Cyclization of the 3-*tert*-Butylhex-5-enyl Radical: A Test of Transition-State Structure

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The reaction of either of the radical precursors **5** or **8** with tributylstannane in benzene gives a mixture of open-chain and cyclized products **11** and **12**, the ratio of yields of which depends, as expected, on the concentration of stannane. The magnitude of the rate constant for cyclization of the radical **9**, $k_c \approx 2 \times 10^8$ s^{-1} at 80 °C, reflects the effect of the bulky *tert*-butyl substituent on the strain energy of the ground state. The ratio of yields of the diastereoisomers of **12** (cis/trans = 4.5) is independent of stannane concentration. The difference of free energies of activation, $\Delta G^{\ddagger}$(trans) − $\Delta G^{\ddagger}$(cis) of 1.0 kcal, is in agreement with theoretical predictions based on the hypothesis that cis cyclization proceeds through a chairlike transition structure **13c** while trans cyclization involves a boatlike transition structure **15c**.

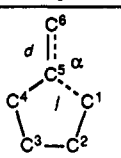
Intramolecular homolytic addition in suitably constituted alkenyl or alkynyl radicals and similar species has attracted intense interest as a synthetically useful method for the construction of a variety of ring systems.[1-3] Usually, such reactions proceed with high regioselectivity and acceptable stereoselectivity,[1-3] while the methods used to generate the required radicals generally offer the considerable advantage of proceeding efficiently in the presence of a wide range of unprotected functional groups.

Ring closure of the 5-hexenyl radical is the archetype of such reactions.[2-6] Its kinetics have been accurately determined,[4,5] and its characteristics are sufficiently well-documented to allow its use as a reliable mechanistic probe and radical clock.[6] The salient feature of hexenyl ring closure is the highly regioselective formation, under kinetic control, of the exo cyclization product. Most simple substituted hexenyl radicals show the same regioselectivity while also conforming to the guideline for stereoselectivity; namely, cyclization of 1- or 3-substituted radicals gives mainly cis-disubstituted products while 2- or 4-substituted radicals give mainly trans.[7]

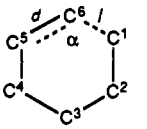
Both the stereoselectivity and the regioselectivity of 5-hexenyl ring closure can be ascribed to the stereoelectronic demands of the intimate transition structure arising from overlap of the SOMO with the π-system. Early qualitative attempts to rationalize the behavior of the 5-hexenyl radical were concerned with the unexpected regiochemistry of cyclization,[8] but later refinements suggested that the observed stereochemistry was consistent with a cyclohexane chairlike transition structure.[2,7,9]

The theoretical treatment of the 5-hexenyl system was first undertaken by Bischof,[10] who used the UHF method to calculate activation parameters for the various possible modes of cyclization of both the parent radical and substituted species. However, neither the regioselectivity nor the diastereoselectivity of cyclization was adequately rationalized: the calculated activation parameters differed substantially from the experimental data, with the enthalpy values being too high and there being negligible difference between those for the endo and exo cyclization modes. Later, Canadell and Igual[11] extended such calculations to several other systems with a similarly unsatisfactory outcome.

Table I. Calculated Dimensions of Transition Structures for Hex-5-enyl Radical Cyclization



exo



endo

	exo B.S.[a]	exo S.H.[b]	endo B.S.[a]	endo S.H.[b]
∠1234, deg	50.5	47.7	−62.7	−63.3
∠2345, deg	−56.7	−58.4	59.0	58.6
∠3456, deg	138.9	147.4	−74.0	−77.5
∠α, deg	104	108.3	98	96.4
d, Å	1.388	1.380	1.392	1.378
l, Å	2.200	2.278	2.200	2.270

[a] Calculated by Beckwith–Schiesser method (ref 9). [b] Calculated by the Spellmeyer–Houk method (ref 12).

Later approaches involved a combination of molecular orbital and molecular mechanics calculations. In the Beckwith–Schiesser method,[9] MNDO–UHF calculations were used to determine the dimensions of the "intimate" transition structure for the three carbon atoms involved in bond making and breaking. These dimensions were incorporated as fixed values into the overall transition structures for cyclization, which were then minimized by the MM2 method. The strain energy component of the activation energy was obtained by subtracting from the total strain energy the sum of (i) the calculated energy of repulsion between C_1 and C_5; (ii) the energy arising from stretching of the C_5–C_6 bond; and (iii) the strain energy of the uncyclized radical. This approach gave remarkably good qualitative agreement between theory and experiment. For more than 50 ring closures it correctly predicted the preferred mode of cyclization and the major diastereoisomer. In all those reactions that proceed by 1,5-ring closure, the preferred transition structure was found to be cyclohexane chairlike with the substituent occupying a

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(8) Beckwith, A. L. J. In *Essays on Free-Radical Chemistry, Special Publication No 24*; The Chemical Society: London, 1970; p 239–270.

(9) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(10) Bischof, P. *Helv. Chim. Acta* **1980**, *63*, 1434.

(11) Canadell, E.; Igual, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1331.

