Intramolecular 4 + 3 Cycloadditions. Theoretical and Experimental Evaluation of Endo/Exo Preferences of a Cyclopentenyl Cation

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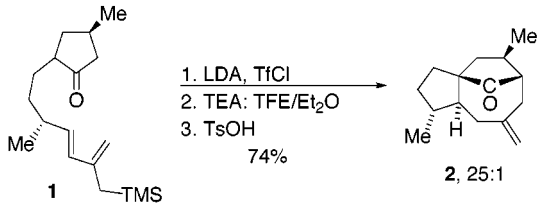
The Harmata group recently reported a synthesis of dactylol, a key step of which involved a highly stereoselective intramolecular 4 + 3 cycloaddition of a cyclopentenyl cation to a diene (Scheme 1).[1] On the basis of previous studies in this area,[2] the high stereoselectivity observed was doubtless a consequence of the presence of the stereogenic centers in the precursor and their influence on facial selectivity and endo/exo preferences.

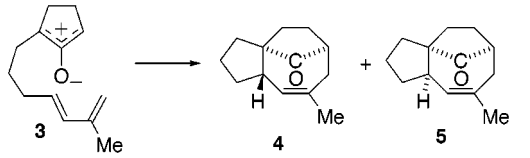
The methodology developed in the context of the synthesis of dactylol promises to be applicable to other 5,8 ring systems.[3] To acquire a good understanding of the inherent preferences for endo/exo selectivity in cycloadditions of this type, we undertook both an experimental and theoretical examination of the unsubstituted intermediate **3** and its cycloaddition to **4** and **5** (Scheme 2). We placed a methyl substituent on the diene to use a system that resembled the precursor used in the dactylol synthesis. We report our findings herein.

Electronic energies for the model system were obtained at the MP2/6-31G* level for structures fully optimized at the HF/6-31G* level; the latter level was also used to compute unscaled thermal contributions to 298 K free energies.[4,5] This theoretical model has shown good agreement both with higher levels of theory and with available experimental information in prior calculational work on cationic 4 + 3 cycloadditions.[6,7] The same prior studies indicated density functional methods to be inadequate for the characterization of the [4 + 3] transition states. Therefore, on the basis of the prior theoretical studies and comparison to experiment, and given that demonstrating convergence of the Schroedinger equation in

Scheme 1



Scheme 2



systems of this size is not an option, we deem the chosen MP2 level to represent the best combination of accuracy and practicality presently available.

Products resulting from exo and endo cycloadditions were found, and TS structures for both modes of cycloaddition were also located. Two different TS structures for each cycloaddition mode were located having different torsions within the forming five-membered ring. As these torsional isomers were reasonably close in energy, all TS energies reported hereafter refer to a 298 K Boltzmann average over the two relevant structures ($G = -RT \ln \sum_i e^{-G_i/RT}$). Because the reactant is floppy and can sample a very large number of conformations, we have not addressed it computationally, and all free energies are reported relative to the most stable product (i.e., the TS energies correspond to free energies of activation for *retro*cyclization). Structures and relative free energies are provided in Figure 1.

Solvation free energies (298 K) in 1,1,1-trifluoroethanol (TFE) were estimated using the corresponding SM5.42R/HF/6-31G* continuum model.[8−10] Relative free energies in solution, computed as the sum of the gas-phase and solvation free energies, are also reported in Figure 1.

Table 1 summarizes the differential activation free energies, the differential product free energies, and the corresponding product ratios that would be expected were the cycloaddition to be under kinetic vs thermodynamic control, respectively. Under conditions of thermodynamic control, the product mixture is predicted to heavily favor endo product and to be highly insensitive to solvation effects. Under conditions of kinetic control, on the other hand, the product mixture is predicted to very slightly favor the endo product in a nonpolar environment and the exo product in a polar environment. The transition-state structures are all consistent with both modes of cycloaddition proceeding in a concerted fashion.

