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ENANTIOSELECTIVE N-SULFINYL DIENOPHILE DIELS-ALDER CYCLOADDITIONS

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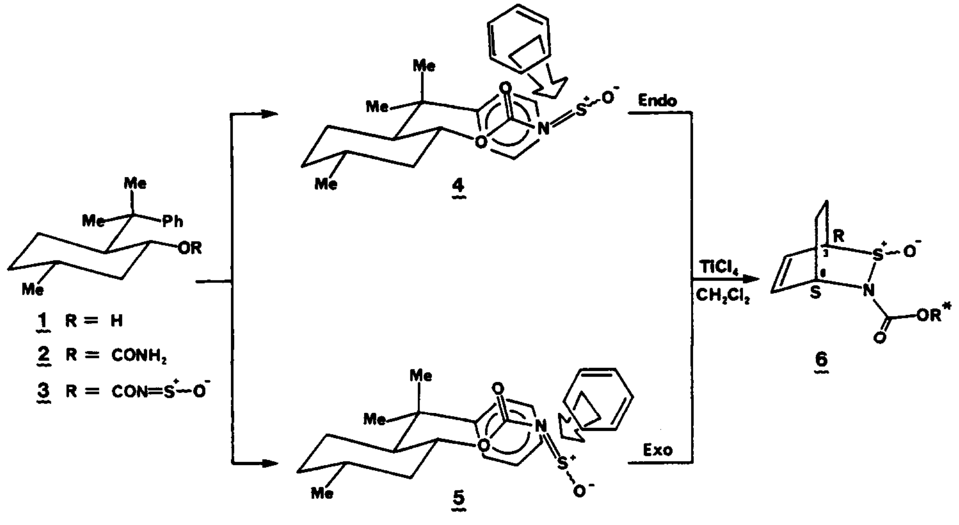
Abstract: N-Sulfinyl carbamates prepared from phenylmenthol (1) and (+)-camphor-derived alcohol 10 display high enantioselectivity in $TiCl_4$ catalyzed [4+2] cycloadditions with 1,3-cyclohexadiene.

Several publications from this laboratory have described the development of new synthetic methodology based upon [4+2] cycloadducts of 1,3-dienes and N-sulfinyl dienophiles.[1] As a part of these studies, we have been actively engaged in developing asymmetric N-sulfinyl Diels-Alder reactions, and a recent report by Whitesell, et al. in this area[2] prompts us to describe our results.[3]

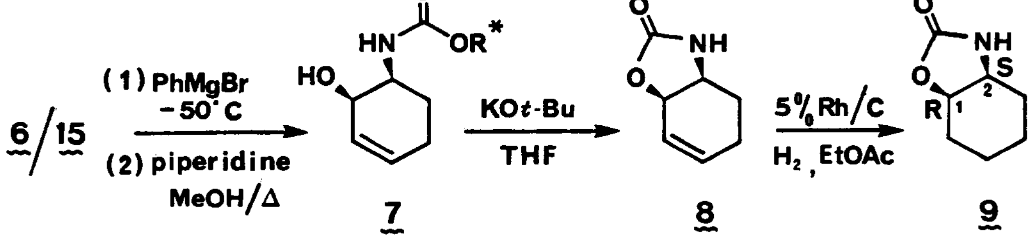
Since we have had considerable success utilizing N-sulfinyl carbamates as hetero dienophiles, and in using the dihydrothiazine oxides resulting from these cycloadditions in further transformations, it seemed reasonable to explore asymmetric Diels-Alder reactions with such dienophiles derived from chiral alcohols. Our initial experiments were performed using phenylmenthol (1) as the chiral auxiliary.[4] This alcohol was converted to carbamate 2 (sodium cyanate/TFA,[5] 93%) which in turn could be transformed to N-sulfinyl compound 3 with $SOCl_2$/pyridine. This dienophile could be stored as a 0.1M solution in CH_2Cl_2 for up to one week at -4°C. Reaction of 3 with cyclohexadiene at room temperature in the absence of a catalyst afforded an 80% of yield a mixture of all four possible diastereomeric Diels-Alder adducts in a 2:4:1:3 ratio in order of HPLC elution. However, treatment of 3 with one equivalent of $TiCl_4$ at -50°C, followed by addition of 1,3-cyclohexadiene yielded a 9:1 mixture of 3,6-dihydrothiazine oxides 6 (77%).

Scheme 1



That these adducts were in fact epimeric at sulfur could be proven by oxidation of the mixture with m-ClPBA to produce a single sultam. Stereochemistry at sulfur in the adducts could not be determined, but the absolute configuration at C-3 and C-6 of the epimers was established by chemical correlation with the known cyclic carbamate 9.[6] Thus, using our previously reported methodology,[1c] the mixture 6 was rearranged to hydroxy carbamate 7 (94%)[7] which was cyclized to carbamate 8 in 70% yield (Scheme 2). Catalytic hydrogenation of 8 provided 9 (60%; [α]$^{20}_{D}$=+25.0° (c=1.0, EtOH)) having the 1R, 2S configuration,[6] and thus 6 must have had the 3S, 6R configuration.