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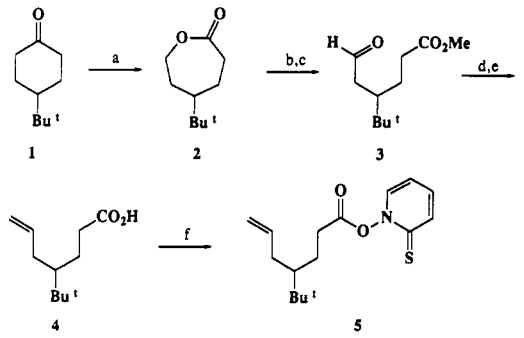
Scheme I[a]



1 2 3 4 5

[a] Reagents: (a) (b) MeOH/PTS; (c) pyridinium chlorochromate; (d) CH_2=PPh_3; (e) KOH/MeOH; (f) *N*-hydroxypyridine-2-thione, sodium salt.

pseudoequatorial position. Unfortunately, the *quantitative* agreement between theory and experiment was less satisfactory: except for 1-substituted hexenyl radicals, calculated diastereoselectivities were always larger than those observed experimentally.

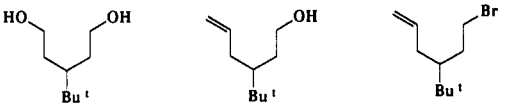
Subsequently, Spellmeyer and Houk[12] adopted a somewhat different approach in which ab initio methods were used, not only to calculate the dimensions of the transition structure for addition of radicals to double bonds, but also to derive pseudo force constants for molecular mechanics calculations. By this device the intimate transition structure is able to respond to the demands of the whole system undergoing cyclization. Although the Spellmeyer–Houk model must resemble reality more closely than the Beckwith–Schiesser model and provides the more accurate prediction of the diastereoselectivities of monosubstituted hexenyl radical cyclizations,[12] the two approaches give very similar dimensions for the chairlike transition structures for the two modes of cyclization of the hexenyl radical (Table I).

A major difference between the two methods was that Beckwith and Schiesser[9] considered only chairlike transition structures, while Spellmeyer and Houk[12] also took boatlike structures into account. For hexenyl radicals bearing small substituents this is of little consequence. However, for cyclization of the 3-*tert*-butylhexenyl radical (**9**) the two approaches lead to very different predictions. Since the axially substituted chairlike transition structure **14c** is much higher in energy than its equatorially substituted isomer **13c**, the cis/trans product ratio should be very large if **14c** lies on the pathway to *trans*-**10**. The energy of the boatlike form **15c** of the transition structure leading to the trans product is considerably less. Consequently, Spellmeyer and Houk concluded that formation of the trans product from the 3-*tert*-butylhexenyl radical would occur through the boatlike transition structure **15c**, and they predicted with "high confidence" that the cis/trans ratio would be 68:32.

In order to test this prediction and to ascertain the involvement of boatlike transition structures in hexenyl ring closures, we have now examined experimentally the behavior of 3-*tert*-butylhex-5-enyl radical (**9**) and have concluded that the formation of the trans product does indeed proceed through a boatlike transition structure **15c**.

Results and Discussion

The radical precursor **5** was prepared by the route illustrated in Scheme I. In the first step 3-*tert*-butylcyclohexanone (**1**) was subjected to Baeyer–Villiger oxidation to give the lactone **2**,[13] which was treated with methanol and acid, then oxidized with pyridinium chlorochromate to give the aldehydo ester **3**. A Wittig reaction of **3** followed by hydrolysis gave the acid **4**, which was converted into the Barton ester **5** in the usual way.[14] The bromide **8** was required in order to verify that the outcome of the radical reaction was independent of the nature of the precursor. In an exploratory approach the diol **6** was



6 7 8

converted in six standard steps into the alcohol **7**, treatment of which with triphenylphosphine/carbon tetrabromide gave the bromo compound **8**. However, the yield in the last step was very poor, and the use of different conditions or of alternative methods was no more successful. Because of this no attempt was made to optimize the earlier steps and the intermediate compounds, although obtained substantially pure, were not fully characterized.

An authentic sample of a mixture of the cis and trans isomers of the expected cyclization product **12** was prepared by methylenation of 3-*tert*-butylcyclopentanone followed by catalytic hydrogenation. Although the two diastereoisomers could not be separated, they could be distinguished by NMR spectroscopy, and in the case of the ^{13}C spectra all of the resonances could be assigned. The assignment of stereochemistry rests (i) on the expectation that catalytic hydrogenation will preferentially afford the cis isomer; (ii) on the assumption that the resonance for C-1 in the ^{13}C NMR spectrum of the cis isomer (δ 51.51), like that for C-1 in *cis*-1,3-dimethylcyclopentane and similar compounds,[15] will occur at lower field strength than that for C-1 in the trans isomer (δ 49.8); and (iii) on the fact that the isomer assigned as cis is the same as the major product from radical cyclization. There appear to be no reported exceptions to the rule that 3-monosubstituted hex-5-enyl radicals give mainly cis-disubstituted cyclized product.[2,7]

Free-radical reactions of the ester **5** were conducted by heating it with an excess of tributylstannane in known concentration in benzene at 80 °C under UV irradiation. The relative yields of uncyclized and cyclized products **11** and **12**, respectively, were determined by gas chromatography on a capillary column. Unfortunately, it was impossible to find conditions under which the cis and trans isomers of the cyclized product could be satisfactorily resolved, but the relative yields of the two diastereoisomers were eventually determined by careful NMR spectroscopy of the mixture to be cis:trans $\approx$ 4.5:1. Approximately the same ratio of diastereomers was formed when the reaction was conducted with the bromide **8**, thus verifying that the outcome of the reaction does not depend on the nature of the precursor and does indeed involve the intermediacy of the free radical **9**.