The high predicted barriers to retrocyclization, together with the excellent agreement between theory and experiment for both the absolute product ratios in solution (vide

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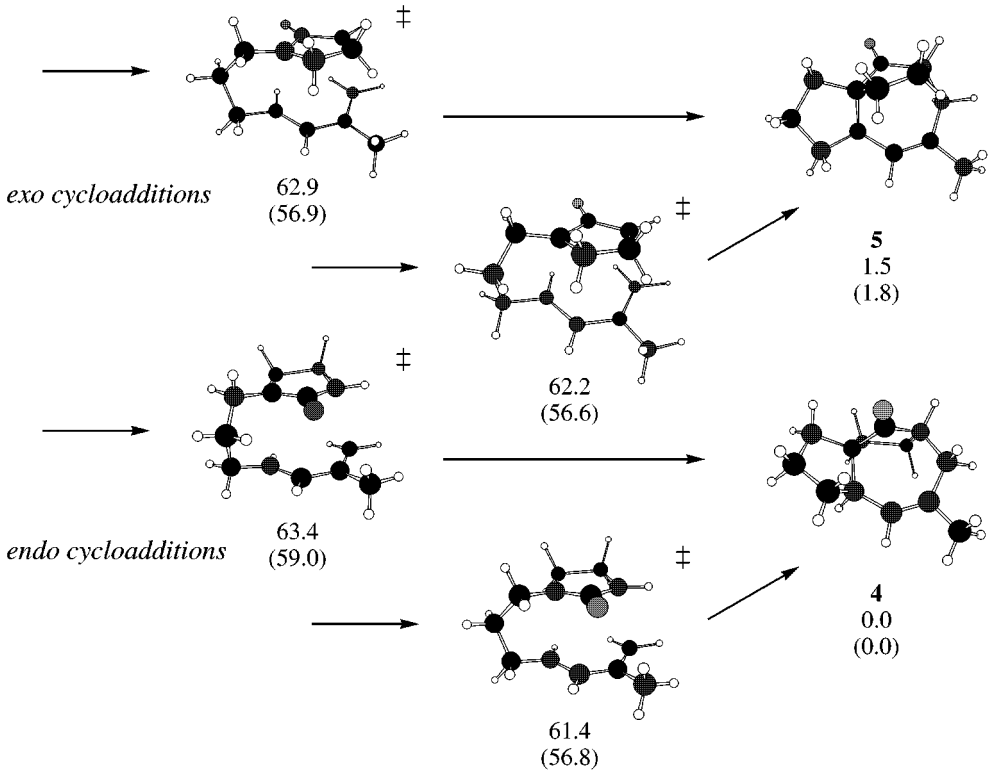


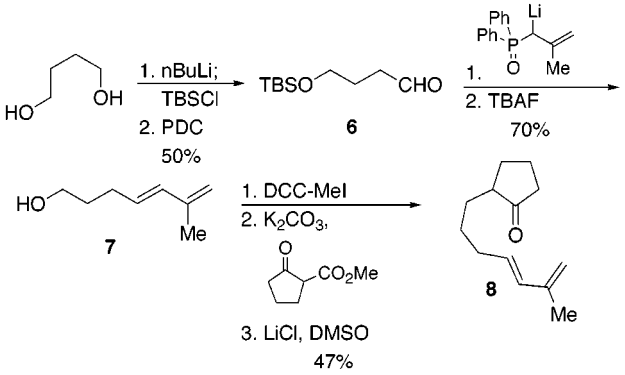
Figure 1. Relative free energies (kcal mol^{-1}) in the gas phase and TFE solution (in parentheses) for exo and endo TS structures and products. Optimized geometries from the HF/6-31G* level are shown.

Table 1. Differential Activation and Product Free Energies (kcal mol^{-1}) for Exo and Endo Cycloadducts and Product Mixtures Predicted Therefrom[a]

	kinetic control		thermodynamic control	
medium	$\Delta\Delta G^{\ddagger}_{298}$	product ratio **5**:**4**	$\Delta\Delta G_{298}$	product ratio **5**:**4**
gas phase ($\epsilon = 1$)	0.8	23:77	1.5	8:92
TFE ($\epsilon = 26.7$)	−0.5	69:31	1.8	5:95

[a] Free energies reported as (exo-endo) and product ratios as exo/endo.

Scheme 3



infra), and the direction of sensitivity to polar solvent effects, suggest that the reaction proceeds under kinetic control.

The synthesis of the substrate used to experimentally evaluate the theoretical results is shown in Scheme 3. Protection of 1,4-butanediol followed by oxidation gave the aldehyde **6** in 50% yield. This was converted to the dienol **7** by reaction of the anion of diphenylmethallyl phosphine oxide[11] followed by removal of the TBS group. The alcohol was transformed into an iodide[12] and reacted with the enolate of methyl 2-cyclopentanonecarboxylate. Removal of the carbomethoxy group afforded ketone **8** in a 47% overall yield from **7**.

