9.8), 2.95 (dd, 1, J = 9.8, 5.2), 3.34 (ddd, 1, J = 10.1, 2.8, 2.5). ^{13}C NMR: δ 22.5, 24.5, 25.6, 31.9, 36.8, 41.5, 69.0, 82.1, 83.0, 120.8. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.01; H, 8.52; N, 7.41.

2-*exo*-2-Hydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-6-one (37). To a solution of diisopropylethylamine (2.5 mL, 18.1 mmol) in THF (120 mL) at −78 °C was added butyllithium in hexanes (10.1 mL, 18.1 mmol). The solution was warmed to 0 °C and stirred for 30 min. Then the solution was recooled to −78 °C, and a solution of nitrile **36** (1.1 g, 6.1 mmol) in THF (5 mL) was added *via* cannula. After stirring for 2 min, dry oxygen gas was bubbled into the solution for 30 min. The reaction was quenched with 12 mL of 1 M stannous chloride in 2 M HCl solution and stirred for 30 min at 0 °C. Then the reaction mixture was diluted with ethyl acetate and washed with water, 1 M NaOH, and brine. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (40% ethyl acetate in hexanes) provided hydroxy ketone **37** (0.80 g, 77%) as colorless crystals; mp 77−79 °C. IR: 3442, 1754 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.24 (s, 3), 1.47−1.55 (m, 4), 1.72−1.86 (m, 3), 2.31−2.41 (m, 3), 3.47 (br d, 1, J = 8.3). ^{13}C NMR: δ 20.0, 22.8, 26.4, 28.6, 46.7, 68.9, 79.6, 83.1, 216.5. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.63; H, 8.59.

2-*exo*-2-(Benzyloxy)-1,5-dimethyl-8-oxabicyclo[3.2.1]-octan-6-one (38). To a solution of hydroxy ketone **37** (1.0 g, 5.9 mmol) in THF (30 mL) was added 60% NaH in oil (350 mg, 8.8 mmol). After stirring for 3 min, benzyl bromide (1.0 mL, 8.8 mmol) was added, and the resulting suspension was stirred for 90 min. The reaction was quenched with saturated $NaHCO_3$ solution and diluted with ethyl ether. The layers were separated, and the organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (10% ethyl acetate in hexanes) provided the benzyl ether **38** (1.3 g, 83%) as a clear oil that crystallized upon standing; mp 74−75 °C. IR: 1758 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.26 (s, 3), 1.42−1.65 (m, 5), 1.87 (ddd, 1, J = 18.8, 13.3, 5.7), 2.01 (dd, 1, J = 14.7, 5.0), 2.23 (d, 1, J = 18.3), 2.31 (d, 1, J = 18.3), 3.15 (br s, 1), 4.47 (d, 1, J = 12.3), 4.72 (d, 1, J = 12.3), 7.27−7.38 (m, 5). ^{13}C NMR: δ 19.9, 21.9, 23.0, 29.2, 47.2, 71.5, 74.5, 79.2, 82.6, 127.8, 128.3, 128.4, 138.1, 217.6. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.97; H, 7.94.

2-*exo*-2-(Benzyloxy)-6,6-dimethoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-7-one (41). To a solution of ketone **38** (850 mg, 3.2 mmol) in methanol (50 mL) at 0 °C was added iodobenzene diacetate (3.1 g, 9.7 mmol), followed by KOH pellets (3.6 g). After the KOH had dissolved in the methanol, the ice bath was removed, and the resulting yellow solution was stirred at room temperature overnight. Then the reaction was recooled to 0 °C and slowly quenched with aqueous saturated $NaHCO_3$. The mixture was diluted with ethyl ether and the layers were separated. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (10% ethyl acetate in hexanes) provided the dimethoxy ketone **41** (690 mg, 66%) as a white solid; mp 85−87 °C. IR: 1766 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.26 (s, 3), 1.45 (s, 3), 1.61−1.73 (m, 2), 1.86−2.02 (m, 2), 3.18 (app d, 1, J = 1.9), 3.33 (s, 3), 3.38 (s, 3), 4.48 (d, 1, J = 12.3), 4.69 (d, 1, J = 12.3), 7.27−7.34 (m, 5). ^{13}C NMR: δ 17.3, 21.4, 23.3, 28.4, 50.3, 51.0, 71.6, 73.1, 81.6, 83.1, 98.0, 127.9, 128.3, 128.4, 137.9, 210.8. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.75; H, 7.63.