The nature and yields of the products obtained are consistent with the mechanism of Scheme II. Thus, when 1.62 M Bu_3SnH was employed, the open-chain product **11**

(12) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
(13) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029.
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Scheme II

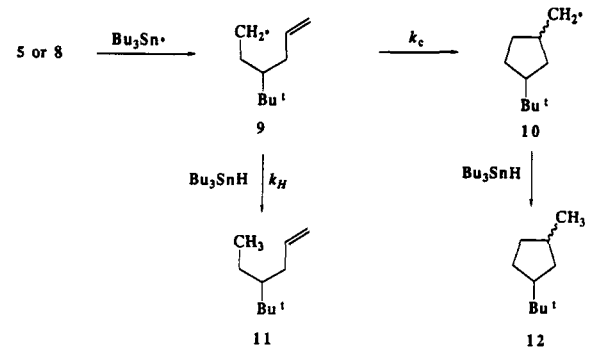


Table II. Calculated Strain Energies (E_S)[a] and Heats of Formation (H_f)[a] of Species Involved in the Cyclization of 3-Substituted Hex-5-enyl Radicals

entry	structure	conformer type	E_S, kcal/mol	H_f, kcal/mol
1	**16a**	open chain	2.9	34.9
2	**16b**	open chain	4.3	28.5
3	**16c**	open chain	13.2	14.5
4	**17a**	open chair	3.9	35.9
5	**17b**	open chair	4.5	28.7
6	**17c**	open chair	11.5	12.8
7	**18c**	open boat	12.2	13.5
8	**13a**	equatorial chair TS	10.4	42.4
9	**13b**	equatorial chair TS	10.6	34.8
10	**13c**	equatorial chair TS	16.4	17.6
11	**14c**	axial chair TS	20.8	22.0
12	**15c**	equatorial boat TS	17.2	18.3
13	**19a**	product	12.0	-21.4
14	**19b**	product	12.3	-21.3
15	**19c**	product	17.3	-22.1

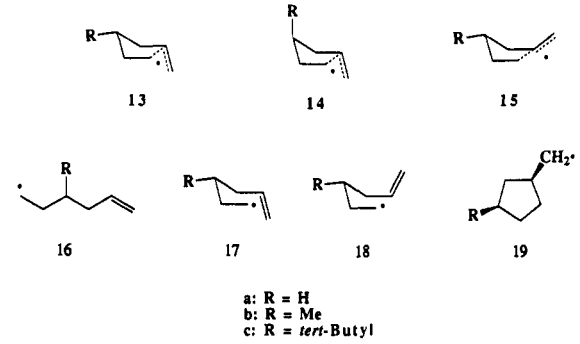
[a] Calculated by the Beckwith–Schiesser method (ref 9).

and a mixture of diastereoisomers of the cyclized product **12** were formed in the ratio of 1:21. As expected, repetition of the reaction with more concentrated Bu_3SnH (3.24 M) gave a smaller ratio (1:9.3). Steady-state kinetic analysis of the reactions of Scheme II, when tributylstannane is in large excess, gives $k_c/k_H = [Bu_3SnH]_m[12]_f/[11]_f$ where $[Bu_3SnH]_m$ is the mean stannane concentration and $[12]_f/[11]_f$ is the ratio of the final concentrations of **12** and **11**. Substitution into this expression of the experimental data gives $k_c/k_H \approx 30$. If k_H for **9** is about the same as that ($k_H = 6.5 \times 10^6$ M^{-1} s^{-1})[5] for the reaction of the butyl radical with Bu_3SnH at 80 °C, then $k_c \approx 2 \times 10^8$ s^{-1} at this temperature. This is the highest rate constant yet recorded for cyclization of a monosubstituted 5-hexenyl radical. Its value approaches that for cyclization of the *o*-butenylphenyl radical.[16]

We have not, as yet, determined experimentally the Arrhenius parameters for the ring closure of **9**. However, log *A* for the corresponding reaction of most simple substituted hexenyl radicals and for the parent radical lies in the range log *A* (s^{-1}) = 10.1 – 10.5.[5] It seems reasonable, therefore, to suggest that the ring closure of **9** has log *A* (s^{-1}) = 10.3 + 0.3 and E_{act} = 3.2 + 0.5 kcal/mol.

According to the proposed mechanism (Scheme II), the cis/trans ratio for the cyclized product **12** should not vary with Bu_3SnH concentration. This was found to be so; each of the experiments gave cis/trans ≈ 4.5. Since the relative yields of the two diastereoisomers reflect directly the rates of formation of the cyclized radicals, it follows that k_c(trans) ≈ 4×10^7 s^{-1} and k_c(cis) ≈ 1.6×10^8 s^{-1} at 80 °C. At this temperature the observed ratio of rate constants k_c(cis)/k_c(trans) corresponds to a difference in free energies of activation, $\Delta\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{trans} - \Delta G^{\ddagger}_{cis}$) of 1.0 kcal/mol. Since the temperature dependence of the cis/trans ratio was not determined, values of $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ cannot be derived from $\Delta\Delta G^{\ddagger}$. However, on the basis of results reported for the cyclization of other substituted hexenyl radicals[5] it seems likely that the contribution of $\Delta\Delta S^{\ddagger}$ will be small and that $\Delta\Delta G^{\ddagger} \approx \Delta\Delta H^{\ddagger}$.