The cycloaddition reaction was conducted in two steps involving the chlorination of the enolate of **8** followed by treatment with base in a polar solvent. In a typical procedure, freshly prepared chloroketone was dissolved in solvent (0.1 M), and the solution was cooled to −78 °C (dry ice bath). Base (3 equiv) was added, and the reaction was allowed to slowly warm to room temperature and stirred for 12 h.

The crude reaction mixtures were examined by 300 MHz proton NMR to ascertain product ratios. We found that the alkene proton of the endo cycloadduct **4** resonated at 5.42 ppm while that of the exo cycloadduct **5** appeared downfield at 5.53 ppm. We have observed this behavior previously and ascribe it to the fact that the vinyl proton in **4** is in the shielding cone of the ketone carbonyl group. The assignment was corroborated by an X-ray structure determination on the oxime derivative of **4**.

The data for the cycloadditions are shown in Table 2. Yields were obtained after chromatographic purification. Elimination is a concern under the reaction conditions used for the cycloaddition. Various amounts of the elimination product **9** were formed in these cycloadditions. Entries 1−6 show that there is essentially no significant variation on the stereochemical outcome of the reaction as a function of the amount of trifluoroethanol

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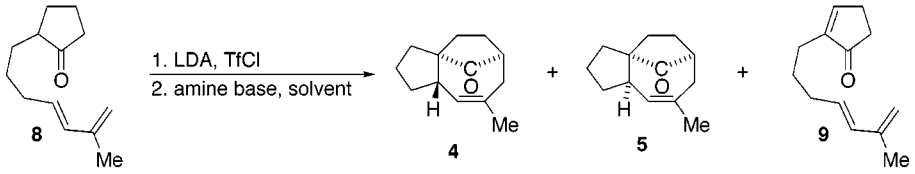
Table 2. Intramolecular 4 + 3 Cycloaddition of Ketone 8



			cycloadduct **4**/**5**		enone
entry	solvent	base[b]	ratio **5**:**4**	yield (%)	**9** yield (%)
1	Et_2O	TEA	50:50	5	7
2	10% TFE[a]	TEA	52:48	22	4
3	25% TFE[a]	TEA	50:50	41	2
4	50% TFE[a]	TEA	45:55	54	3
5	75% TFE[a]	TEA	50:50	59	2
6	TFE	TEA	52:48	53	2
7	1 M $LiClO_4$[a]	TEA	71:29	37	38
8	2 M $LiClO_4$[a]	TEA	71:29	34	40
9	3 M $LiClO_4$[a]	TEA	71:29	31	41
10	50% TFE[a]	diisopropylamine	45:55	59	3
11	50% TFE[a]	diisopropylethylamine	45:55	57	2
12	50% TFE[a]	tributylamine	48:52	54	2
13	50% TFE[a]	dicyclohexylamine	45:55	55	1
14	50% TFE[a]	2,6-lutidine	42:58	19	0
15	50% TFE[a]	2,2,6,6-tetramethylpiperidine	45:55	58	2
16	50% TFE	DABCO	42:58	22	0

[a] In ether. [b] Three equivalents of base was used.

used as solvent relative to ether. Clearly, however, more than 25 vol % of TFE is necessary to begin to achieve acceptable yields. The lack of change associated with endo/exo selectivity as compared to prediction made by theory must be weighed against the fact that the theoretical work compared vacuum ($\epsilon = 1$) to trifluoroethanol ($\epsilon = 26.7$) and the experimental studies compared ether ($\epsilon = 17.1$) and trifluoroethanol. The experimental results are therefore in line with theoretical predictions, which suggest only a slight excess of the exo adduct as solvent polarity increases in going from a vacuum to trifluoroethanol. The subtleties of solvation in solvent mixtures render further conclusions dubious.

That solvent polarity will affect diastereoselectivity in the cycloaddition reaction is supported by the experiments shown in entries 7−9 in Table 2, though there may be specific salt effects which also contribute to the product ratio observed. While not a function of lithium perchlorate concentration between the values of 1−3 M, the endo/exo ratio changed measurably relative to those cycloadditions run in ether/trifluoroethanol mixtures in favor of the exo isomer, as predicted by our calculations. Unfortunately, yields of cycloadducts were relatively low in these cases, with elimination product **9** predominating. Further, the changes in selectivity were not substantial enough to warrant further investigation.