2-*exo*-(Benzyloxy)-7-*exo*-butyl-6,6-dimethoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-7-*endo*-ol (43) and 2-*exo*-(Benzyloxy)-6,6-dimethoxy-1,5-dimethyl-8-oxabicyclo-[3.2.1]octan-7-*endo*-ol (44). To a solution of TMEDA (0.76 mL, 5.0 mmol) in THF (20 mL) at −20 °C was added butyllithium in hexanes (1.1 mL, 3.3 mmol). Then a solution of ketone **41** (540 mg, 1.7 mmol) in THF (1 mL) was added dropwise. After stirring at −20 °C for 5 min, the reaction was quenched with aqueous saturated $NaHCO_3$ and diluted with ethyl ether. The layers were separated, and the organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (10% ethyl acetate in hexanes) provided the addition product **43** (420 mg, 65%), and the reduced product **44** (90 mg, 17%).

43: White solid; mp 85−86 °C. IR: 3509 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.3), 1.24 (s, 3), 1.25 (s, 3), 1.28−1.45 (m, 3), 1.53−1.70 (m, 4), 1.72−1.80 (m, 2), 2.17 (m, 1), 2.42 (br s, 1), 3.26 (dd, 1, J = 3.9, 1.6), 3.39 (s, 3), 3.45 (s, 3), 4.44 (d, 1, J = 12.1), 4.64 (d, 1, J = 12.1), 7.27−7.36 (m, 5). ^{13}C NMR: δ 14.1, 18.8, 23.1, 23.6, 23.9, 26.7, 29.5, 35.5, 52.3 (2 C), 71.7, 74.0, 82.6, 84.9, 85.1, 108.7, 127.4, 128.2, 128.3, 138.9. Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.85; H, 9.15.

44: White solid; mp 121−122 °C. IR: 3520 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.31 (s, 3), 1.36 (s, 3), 1.52 (app dd, 1, J = 12.6, 5.8), 1.74−1.82 (m, 2), 1.93 (ddd, 1, J = 20.1, 9.4, 6.0), 2.66 (d, 1, J = 4.5), 3.20 (s, 3), 3.29 (br d, 1, J = 3.4), 3.34 (s, 3), 3.75 (d, 1, J = 4.5), 4.45 (d, 1, J = 12.3), 4.66 (d, 1, J = 12.3), 7.23−7.37 (m, 5). ^{13}C NMR: δ 22.2, 22.7, 23.0, 29.1, 48.7, 50.4, 71.5, 72.2, 80.0, 81.7, 82.5, 104.2, 127.4, 128.1, 128.2, 138.6. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.26; H, 8.36.

7-*exo*-Butyl-6,6-dimethoxy-1,5-dimethyl-8-oxabicyclo-[3.2.1]octane-2-*exo*-7-*endo*-diol (46). To a solution of benzyl ether **43** (415 mg, 1.1 mmol) in ethyl acetate (20 mL) was added 20% palladium hydroxide on carbon (30 mg). The resulting suspension was stirred under 1 atm of H_2 for 90 min. The reaction mixture was then filtered through Celite, and the filtrate was concentrated *in vacuo* to produce diol **46** (295 mg, 94%) as white needles; mp 102−103 °C. IR: 3434 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.92 (t, 3, J = 7.2), 1.22 (s, 3), 1.24 (s, 3), 1.33−1.50 (m, 3), 1.52−1.80 (m, 7), 2.13 (br s, 1), 2.36−2.46 (m, 1), 3.38 (s, 3), 3.46 (s, 3), 3.49 (br s, 1). ^{13}C NMR: δ 14.1, 18.9, 23.5, 23.9, 26.7, 27.4, 28.8, 35.8, 52.3, 52.4, 67.8, 83.4, 85.1, 85.1, 108.6. Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.66; H, 9.92.