We now turn to the question of whether the kinetic features of this cyclization can be adequately modeled by our earlier theoretical approach involving a combination of molecular orbital and molecular mechanics calculations. In Table II are given the strain energies E_s as calculated by the Beckwith–Schiesser method[9] for the various transition structures **13c**, **14c**, and **15c** for ring closure of the



a: R = H
b: R = Me
c: R = *tert*-Butyl

radical **9** and for some conformers **16c**, **17c** and **18c** of the ground state of the radical **9**. The most significant feature of these data is the large difference in strain energy (ΔE_s = 4.4 kcal/mol) between the chairlike transition structure **13c**, in which the substituent occupies a pseudoequatorial position, and its isomer **14c**, in which the substituent is pseudoaxial. Calculations by the Spellmeyer Houk method give a very similar result (ΔE_s = 4.5 kcal/mol).[12] If the two isomers of **10** were to be formed through these two transition structures, the predicted cis/trans isomer ratio of about 500 would be much larger than that observed experimentally, i.e., 4.5. It appears, therefore, that the transition structure for formation of the *cis*-**10** must be the boatlike form, **15c**.

Although the Beckwith–Schiesser and Spellmeyer–Houk methods each correctly predict the preferential formation of *cis*-**10** from **9**, neither accounts quantitatively for the degree of diastereoselectivity. The observed cis/trans ratio of 4.5 is higher than either of the values based on the difference between the calculated strain energies of the chairlike transition structure **13c** and the boatlike form **15c**, namely cis:trans = 3.1 (ΔE_s = 0.8 kcal/mol; Beckwith–Schiesser) or 2.0 (ΔE_s = 0.5 kcal/mol; Spellmeyer–Houk).[12] Nevertheless, it is clear that cyclization of the 3-*tert*-butylhexenyl radical (**9**) does indeed proceed either through the chairlike transition structure **13c** to give the radical *cis*-**10** or through the boatlike transition structure **15c** to give *trans*-**10**. The axially substituted chairlike structure **14c** is, however, too high in energy to provide a significant pathway to *trans*-**10**.

The same is probably true for the cyclization of hexenyl radicals with an alkyl or similar moderately bulky group in the 3-position. However, for small substituents the route to the trans product may involve an axially substituted chairlike transition structure. Since the size of the substituent has little effect on the energy of boatlike transition structures (e.g., **15a–c**), we conclude that the cis/trans ratio of about 4.5 observed for cyclization of **9** is probably close to the maximum obtainable at 80 °C for radicals of this general type. Highly diastereoselective radical cyclization of monosubstituted hexenyl radicals cannot, therefore, be

(16) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 464.

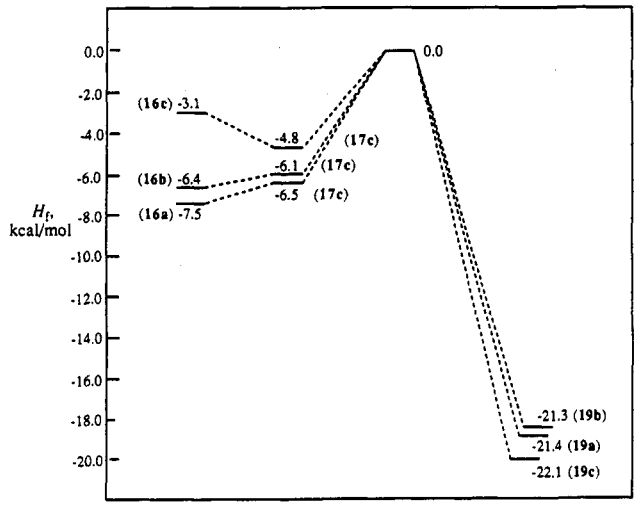


Figure 1. Calculated relative heats of formation (H_f) of species involved in the reactions **16a** → **19a**, **16b** → **19b**, and **16c** → **19c**.

achieved by increasing the bulk of the substituent. However, if, as we believe, the difference in strain energies between the diastereoisomeric transition structures is mainly reflected in $\Delta\Delta H^{\ddagger}$, relatively high diastereoselectivity (ca. 10:1) should be attainable by conducting cyclization reactions at relatively low temperatures (−40 °C) with UV irradiation.

An interesting feature of the data presented in Table II is that the open-chain form **16c** of the 3-*tert*-butylhexenyl radical is the least stable of the three low-energy conformers **16c**, **17c**, and **18c**. The most stable is **17c**, which closely resembles the chairlike transition structure **13c**, while **18c**, which resembles the boatlike transition structure **15c**, is intermediate in energy. Interestingly, the calculated difference in energy between the ground-state conformers **17c** and **18c** is about the same as that between the corresponding transition structures **13c** and **15c**.

In agreement with previous estimates[17] of the barrier to rotation adjacent to a double bond of 2–3 kcal/mol, molecular mechanics calculations suggest that the barrier to the interconversion of **17c** and **18c** is about 3 kcal/mol. Since this is similar to the estimated energy of activation for the ring closure (see above) the question arises of whether the outcome of the reaction reflects the conformational distribution of the radical precursor. Molecular mechanics calculations on the bromide **8** appear to preclude this possibility as the calculated difference of 0.4 kcal/mol between the boat and chair conformers of **8** is less than that (0.8 kcal/mol) between **13c** and **15c**. Also, it is pertinent that the bromide **8** and the Barton precursor **5** give precisely the same cis/trans ratio. We prefer the view, therefore, that **9** exists mainly as the two conformers **17c** and **18c** in rapid equilibrium. Each is converted into the appropriate diastereoisomer of the cyclized radical at essentially the same rate, i.e., the cis/trans ratio reflects the relative equilibrium concentrations of **17c** and **18c**.