As shown in entries 10−16 (Table 2), we also examined the effect of base on this reaction. The endo isomer **4** is marginally favored in all cases, but not to an extent that would make a base change in this process synthetically interesting.

Finally, it should be stated that these reactions appear to be under kinetic control. Treatment of cycloaddition products under the reaction conditions results in no change.

The results described herein suggest that simple diastereoselectivity in 4 + 3 cycloaddition reactions of systems such as **8** is not likely to be high without the participation of other factors that help to direct the approach of the diene to the dienophile, as observed in the synthesis of dactylol. Synthetic design and appropriate target choice thus become quite significant in the application of this methodology. The good agreement between theory and experiment for the unsubstituted parent system suggests that theory may profitably be used to screen the utility of different substitution patterns with respect to enhancing diastereoselectivity. Further studies on 4 + 3 cycloaddition reactions and their applications are in progress and will be reported in due course.

Experimental Section

4-(*tert*-Butyldimethylsilanyloxy)butyraldehyde (6). A solution of 1,4-butanediol (25.11 g, 278.64 mmol) in THF (150 mL) was cooled to −78 °C under N_2, and the resulting white suspension was treated, with vigorous stirring, with a 2.5 M solution of BuLi in hexane (45 mL, 111.46 mmol). The mixture became very viscous. After being stirred for an additional 5 min, a solution of TBSCl (14 g, 92.88 mmol) in THF (10 mL) was added to the reaction mixture, which was allowed to warm to room temperature and stirred for 40 min. To the white suspension was added 150 mL of half-saturated NH_4Cl, and the separated aqueous phase was extracted with ether (100 mL × 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (400 mL), PDC (34.9 g, 92.8 mmol) was added, and the mixture was stirred at room temperature for 12 h. The resulting deep green solution was diluted with Et_2O (200 mL) and filtered through a plug of Celite, and volatiles were removed in vacuo. The crude product was purified by flash chromatography (silica gel, 10% EtOAc in hexanes). Compound **6** was obtained as a colorless liquid (9.5 g, 50%). The ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[13]

6-Methylhepta-4,6-dien-1-ol (7). To a suspension of phosphine oxide (3.78 g, 14.57 mmol) in THF (40 mL) was added HMPA (5.1 mL, 29.5 mmol). The mixture was cooled to −78 °C. The mixture was treated with a 2.5 M solution of BuLi in hexanes (5.9 mL, 14.75 mmol) and stirred for 30 min. A solution of aldehyde **6** (2.98 g, 14.75 mmol) in THF (10 mL) was added.

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The mixture was stirred at −78 °C for 6 h, quenched with water (100 mL), and extracted with ether (50 mL × 3). The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in THF, and a 1.0 M solution of TBAF in THF (14.75 mL, 14.75 mmol) was added. The mixture was stirred at room temperature for 3 h and then washed with water. The aqueous phase was extracted with ether (50 mL × 3). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica gel, 20% EtOAc in hexanes) afforded 1.3 g (70%) of the product as a colorless liquid. The ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[14]

7-Iodo-2-methyl-hepta-1,3-diene. To a solution of alcohol **7** (1.3 g, 10.38 mmol) in THF (100 mL) was added DCC−MeI salt (7.23 g, 20.76 mmol), and the mixture was stirred under N_2 at 35 °C for 6 h. The volatile solvent was removed in vacuo, and the crude product was purified by flash chromatography (silica gel, 100% hexanes). The product was obtained as a colorless liquid.

2-(6-Methylhepta-4,6-dienyl)cyclopentanone (8). To a solution of methyl 2-oxocyclopentanecarboxylate (1.20 g, 8.47 mmol) in acetone (50 mL) were added the above iododiene (1.00 g, 4.24 mmol) and K_2CO_3 (1.76 g, 12.71 mmol). The reaction was heated under reflux under N_2 for 12 h, allowed to cool to room temperature, and diluted with water. The mixture was extracted with ether, and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in DMSO (20 mL), water (0.3 mL, 16.94 mmol) and KCN (1.10 g, 16.94 mmol) were added, and the mixture was heated under reflux for 30 min. After it had cooled to room temperature, the mixture was partitioned between ether and water. The organic phase was dried over $MgSO_4$, filtered, and dried in vacuo. The crude product was purified by flash chromatography (silica gel, 5% Et_2O in pentane). The product was obtained as a colorless liquid (0.42 g, 52%): ^1H NMR (250 MHz, $CDCl_3$) δ 6.13 (d, J = 15.6 Hz, 1H), 5.64 (dt, J = 6.9, 15.6 Hz, 1H), 4.86 (s, 2H), 2.35−1.95 (m, 7H), 1.85−1.71 (m, 3H), 1.80 (s, 2H), 1.60−1.23 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 221.3, 142.1, 133.1, 130.3, 114.4, 49.1, 38.1, 32.7, 29.6, 29.3, 27.4, 20.7, 18.7; IR (neat) 2933 (s), 2860 (m), 1745 (s), 1450 (w), 1158 (m), 972 (m), 881 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.96; H, 10.60.

