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Influence of norbornanone substituents on both the Wagner–Meerwein skeletal rearrangements under sulfonation conditions and the diastereoselectivity of the corresponding *N,N′*-bis-fumaroyl sultams in uncatalyzed Diels–Alder cycloadditions to cyclopenta-1,3-diene

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ABSTRACT

The Wagner–Meerwein domino rearrangement of norbornanone skeletons, under sulfonation conditions, is strongly influenced by the absence of a *gem*-dimethyl moiety at C(7). As a result, sulfonation at C(10) is less efficient due to a divergent pathway in the intermediate double bond formation and/or isomerization. Furthermore, the absence of such a *gem*-dimethyl moiety in the corresponding norbornane[10,2]sultam derivatives, sterically influences the orientation of the S=O(1) and S=O(2) substituents, hence on the π-facial steric shielding of the thermodynamically more stable *anti*-s-*cis* *N*-alkenoyl dienophiles. As a consequence, their diastereoselective [4+2] cycloadditions to cyclopenta-1,3-diene, under nonchelating conditions, are not as efficient due to a less pseudo axial S=O(1) and the consequent loss of pseudo C_2-symmetry.

(+)-(1*R*,4*R*)-Camphor **1a**, due to its availability in both enantiomeric forms, the crystalline properties imparted to its derivatives, as well as its widely studied chemistry, is an excellent starting material for the synthesis of chiral auxiliaries[1] and catalysts.[2] Its corresponding 10-sulfonic acid **2a**,[3] via intermediates **3a**,[4] **4a**,[5] and **5a**,[6] led to the discovery of the well-known (2*R*)-bornane-10,2-sultam **6a**.[7] (Scheme 1) This imparts a very high reactivity and diastereoselectivity to a variety of dienophiles and its efficiency was extended to a wide range of diverse reactions.[8] Its Me(9) substituent was initially thought to have a steric influence on the approach of the reactant,[9] but very quickly, in view of non-inversion of the chiral induction under either chelated and non-chelated conditions, this hypothesis had to be abandoned.[10] A disguised pseudo C_2-symmetry, resulting from the pseudo axial orientation of the S=O(1), and pseudo equatorial orientation of C(2)–C(3), as sterically important substituents, in either the SO_2/C=O *anti* or *syn* conformations, thus mimicking a (2*R*,5*R*)-dimethylpyrrolidine model, was subsequently recognized.[11]

We earlier synthesized and studied the influence of the S=O(1) devoid sulfinamide analogue,[12] the six-membered ring camphor sultam analogue,[13,14d] as well as auxiliary **6b**,[15] similarly obtained from (−)-(1*R*,4*R*)-fenchone (**1b**). Based on X-ray analyses of their *N*-alkenoyl derivatives, as well as those of saccharin derived sultams,[16] we concluded that Me(9) has a decisive steric impact on the pseudo equatorial orientation of S=O(2), and hence on the pseudo C_2-symmetry, which is thus lost in its absence. Nevertheless, the presence of a *gem*-dimethyl moiety in position C(3) influenced strongly the *anti*/*syn* SO_2/C=O conformation, which is particularly important in the absence of either a chelating Lewis acid, or pseudo C_2-symmetry.[17] We thus became interested in preparing analogues devoid of *gem*-dimethyl substitution at both C(3) and C(7).

We initially started from the reported (−)-(1*S*,4*S*)-*iso*-fenchone **1c**,[18] but unfortunately, this substitution influenced strongly the kinetics of the Wagner–Meerwein rearrangements during its sulfonation, and precluded the expected skeletal transformation according to the well established mechanism.[19] As a consequence, the secondary sulfonated intermediate **F**[20] was recovered and did not furnish the desired primary sulfonic acid **2c** under various conditions.[21] We next turned our attention toward the reported (−)-(1*R*,4*S*)-1-methyl-2-norbornanone **1d**,[22,23] and fortunately, in this case, the Wagner–Meerwein cascade rearrangements allowed isolation of the new sulfonic acid **2d**[24] (H_2SO_4, Ac_2O,[20] 26% yield)