Finally, it is instructive to compare the rates of cyclization of hexenyl radical (**16a**), 3-methylhexenyl radical (**16b**), and 3-*tert*-butylhexenyl radical (**16c**) in the light of their calculated ground-state and transition-state strain energies. The data are presented in Table II and in Figure 1 in which the heat of formation of each of the transition structures has been arbitrarily assigned as zero. The first noteworthy feature of these data is that the open-chain conformation **16a** of the parent hex-5-enyl radical is considerably less strained than the chairlike form **17a**. In the case of the 3-methylhex-5-enyl radical the energy difference is small but favors the open-chain conformation **16b** over the chairlike form **17b**, while, as noted above, the *tert*-butyl-substituted radical preferentially assumes the chairlike conformation **17c**.

As expected from the Allinger–Zalkow[18] treatment of the Thorpe–Ingold effect the relative strain energy of the ground state increases with the increasing bulk of the substituent, but this is not reflected to the same degree in transition-state energies. Thus, the strain energies of the three chairlike transition structures are in the order **13a** < **13b** < **13c**, but the differences between them are less than the differences in energy between the corresponding low-energy conformers, **16a** < **16b** < **17c**, of the ground states. This phenomenon is clearly evident in Figure 1, which shows the reaction profiles based on calculated values of the heats of formation of the various species involved. Figure 1 also shows the difference in calculated strain energy between the lowest energy conformers of the ground states and the corresponding transition structures. It is noteworthy that they are qualitatively similar to the experimentally determined activation energies. Thus, for **16a** → **13a**, $\Delta E_s \approx 7.5$ kcal/mol and $E_{act} = 6.9$ kcal/mol,[5] for **16b** → **13b**, $\Delta E_s = 6.3$ kcal/mol and $E_{act} = 6.6$ kcal/mol,[5] while for **17c** → **13c**, $\Delta E_s = 4.9$ kcal/mol and $E_{act} = 3.2$ kcal/mol. In view of the many approximations involved in the calculations, including the complete neglect of electronic interactions, this degree of concordance is impressive and illustrates nicely the value of MNDO-MM2 methods for the estimation of strain energies.

Conclusion

Molecular calculations by the Beckwith–Schiesser[9] and Spellmeyer–Houk[12] methods predict the preferential cis cyclization of the 3-*tert*-butylhexenyl radical (**9**), but both underestimate the degree of diastereoselectivity with the former being somewhat better than the latter. However, comparison of experimental results with the calculations firmly indicates that the formation of the trans product radical *trans*-**10** proceeds through a cyclohexane boatlike transition structure **15c** and precludes routes proceeding via an axially substituted chairlike transition structure **14c**. The relatively high rate of ring closure for **9** is consistent with the calculated ground-state and transition-structure energies.

Experimental Section

General. ^{1}H NMR spectra were measured at 500 MHz on a Varian XL-500 spectrometer or at 200 MHz on a JEOL FX-200 or a Varian XL-200 spectrometer. ^{13}C NMR spectra were measured on a Varian XL-500 or a JEOL FX-200 spectrometer. Unless otherwise mentioned, spectra were run with $CDCl_3$ as solvent, and chemical shifts were determined relative to tetramethylsilane (δ 0.0). Gas chromatography (GC) was performed on a Varian 6000 chromatograph equipped with a flame ionization detector and coupled to a Hewlett-Packard 3390A recorder/integrator. A vitreous silica capillary column (SGE 25QC2/BP-1.0) was used with helium as carrier gas. Flash chromatography[19] was conducted on Merck silica gel 60 (230–400 mesh).

Unless otherwise noted all reactions were run under a positive pressure of dry N_2. THF was freshly distilled from sodium/benzophenone ketyl prior to use. Benzene and CH_2Cl_2 were AR grade and were stored over 4-μm molecular sieve. Tributylstannane (Aldrich) was stored under nitrogen. Organic solutions

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(18) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.

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were dried over anhydrous $MgSO_4$ and, where necessary, concentrated under reduced pressure with a Buchi rotary evaporator.

Methyl 4-*tert*-Butyl-6-hydroxyhexanoate. Lactone 2[13] (5 g, 29.4 mmol) was refluxed in methanol (150 mL) with *p*-toluenesulfonic acid (50 mg) for 3 h. After concentration under reduced pressure to a volume of ca. 50 mL, water (100 mL) was added, and the mixture was extracted with ether. Evaporation of the combined extracts gave the required hydroxy ester (5.5 g, 92%) as a pure (^{1}H NMR) liquid: ^{1}H NMR δ 0.88 (s, 9 H, *tert*-butyl), 1.1–2.3 (m, 7 H), 3.65 (t, J = 8.5 Hz, 2 H, CH_2OH), 3.68 (s, 3 H, OCH_3); ^{13}C NMR δ 26.2, 27.5, 33.5, 33.6, 33.7, 44.1, 50.9, 62.3, 174.7; MS *m/e* 203 (M^+ + 1, 0.03), 169 (0.8), 155 (1.1), 128 (14), 115 (14), 114 (16), 57 (100). The analytical sample was further purified by flash chromatography. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.43; H, 10.65.