7-*exo*-Butyl-2-*exo*-[(methanesulfonyl)oxy]-6,6-dimethoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-7-*endo*-ol (47). To a solution of diol **46** (30 mg, 0.10 mmol) in methylene chloride (1.0 mL) at 0 °C was added triethylamine (44 μL, 0.30 mmol), followed by methanesulfonyl chloride (12 μL, 0.15 mmol). After stirring for 5 min, the reaction was quenched with H_2O and diluted with CH_2Cl_2. The layers were separated, and the organics were dried and concentrated *in*

vacuo. Flash chromatography of the residue (30% ethyl acetate in hexanes) provided mesylate **47** (35 mg, 92%) as a white solid; mp 99−100 °C. IR: 3519 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.92 (t, 3, J = 7.2), 1.24 (s, 6), 1.29−1.40 (m, 3), 1.58−1.73 (m, 4), 1.78−1.95 (m, 2), 2.32 (br s, 1), 2.56−2.65 (m, 1), 3.02 (s, 3), 3.38 (s, 3), 3.45 (s, 3), 4.72 (t, 1, J = 2.0). ^{13}C NMR: δ 14.1, 19.2, 23.3, 23.8, 25.9, 26.5, 28.7, 35.6, 38.7, 52.2, 52.4, 79.0, 83.0, 83.9, 85.4, 108.5. Anal. Calcd for $C_{16}H_{30}O_7S$: C, 52.44; H, 8.25. Found: C, 52.57; H, 8.48.

1-Butyl-9,9-dimethoxy-6,8-dimethyl-2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonane (48). To a solution of mesylate **47** (246 mg, 0.67 mmol) in THF (8 mL) at reflux was added 60% NaH in oil (107 mg, 2.7 mmol). The resulting suspension was stirred at reflux for 2 h. The reaction mixture was then cooled to 0 °C and quenched by the dropwise addition of aqueous saturated $NaHCO_3$. When the bubbling had ceased, the solution was diluted with diethyl ether and the layers were separated. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexanes) provided oxetane **48** (160 mg, 88%) as a colorless liquid. ^{1}H NMR (400 MHz): δ 0.93 (t, 3, J = 7.3), 1.32−1.40 (m, 8), 1.53−1.71 (m, 4), 1.74−1.91 (m, 3), 2.32−2.39 (m, 1), 3.40 (s, 3), 3.43 (s, 3), 4.46 (app d, 1, J = 3.9). ^{13}C NMR: δ 14.1, 17.3, 22.6, 23.5, 23.9, 25.1, 25.8, 29.9, 51.2, 52.5, 80.6, 82.8, 83.8, 95.1, 107.5. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.61; H, 9.83.

1-Butyl-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9-one (49). A solution of oxetane **48** (135 mg, 0.50 mmol) in 3 mL of a 1:1:1 mixture of TFA:$CHCl_3$:H_2O was stirred at room temperature for 48 h. Then the reaction was cooled to 0 °C and quenched with 3 mL of aqueous saturated $NaHCO_3$. After diluting the mixture with CH_2Cl_2, the layers were separated, and the organic layer was washed with H_2O. The organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexanes) provided ketone **49** (103 mg, 92%) as a colorless liquid. IR: 1762 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.2), 1.21−1.37 (m, 7), 1.49 (s, 3), 1.80−2.06 (m, 6), 4,64 (dd, 1, J = 3.5, 2.0). ^{13}C NMR: δ 13.8, 17.0, 21.1, 22.5, 23.3, 24.4, 27.3, 27.6, 79.7, 80.3, 83.8, 87.6, 211.8. Analyses performed were repeatedly low in carbon due to the hydroscopic nature of this compound.