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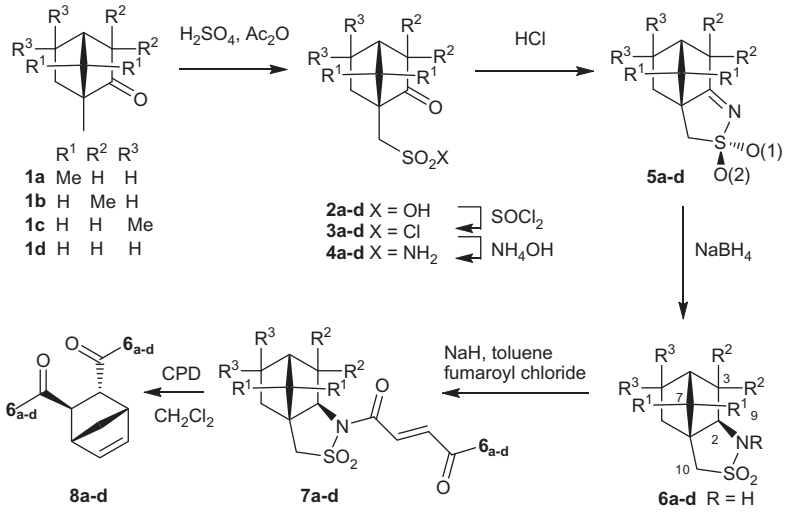
(Scheme 1). By analogy, this latter compound was subjected to a series of reported conditions, used earlier for the synthesis of **6a**[25,26] and **6b**,[15] so that via the corresponding sulfonyl chloride **3d** ($SOCl_2$, 60% yield), sulfonamide **4d** (NH_4OH, 1,4-dioxane, 55% yield), and sulfonimide **5d** (concd HCl, 88% yield), the desired desmethyl sultam **6d**[20] was isolated in 33% yield, after $NaBH_4$ reduction in $MeOH/H_2O$[15] (Scheme 1). This was acylated with fumaroyl chloride (NaH, toluene, 75% yield), and its [4+2] cycloaddition to cyclopenta-1,3-diene, in the absence of a chelating Lewis acid, in CH_2Cl_2 is reported in Table 1.

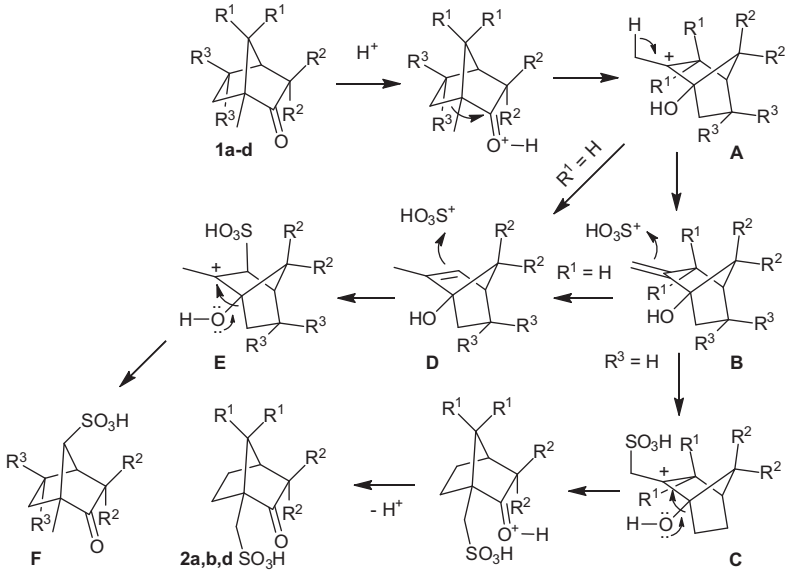


Scheme 1.

Table 1

Entry	Dienophile	Time (h)	Temperature (°C)	Conversion (%)	Yield (%)	de (%)	C(2)–N–S=O(1) (°)	S–N–C=O (°)	ΔhN (Å)
1	**7a**	4	−78	>99	95	89	103.5[a]	150.7[a]	0.230[a]
2	**7a**	1	20	>99	>98	84			
3	**7b**	4	−78	92	83	82	124.0[a]	153.4[a]	0.155[a]
4	**7b**	4	20	>99	95	85			
5	**7d**	24	−78	21	[b]	61	115.9[c]	159.0[c]	0.156[c]
6	**7d**	24	20	90	80	10			

[a] From X-ray structure analyses of the corresponding *anti*-s-*cis* *N*-crotonoyl derivatives.[15]
[b] Not determined
[c] Calculated at the B3LYP-6.31G** level on the corresponding *anti*-s-*cis* *N*-crotonoyl derivative. The *syn*-s-*cis* conformer (S–N–C=O = −13.7°; C(2)–N–S=O(1) = 120°, Δ*h*N = 0.066 Å) being 5.24 and 1.46 kcal/mol higher in energy in either the gas phase, or in CH_2Cl_2, respectively.



Scheme 2.