Methyl 4-*tert*-Butyl-6-oxohexanoate (3). Pyridinium chlorochromate (5.6 g, 26 mmol) was added to a solution of the preceding hydroxy ester (4.04 g, 20 mmol) in CH_2Cl_2 (200 mL), and the mixture was stirred for 2.5 h, by which time all of the starting material had been consumed (TLC; hexane/ether (3:1)). Ether (300 mL) and Florisil (20 g) were added, the suspension was filtered, and the filtrate was evaporated to give crude **3** (4.0 g, 95%), which was used without further purification. A small sample obtained by flash chromatography (hexane/ether (3:1)) was a colorless oil: ^{1}H NMR δ 0.88 (s, 9 H, *tert*-butyl), 1.2–2.6 (m, 7 H), 3.65 (s, 3 H, OCH_3), 9.62 (br s, 1 H, CHO); ^{13}C NMR, δ 26.2, 27.3, 33.0, 33.4, 41.7, 45.6, 51.3, 174.8, 202.2; MS *m/e* 200 (M^+, 8), 199 (71), 185 (39), 171 (21), 167 (20), 114 (25), 83 (30), 57 (100).

Methyl 4-*tert*-Butylhept-6-enoate. Methyltriphenylphosphonium bromide (7.14 g, 22 mmol) was suspended in ether (100 mL), and butyllithium (20.1 mmol in hexane) was added at 0 °C to give a yellow solution. A solution of **3** (4.0 g, 20 mmol) in ether (20 mL) was added at 0 °C during 15 min, and the resultant white suspension was stirred for 2 h at 20 °C and then under reflux for 1 h. Water (20 mL) was then added, and the crude product was obtained by extraction with ether. Flash chromatography (hexane/ether (3:1)) gave pure methyl 4-*tert*-butylhept-6-enoate (1.6 g, 41%); ^{1}H NMR δ 0.88 (s, 9 H, *tert*-butyl), 1.85 (m, 3 H), 2.33 (m, 4 H), 3.66 (s, 3 H, OCH_3), 4.97 (d, J = 8 Hz, 1 H, C*H*H=), 5.02 (d, J = 16 Hz, 1 H, CH*H*=), 5.82 (m, 1 H, CCH=); ^{13}C NMR δ 25.87, 27.80, 34.11, 35.33, 47.77, 51.36, 115.10, 139.16, 175.49; MS *m/e* 199 (M^+ - 1, 0.5), 171 (25), 115 (41), 114 (20), 97 (21), 57 (100). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.53; H, 11.19.

4-*tert*-Butylhept-6-enoic Acid (4). The preceding ester (1.4 g, 7 mmol) was refluxed in methanolic KOH (10 mL, 2 M) for 1 h. The solution was then diluted with water (50 mL), acidified with dilute H_2SO_4, and extracted with ether (3 × 30 mL) to give, after evaporation of the ether solution, the required acid (1.2 g, 92%), which was used for the next step without further purification. Flash chromatography (hexane/ether (1:1)) of a small sample gave a clear liquid: ^{1}H NMR δ 0.89 (s, 9 H, *tert*-butyl), 1.88 (m, 3 H), 2.37 (m, 4 H, CH_2C=C and CH_2C=O), 5.01 (m, 2 H, CH_2=), 5.84 (m, 1 H, CH=); ^{13}C NMR δ 25.49, 27.71, 33.87, 34.02, 35.24, 47.57, 115.22, 138.90, 188.51; MS *m/e* 185 (M^+ + 1, 0.02), 151 (2), 128 (14), 125 (11), 97 (14), 83 (51), 69 (23), 57 (100). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.63; H, 11.04.

***N*-[(4-*tert*-Butylhept-6-enoyl)oxy]pyridine-2-thione (5).** One drop of DMF was added to the preceding acid (260 mg, 1.4 mmol) and oxalyl chloride (1.0 mL, 11 mmol) in benzene (8 mL), and the solution was stirred at 20 °C for 2 h and then evaporated. The residue was redissolved in benzene, and the solution was evaporated again. The residue was then dissolved in benzene (5 mL), 4-(dimethylamino)pyridine (14 mg, 0.1 mmol) and the sodium salt of *N*-hydroxypyridine-2-thione (240 mg, 1.6 mmol) were added, and the mixture was stirred for 4 h at 20 °C. Evaporation of the mixture and flash chromatography of the residue with ether/hexane (3:1) afforded pure **5** (320 mg, 77%) as a yellow oil: ^{1}H NMR δ 0.91 (s, 9 H, *tert*-butyl), 1.5–2.0 (m, 4 H), 2.28 (m, 1 H), 2.69 (m, 2 H, CH_2CO), 5.01 (d, J = 8 Hz, 1 H, C*H*H=), 5.09 (d, J = 14 Hz, 1 H, CH*H*=), 5.87 (m, 1 H, HC=), 6.62 (m, 1 H), 7.24 (m, 1 H), 7.65 (m, 2 H); ^{13}C NMR δ 25.20, 27.71, 31.39, 33.96, 35.16, 47.51, 112.30, 115.48, 133.27, 137.29, 137.59, 138.81, 169.03, 175.89. Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.73; H, 8.22; N, 4.81.

