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THE CONSEQUENCES OF STRAIN RELEASE IN THE NORBORNYL SUBUNIT OF ISODICYCLOPENTADIENE ON CYCLOADDITION STEREOCHEMISTRY. FURTHER EVIDENCE THAT ORBITAL TILTING SERVES AS THE KEY DETERMINANT OF CONTRASTERIC π-FACIAL SELECTIVITY

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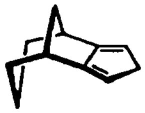
Abstract: Diels-Alder cycloadditions to **2** and **3** occur preferentially from the top face in contradistinction to the behavior of isodicyclopentadiene (**1**). This reversal in facial stereoselectivity is shown not to arise from torsional constraints, but to be consistent with the overriding of steric effects by orbital tilting in **1**.

The design of diene substrates for the purpose of defining the role played by fused norbornyl subunits in controlling [4+2] cycloaddition stereoselectivity has proven to be more problematical than anticipated.[1] With the present work, we believe the weight of evidence to have become sufficient to justify the acceptance of orbital distortion as the key determinant of the contrasteric below-plane π-facial kinetic preference exhibited by isodicyclopentadiene (**1**) toward dienophiles. 2,4,5,6,7,8-Hexahydro-4,8-methanoazulene (**2**) and 2,3b,4,5,6,7,7a,8-octahydro-5,8-methanocyclopent[*a*]indene (**3**) have been synthesized in order to confirm that strain release in the bicyclic component results in loss of the kinetic driving force for attack from the bottom face.

1



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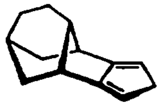
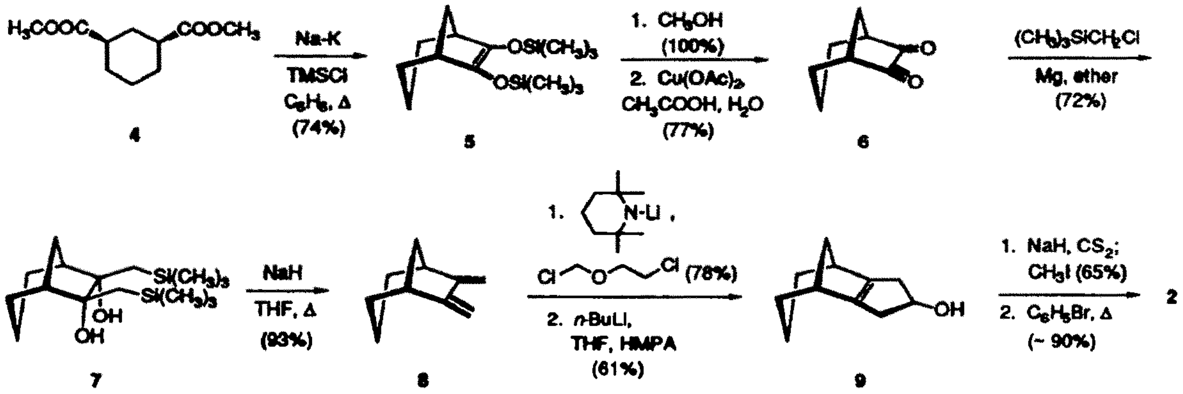


3

To arrive at **2**, diester **4**[2] was cyclized under acyloin conditions[3] to give **5**, which was hydrolyzed to the α-hydroxy ketone simply by stirring in deoxygenated methanol at 20 °C (Scheme I). Subsequent oxidation with copper(II) acetate monohydrate in aqueous acetic acid[4] provided **6**. Twofold addition of ethereal trimethylsilylmethylmagnesium chloride[5] to **6** led to **7** as the only product and set the stage for double Peterson olefination[6] and formation of **8**. Adaptation of Danheiser's two-step method for cyclopentenol annulation[7] furnished **9**, dehydration of which was accomplished via the xanthate.

In light of the recognized availability of ketone **10**,[8] the serviceability of the Skattebøl rearrangement[9] as a means of obtaining **3** in preparatively useful amounts was explored (Scheme II). Exposure of **10** to vinylmagnesium bromide resulted in exo addition to give an allylic alcohol, dehydration of which was conveniently effected with the Burgess reagent [(methoxycarbonylsulfamoyl)-triethylammonium hydroxide inner salt].[10] Dibromocarbene addition to **11** provided a mixture of three dibromides from which **12** could be separated (30%) and immediately treated with the $CH_3Li \cdot LiBr$

Scheme I

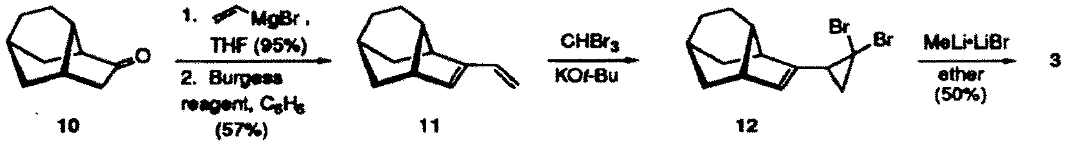


complex. The ability of structurally related carbenoids to isomerize suitably to cyclopentadienes has recently been demonstrated.[11] In the case at hand, 3 was isolated in 50% yield.