Sulfonation of **1** is particularly efficient when R^1 = Me (**1a**). In cases where R^1 = H, the yields of the corresponding sulfonic acid **2** are much lower. Indeed, in these cases, the intermediate exocyclic allylic alcohol **B** has both the possibility and the time to isomerize into the thermodynamically more stable endocyclic isomer **D**, which under sulfonation conditions concurrently affords the secondary sulfonic acids **F** (Scheme 2). When R^2 is not Me, this pathway becomes the major one, especially for R^3 = Me (**1c**). We earlier studied and rationalized in detail, for both mono,[27] and bis fumaroyl sultams, the influence of either the solvent,[14] the temperature, or the chelating rigidifying effect of the Lewis acids[28] on the [4+2] cycloadditions of **7a**,[25,26] and 7**b**,[15,28] for which the obtained absolute configuration was ascertained by both X-ray structure analyses of the cycloadducts,[14d,27] and the optical properties of the known diol, after reduction with $LiAlH_4$.[29] In the specific case of **7d**, both the conversion and the diastereoselectivity were measured by ^{1}H NMR analyses of the crude cycloadduct, by integration of the olefinic protons at 7.46 ppm for **7d**, 5.91 ppm for the major diastereoisomer (2*S*,3*S*)-**8d,** and 5.45 ppm for the minor example. Dienophile **7d**, of opposite topicity, is less reactive than its analogues **7a**, and 7**b**. Furthermore, when R^1 = H (**7b**, 7**d**), due to the absence of steric pressure on S=O(2), the S=O(1) substituent tends to adopt a pseudo equatorial orientation. As a consequence, in the dipole-stabilized and thermodynamically more stable *anti*-s-*cis* disposition of the dienophile, the bottom Cα-*si* face is less efficiently protected by the S=O(1) substituent, and thus at −78 °C, the diastereoselectivity diminishes as observed for **7b** (entry 3), and more evidently for **7d** (entry 5), as compared to **7a** (entry 1). At room temperature, the efficiency of **7d**, due to the lost pseudo C_2-symmetry, is practically zero (entry 6), as a result of the lack of conformational SO_2/C=O *anti*/*syn*-s-*cis* rigidity, in contrast to **7b** (entry 4), and to the pseudo C_2-symmetrical **7a** (entry 2). The lack of reactivity for **7d** may eventually be rationalized by a poorer electronic delocalization of the π-dienophilic system into the sultam moiety, as a result of an inefficient anomeric stabilization of the nitrogen lone pair into the less anti-periplanar S=O(1) σ* bond.[10]

In conclusion, we have confirmed that **7d**, with a less pseudo axial S=O(1), hence lacking pseudo C_2-symmetry, resulting from the absence of a *gem*-dimethyl moiety at C(7), is less efficient in terms of reactivity and diastereoselectivity. In order to confirm our hypothesis, we are preparing the nor-(2*R*)-bornane-10,2-sultams, lacking a single Me substituent at either position 8,[30] or 9.[31]

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20. *Selected data:* **F** R^2 = H, R^3 = Me: ^{1}H NMR (200 MHz): 9.52 (br s, 1OH); 3.88 (d, *J* = 3.2, 1H); 2.60–2.35 (m, 2H); 2.14–1.88 (m, 2H); 1.80–1.74 (m, 1H); 1.19 (s, 3H); 1.00 (s, 6H). ^{13}C NMR (50 MHz): 211.3; 64.6; 56.2; 44.8; 42.6; 38.3; 37.4; 32.1; 23.2; 20.6. HRMS(ESI) calculated for $C_{10}H_{16}O_4NaS$ [M+Na]: 255.0667, found: 255.0669. **2d**: ^{1}H NMR (500 MHz): 5.67 (br s, 1OH), 3.38 (d, *J* = 14.5, 1H); 3.11 (d, *J* = 14.5, 1H), 2.85–2.82 (m, 2H), 1.96–1.89 (m, 2H), 1.82 (m, 1H), 1.50–1.46 (m, 4H). ^{13}C NMR (125 MHz): 218.1 (C2, s), 56.1 (C1, s), 51.2 (C8, t), 42.5 (C3, t), 39.3 (C4, d), 33.2 (C6, t), 28.6 (C7, t), 28.6 (C5, t). HRMS(ESI) calculated for $C_8H_{11}O_4S$ [M−H]: 203.0378, found: 203.0384. **6d**: ^{1}H NMR (200 MHz): 4.37 (br s, 1NH); 3.36 (d, *J* = 13.4, 1H); 3.29–3.27 (m, 1H); 3.24 (d, *J* = 13.4, 1H); 2.32 (br s, 1H); 1.79–1.68 (m, 4H); 1.55–1.20 (m, 4H). ^{13}C NMR (50 MHz): 61.6; 53.8; 53.5; 40.7; 38.9; 37.2; 30.7; 28.8. HRMS(ESI) calculated for $C_8H_{12}NO_2S$ [M−H]: 186.0589, found: 186.0594.
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