6-Bromo-4-*tert*-butylhex-1-ene (8). An exploratory route to 8 involved the formation of the alcohol **7** by conversion of **6**[20] into its *p*-nitrobenzoate, which was oxidized with pyridinium chlorochromate then subjected to a Wittig reaction followed by deprotection. Full experimental details are given in the supplementary material. Although the intermediates were judged to be substantially pure by TLC and GC, where appropriate, they were not fully characterized. 3-*tert*-butylhex-5-en-1-ol (**7**) was obtained as a clear liquid: ^{1}H NMR δ 0.9 (s, 9 H, *tert*-butyl), 1.1–1.8 (m, 3 H), 2.2 (m, 2 H, CH_2C=), 3.6 (m, 2 H, CH_2O), 5.0 (m, 2 H, CH_2=), 5.7 (m, 1 H, CH=).

Tetrabromomethane (270 mg, 0.8 mmol) was added to **7** (100 mg, 0.64 mmol) and triphenylphosphine (210 mg, 0.8 mmol in dichloromethane (1.0 mL)), and the mixture was stirred for 17 h at 25 °C. After filtration, the solution was evaporated and the residue subjected to flash chromatography (hexane/ether (4:1)) to give pure (by GC) 6-bromo-4-*tert*-butylhex-1-ene (**8**; 10.2 mg, 8%): ^{1}H NMR δ 0.9 (s, 9 H, *tert*-butyl), 1.1–2.0 (m, 3 H), 2.2 (m, 2 H, CH_2C=), 3.4 (m, 2 H, CH_2Br), 5.0 (m, 2 H, CH_2=), 5.8 (m, 2 H, CH=).

1-*tert*-Butyl-3-methylcyclopentane (12). 3-*tert*-Butyladipic acid[21] was heated with barium hydroxide to produce 3-*tert*-butylcyclopentanone[22] (85%), which was purified by steam distillation and chromatography: ^{1}H NMR δ 0.92 (s, 9 H, *tert*-butyl), 1.5–1.7 (m, 1 H), 1.85–2.15 (m, 3 H), 2.15–2.4 (m, 3 H); ^{13}C NMR δ 24.22, 27.13, 31.61, 39.32, 40.43, 48.12, 219.8. A sample (1.39 g) of the ketone was treated with zinc powder (5.2 g), zirconocene dichloride (3.5 g), and CH_2Br_2 (3.8 g) in THF (25 mL) for 4 h at rt[23] to give 3-methylene-*tert*-butylcyclopentane (0.79 g, 57%)[24] after purification by flash chromatography: ^{1}H NMR δ 0.97 (s, 9 H), 1.25–1.4 (m, 1 H), 1.65–1.8 (m, 2 H), 1.95–2.05 (m, 1 H), 2.15–2.45 (m, 3 H), 4.80 (unresolved m, 2 H); ^{13}C NMR δ 27.45, 27.63, 31.69, 33.00, 34.56, 52.47, 104.59, 152.23.

Hydrogenation of the preceding methylene compound (0.50 g) was conducted over Adams catalyst (45 mg) in methanol/acetic acid (10:1; 30 mL). After filtration through Celite the reaction mixture was poured into water and the product isolated by extraction with pentane. GC analysis of the extract showed it to contain two diastereomers of **12** in the ratio 3:2 in approximately quantitative yield. Because of its very high volatility purification of **12** was difficult. Eventually, a pure sample of the mixture (3:2) of the cis and trans isomers was obtained by preparative GC: ^{1}H NMR δ 0.842 (s, *trans-tert*-butyl), 0.849 (s, *cis-tert*-butyl), 0.964 (d, J = 6.7 Hz, *trans*-Me),) 0.982 (d, J = 6.5 Hz, *cis*-Me), 1.02–1.93 (complex multiplet); ^{13}C NMR (cis) δ 20.61 (CH_3) 26.44 (C-5), 27.56 (3 × CH_3), 32.07 (quat C) 34.41 (C-4), 35.00 (C-3), 37.29 (C-2), 51.51 (C-1); ^{13}C NMR (trans) δ 21.17 (CH_3), 27.48 (3 × CH_3), 28.23 (C-5), 32.26 (quat C), 34.37 (C-3), 35.00 (C-2), 35.70 (C-4), 49.80 (C-1); MS *m/e* 140 (M^+, <1%), 125 (7), 83 (28), 82 (40), 69 (32), 67 (28), 57 (92), 56 (100), 55 (44), 41 (67). Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.73; H, 14.53.

Reaction of 5 with Tributylstannane. A solution of **5** (170 mg, 0.58 mmol) and tributylstannane (250 mL, 0.74 mmol) in hexadeuteriobenzene (4.0 mL) was refluxed for 3 h while being irradiated with UV light. Distillation of the mixture (bath 120 °C) gave the cis (major) and trans (minor) isomers of **12**, which were identified by comparison of the ^{1}H and ^{13}C NMR spectra with those of the authentic material. The relative proportions of the two isomers were determined by careful integration of the *tert*-butyl and methyl signals in the ^{1}H NMR spectrum of the mixture recorded at 500 MHz. There was some variation in the results obtained from different runs and from the integration of different spectra but the ratio always lay between 4.0 and 5.0. The mean result was cis/trans = 4.5 ± 0.5. When the reaction was carried out in neat tributylstannane, 4-*tert*-butylhex-1-ene (**11**) was also detected by GC/MS, *m/e* 140 (M^+, <1%) 125 (<1) 99 (16), 83 (6), 69 (13), 57 (100), 56 (19), 41 (41). In further

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experiments samples of 5 were added to a 10-fold excess of tributylstannane in benzene (1.62 or 3.24 M), and the solutions were degassed, heated at 80 °C for 3 h, and then analyzed for 11 and 12 by GC. The results are given in the text.