1-Butyl-6,8-dimethyl-9-methylene-2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonane (50). To a solution of methylenetriphenylphosphorane[38] (130 mg, 0.47 mmol) in 3 mL of THF at −78 °C was added ketone **49** (72 mg, 0.32 mmol) as a 1 mL THF solution. After warming to room temperature, the yellow reaction mixture was heated to reflux and stirred overnight. Then the reaction was cooled to room temperature and quenched with aqueous saturated $NaHCO_3$. The mixture was extracted with ethyl ether, and the organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexanes) provided the exocyclic methylene **50** (66 mg, 93%) as a colorless liquid. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.2), 1.19−1.28 (m, 2), 1.31−1.38 (m, 2), 1.45 (s, 6), 1.73−1.96 (m, 6), 4.40 (br s, 1), 4.98 (s, 1), 5.03 (s, 1). ^{13}C NMR: δ 13.9, 17.0, 23.2, 23.4, 24.8, 26.4, 30.8, 31.7, 80.8, 81.8, 82.8, 93.3, 104.3, 156.7. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.64; H, 9.97. Found: C, 75.85; H, 10.09.

1-Butyl-6,8,9-*exo*-trimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]-nonane (51) and 1-Butyl-6,8,9-*endo*-trimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane (4). A suspension of alkene **50** (20 mg, 0.09 mmol) and rhodium on alumina (3 mg) in ethyl acetate (3 mL) was stirred under an atmosphere of H_2 for 75 min. The reaction mixture was then filtered through Celite and washed with ethyl acetate. The filtrate was concentrated *in vacuo*, and the remaining residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide a 3:1 mixture (17 mg, 84%) of oxetane diastereomers **51** and **4** as a colorless oil. IR: 2958, 2930, 1453, 1385, 1071, 962 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.98; H, 10.88.

Compound 51: ^{1}H NMR (500 MHz): δ 0.77 (d, 3, J = 7.3), 0.93 (t, 3, J = 7.2), 1.29 (s, 3), 1.31 (s, 3), 1.33−1.38 (m, 2), 1.49−1.57 (m, 3), 1.65−1.75 (m, 2), 1.82−1.93 (m, 3), 1.96 (q, 1, J = 7.3), 4.38 (d, 1, J = 2.5). ^{13}C NMR: δ 12.5, 14.0, 17.0, 23.3, 23.4, 24.7, 24.9, 31.5, 32.4, 50.2, 81.4, 81.5, 82.2, 99.3.

Compound 4: ^{1}H NMR (500 MHz, toluene-d_8): δ 0.89 (t, 3, J = 7.0), 0.92 (d, 3, J = 6.9), 1.22 (s, 3), 1.26 (s, 3), 1.27−1.37 (m, 5), 1.44−1.54 (m, 2), 1.61−1.79 (m, 4), 4.18 (t, 1, J = 1.8). ^{13}C NMR ($CDCl_3$): δ 7.1, 14.0, 17.0, 23.1, 23.5, 23.8, 26.4, 26.9, 33.1, 48.8, 81.4, 81.8, 82.3, 96.7.

1-Butyl-6,8,9-*endo*-trimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]-nonane (4). Method 2. To a solution of **50** (10.0 mg, 0.045 mmol) in 1 mL of 1:1 THF:H_2O was added sodium acetate (26 mg, 0.32 mmol), followed by *p*-toluenesulfonyl hydrazide (42 mg, 0.23 mmol). The resulting mixture was heated to reflux and stirred for 3 h. After cooling to room temperature, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ and diluted with ethyl ether. The layers were separated, and the organics were dried and concentrated *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexanes) provided oxetane **4** (9 mg, 89%).

Acknowledgment. This research was supported by a research grant from the National Science Foundation (CHE 93-14741).

Supporting Information Available: Determination of relative configuration of **4** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961680K

(38) Koster, R.; Simic, D.; Grossberger, M. A. *Justus Liebigs. Ann. Chem.* **1970**, *739*, 211.