2-Chloro-5-(6-methylhepta-4,6-dienyl)cyclopentanone. To a cooled (−78 °C) solution of **8** (0.10 g, 0.52 mmol) in THF (5.0 mL) was added a solution of LDA (freshly prepared from 0.11 mL (0.78 mmol) of DIPA and 0.26 mL (0.67 mmol) of 2.5 M solution of BuLi in hexane). The mixture was stirred for 30 min, and TfCl (0.11 mL, 1.04 mmol) was added. The mixture was stirred for an additional 5 min and quenched with water. The organic phase was separated, and the aqueous phase extracted with ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was used in the next step without further purification.

[4 + 3] Cycloaddition in TFE−Et_2O Medium. A solution of the aforementioned α-chloro cyclopentanone (0.52 mmol) in 1:1 mixture of TFE−Et_2O (5.0 mL) was cooled to −78 °C, and NEt_3 (0.22 mL, 1.56 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with water and extracted with ether. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes).

[4 + 3] Cycloaddition in $LiClO_4$/Et_2O Medium. Into a 25 mL round-bottomed flask were placed $LiClO_4$ (0.53 g, 5.0 mmol) and ether (4.0 mL). The mixture was stirred until a homogeneous solution was obtained, then a solution of the α-chloro cyclopentanone (0.52 mmol) in 1 mL of THF was added followed by TEA (0.21 mL, 1.54 mmol). The mixture was stirred at room temperature for 3 h and slowly quenched with 20 mL of water. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes).

8-Methyl-(3aα,6α,9a*β*)-1,2,3,4,5,6,7,9a-octahydro-3a,6-cyclopentacycloocten-10-one (4). The compound was isolated as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (s, 1H), 2.57−1.71 (m, 11H), 1.68 (s, 3H), 1.59−1.46 (m, 2H), 1.43−1.20 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.6, 129.0, 125.9, 59.2, 51.9, 43.4, 37.4, 35.6, 35.5, 31.5, 27.1, 23.9, 23.6 ppm; IR (neat) 2953 (s), 2867 (m), 1738 (s), 1448 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.15; H, 9.70.

8-Methyl-(3aα,6α,9aα)-1,2,3,4,5,6,7,9a-octahydro-3a,6-cyclopentacycloocten-10-one (5). The compound was isolated as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (s, 1H), 2.57−2.50 (m, 1H), 2.40−2.28 (m, 1H), 2.21−2.08 (m, 2H), 2.03−1.83 (m, 4H), 1.72−1.32 (m, 6H), 1.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.7, 135.5, 126.4, 59.5, 50.3, 46.5, 37.2, 32.8, 32.3, 30.9, 28.4, 22.5, 22.3 ppm; IR (neat) 2953 (s), 2867 (m), 1738 (s), 1448 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.24; H, 9.64.

2-(6-Methylhepta-4,6-dienyl)cyclopent-2-enone (9). The compound was isolated as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.14 (d, J = 15.6 Hz, 1H), 5.64 (dt, J = 6.9, 15.6 Hz, 1H), 4.86 (s, 2H), 2.57−2.55 (m, 2H), 2.41−2.38 (m, 2H), 2.22−2.10 (m, 4H), 1.82 (s, 3H), 1.61 (quin, J = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 157.4, 146.2, 142.0, 133.3, 130.0, 114.4, 35.6, 32.4, 27.4, 26.4, 24.4, 18.6; IR (neat) 2925 (m), 2863 (m), 1704 (s), 1638 (w), 1444 (m), 965 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.98; H, 9.66.

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Supporting Information Available: Pictures of transition-state structures and Cartesian coordinates. X-ray data on the oxime derivative of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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