Reaction of 8 with Tributylstannane. The bromide 8 (10.2 mg, 0.046 mmol) was dissolved in benzene (2.0 mL). Tributylstannane (6.2 μL, 0.023 mmol) and a trace of AIBN were added to an aliquot (0.50 mL) of this solution, which was then heated in a sealed tube at 80 °C for 17 h. After distillation (bath 60 °C (50 mm)), the mixture was analyzed by GC-MS analysis (40 °C isothermal). Varying amounts of tributylstannane were added to other aliquots, which were then heated and analyzed in the same way for 11 and 12. Within experimental error the results obtained were the same as those from reactions of 5.

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Registry No. 2, 34680-83-6; 3, 135561-11-4; 4, 135561-12-5; 5, 135561-13-6; 6, 50635-65-9; 7, 135561-14-7; 8, 135561-15-8; 9, 135561-16-9; 11, 135561-17-0; *cis*-12, 13398-31-7; *trans*-12, 14671-83-1; 16a, 16183-00-9; 16b, 75375-38-1; 19a, 23907-66-6; *cis*-19b, 100649-36-3; *cis*-19c, 135561-18-1; $HO(CH_2)_2CH(t\text{-}Bu)(CH_2)_2CO_2Me$, 135561-19-2; $MeP(Ph)_3^+ \cdot Br^-$, 1779-49-3; $H_2C{=}CHCH_2CH(t\text{-}Bu)(CH_2)_2CO_2Me$, 135561-20-5; $HO_2C(CH_2)_2CH(t\text{-}Bu)CH_2CO_2H$, 10347-88-3; Bu_3Sn, 688-73-3; $p\text{-}O_2NC_6H_4COCl$, 122-04-3; $o\text{-}O_2NC_6H_4C(O)O(CH_2)_2CH(t\text{-}Bu)(CH_2)_2OH$, 135561-21-6; $o\text{-}O_2NC_6H_4C(O)O(CH_2)_2CH(t\text{-}Bu)CH_2CHO$, 135561-22-7; $H_2C{=}CHCH_2CH(t\text{-}Bu)CH_2C(O)OC_6H_4NO_2\text{-}p$, 135561-23-8; *N*-hydroxypyridine-2-thione, sodium salt, 15922-78-8; 3-*tert*-butylcyclopentanone, 5581-94-2; 1-*tert*-butyl-3-methylenecyclopentane, 69217-81-8.

Supplementary Material Available: Experimental procedures for the four-step conversion of 6 to 7; ^1H NMR spectra of 7, 8, and intermediates between 6 and 7; and the 0.60–0.95 ppm region of the 500-MHz ^1H NMR spectrum of a 3:2 mixture of *cis*- and *trans*-12 (9 pages). Ordering information is given on any current masthead page.

Heck Reaction on Anthraquinone Derivatives: Ligand, Solvent, and Salt Effects

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The palladium-catalyzed Heck reaction of trifluoromethanesulfonates of anthraquinoid systems is described. The outcome of the reaction between methyl acrylate 4 and 1-(9,10-anthraquinoyl)trifluoromethanesulfonate 7 (reduction versus arylation) is strongly correlated to the choice of ligand, solvent, and added salt. The results are explained in terms of different coordination-insertion pathways as a function of the reaction conditions. Best conditions have been transferred to the synthesis of novel anthracyclinone, 4-demethoxy-4-(2'-methoxycarbonyl)ethenyl-13-dioxolanyldaunomycinone 5.

Introduction

During our studies of structure–activity relationships of antitumor anthracyclines,[1] we needed to prepare substantial quantities of novel 4-substituted anthracyclinones for glycosidation and biological evaluation.[2]

In this context, we have recently developed a new process for the preparation of 4-demethoxydaunomycinone 3, based on the palladium-catalyzed reduction of the key intermediate ketal triflate 2,[3] readily available from the natural daunomycinone 1 (Scheme I).[4] Accordingly, we decided to extend palladium catalysis to carbon–carbon bond formation by exploiting the Heck reaction (arylation of olefin by palladium catalyst).[5]

Unfortunately, the reported procedure for aryl triflates ($Pd(PPh_3)_2Cl_2$, methyl acrylate 4, Et_3N, in DMF at 90 °C) failed when 2 was used as substrate.[6] The desired acrylate 5 was not formed, and the only product present in the reaction mixture after 24 h was 6 (Scheme II).

This result prompted us to study in some detail the mechanism of the Heck reaction on anthraquinoid systems, in order to understand the main factors affecting the reaction course.

Results and Discussion

In our previous work on the palladium-catalyzed reduction of aryl sulfonates in the presence of triethylammonium formate,[3,7] we reported that catalytic systems generated in situ from $Pd(OAc)_2$ and bidentate phosphine ligands like 1,3-bis(diphenylphosphino)propane (DPPP) or 1,1'-bis(diphenylphosphino)ferrocene (DPPF) were much more effective than the PPh_3-based one.

These results are in agreement with a recent paper by Dolle and co-workers on palladium-catalyzed alkoxycarbonylation of aryl triflates, where the use of DPPP

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