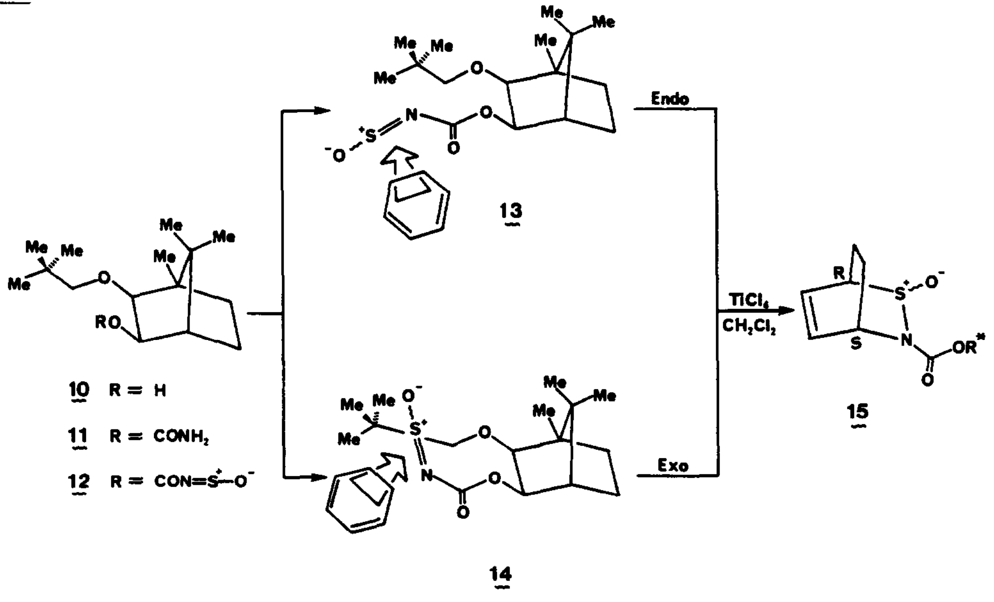
Scheme 2



Formation of adducts 6 can be rationalized by either of the two types of facial attack shown in Scheme 1. Nothing is currently known regarding the favored conformation(s) of N-sulfinyl carbamates, but the parallel conformations shown in 4 and 5 both seem reasonable for dienophile 3. In order to produce the observed adducts 6, conformer 4 would have to be attacked from the least encumbered face by the diene in an *endo* transition state. Alternatively, conformer 5 could react with cyclohexadiene to give 6 *via* an *exo* mode of attack. Although the former mode of attack seems most likely, the latter case should not be summarily dismissed since the importance of secondary orbital effects in this type of [4+2] cycloaddition has not been established. In addition, the Lewis acid clearly plays an important role in the asymmetric induction, probably by chelation with the N-sulfinyl carbamate dienophile. Our stereochemical results are in accord with the observations of the Whitesell group, who used dienophile 3 in $SnCl_4$ catalyzed reactions with two acyclic dienes.[2]

We have also investigated a cycloaddition of the chiral N-sulfinyl dienophile prepared from alcohol 10, readily available from (+)-camphor.[8] This alcohol was converted to carbamate 11 (83%) and then to dienophile 12 exactly as in the phenylmenthol series. Uncatalyzed cycloaddition of 12 with 1,3-cyclohexadiene afforded a complex mixture of four diastereomers, whereas the reaction promoted by $TiCl_4$ at -50°C gave *exclusively one* cycloadduct 15 (75%). Once again, stereochemistry at sulfur of the adduct could not be determined, but the configuration at carbon was found to be 3S, 6R by conversion of 15 to cyclic carbamate 9 (32% overall) *via* the sequence in Scheme 2 ($[\alpha]_D^{20}$=+23.7°(c=0.45, EtOH)).[6]

Scheme 3



The stereochemistry produced at C-3 and C-6 in dihydrothiazine oxide 15 can be rationalized by a cycloaddition occurring through N-sulfinyl dienophile conformer 13 *via* an *endo* transition state with the diene approaching from the more exposed outer face. Alternatively, conformer 14 reacting *via* an *exo* transition state would also give 15. Sufficient information is not currently available to allow us to distinguish between these possibilities.

We are currently extending these studies to other chiral N-sulfinyl dienophiles and plan to use the methodology in enantioselective natural product total syntheses.

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6.) Kay, J. B.; Robinson, I. B. *J. Chem. Soc. (C)* 1969, 248. These workers have reported $[\alpha]_D^{20}$=+35.6° (c=0.36, EtOH) for 9. We believe that the *magnitude* of this rotation is too high, since we have prepared (+)-9 by the two independent cycloaddition routes described here, and in both cases a rotation of about +25° was obtained.[7]

7.) Compounds 7 in both the phenylmenthol and camphor series were found to be diastereomerically pure by ^1H and ^{13}C NMR spectroscopy.

8.) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* 1982, *23*, 4781. We are grateful to Professor Oppolzer for details concerning preparation of chiral auxiliary 10.

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