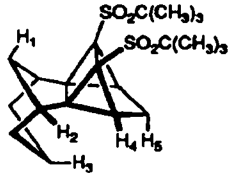
The level and direction of π-facial selectivity operational during cycloaddition of N-phenylmaleimide,[12] maleic anhydride,[13] and (*Z*)-1,2-bis(phenylsulfonyl)ethylene[14] to 1 have previously been documented. For the present purposes, bis(*tert*-butylsulfonyl)acetylene (TBSA)[15] was also examined and found to prefer below-plane attack to the extent of 76% (Table I). The same four dienophiles were subsequently reacted with 2 and 3. Some variation in the nature of the solvent was unavoidable because of the manner in which 2 was generated. Nevertheless, the extent to which 1 prefers bottom-face addition (55-100%) is not paralleled by 2 and 3. In actuality, the latter two dienes exhibit a convincing kinetic preference[16] for cycloaddition from above (75-100%). The argument can be made that 2 is attacked from the top face because of steric shielding provided by the added methylene group in the chair conformation shown. This feature is not present in 3 where the cyclohexane ring is necessarily boat-shaped. The close similarity in product distributions observed for 2 and 3 suggests that the energy barrier for conformational flexing in 2 is low.

The stereochemical features of those adducts produced from olefinic dienophiles could be unequivocally defined by high-field NMR spectroscopy including nOe measurements.[17] The reduced number of diagnostic protons in the products of TBSA addition and their inseparability required derivatization before rigorous stereochemical identification could be made of pure compounds. In

Scheme II

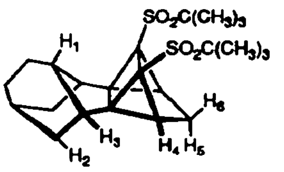


both examples, this involved direct irradiation of the major adducts in CH_2Cl_2 solution to generate **13** and **14**, respectively. The more highly caged nature of these derivatives was accommodating of spectroscopic structural analysis.



13

Protons	Enhancement
$H_1 \rightarrow C(CH_3)_3$	0.4%
$H_3 \rightarrow H_5$	4.5%
$H_5 \rightarrow H_3$	5.1%
$C(CH_3)_3 \rightarrow H_1$	6.3%
$C(CH_3)_3 \rightarrow H_2$	11.4%
$C(CH_3)_3 \rightarrow H_4$	14.1%



14

Protons	Enhancement
$H_1 \rightarrow C(CH_3)_3$	0.3%
$H_1 \rightarrow H_6$	8.0%
$H_6 \rightarrow H_2$	1.9%
$H_6 \rightarrow H_4$	9.0%
$H_5 \rightarrow H_6$	27.7%
$C(CH_3)_3 \rightarrow H_1$	10.6%
$C(CH_3)_3 \rightarrow H_4$	16.2%
$C(CH_3)_3 \rightarrow H_6$	2.5%

The π-facial stereochemical crossover reflected in Table I cannot be attributed to control by torsional factors.[18] This is because **2** and **3**, like **1**, are predicted by MM2 methods[19] to experience greater torsional compression in their top-face, endo transition states than in the bottom-face, exo alternatives (Table II). On the other hand, the less strained nature of the bicyclic part-structures in **2** and **3** depletes these systems of high-lying σ orbitals, such that σ/π interaction does not operate and steric factors gain importance.[20] As earlier proposed,[21] this trend is reversed in **1** as a consequence of strain-induced orbital tilting and its stereoelectronic consequences.

Table I. Distribution of Stereoisomeric Diels-Alder Adducts to **1**-**3** with Various Dienophiles.

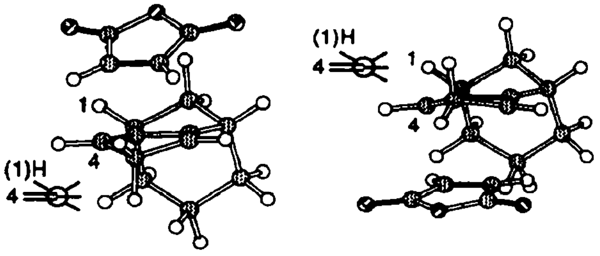
		top-face addition		bottom-face addition	
diene	dienophile[a]	exo	endo	exo	endo
1	NPM	—	—	100	—
	MA	—	33	67	—
	PSE	45	—	55	—
	TBSA	24		76	
2	NPM	15	66	19	—
	MA	—	100	—	—
	PSE	20	80	—	—
	TBSA	75		25	
3	NPM	31	52	17	—
	MA	b	78	b	—
	PSE	19	75	6	—
	TBSA	78		22	

[a] NPM = N-phenylmaleimide; MA = maleic anhydride; PSE = (*Z*)-1,2-bis(phenylsulfonyl)-ethylene; TBSA = bis(*tert*-butylsulfonyl)acetylene. [b] Combined yield of 22%; specific identification of the constitution of this mixture could not be made.

Table II. Calculated Transition StateTorsional Angles for the Diels-Alder Addition of MA.[a]

Compd	top-face, endo	bottom-face, exo
1	20.1°	26.2°
2	33.4°	37.1°
3	32.3°	35.6°

[a] The torsional angles in question are defined in the drawings of **2** to the right.



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