Asymmetric Induction in the Cycloaddition Reactions of the *N*-Sulphinylcarbamate of 8-Phenylmenthol

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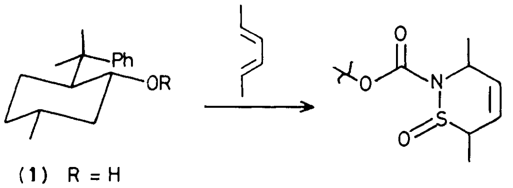
High levels of asymmetric induction at the carbon atoms which bear nitrogen and sulphur as well as at sulphur were observed in the cycloaddition reactions of a chiral *N*-sulphinylcarbamate with dienes under the influence of a Lewis acid.

We[1] and others[2,3] have reported on the high levels of asymmetric induction that can be obtained in a variety of practical reactions that employ 8-phenylmenthol (**1**) as the chiral auxiliary. In our continuing studies along these lines we have found that the *N*-sulphinylcarbamate (**2**) undergoes cycloaddition reactions with dienes with high levels of absolute stereochemical control at three newly formed chiral centres. The 3,6-dihydro-1,2-thiazine 1-oxides thus produced are versatile intermediates that can be transformed to a variety of useful functionalities.

The cycloaddition reaction between *N*-sulphinylcarbamates and dienes has been known for some time.[4] Recently, Weinreb reported[5] on the stereochemical implications of this reaction and showed that the thiazines thus obtained could be readily transformed into unsaturated amines and amino alcohols. It occurred to us that incorporation of the chiral auxiliary 8-phenylmenthol[2] could impart absolute stereochemical control by asymmetric induction in these reactions and thus lead to chiral intermediates for elaboration to natural products such as amino sugars as well as a variety of unnatural, biologically active amino alcohol derivatives such as propranolol and propoxyphene. Indeed, reaction of the *N*-sulphinylcarbamate (**2**) (from the carbamate, SOCl$_2$, and pyridine in benzene) and (*E,E*)-hexa-2,4-diene in the presence of 1 equivalent of SnCl$_4$ (CH$_2$Cl$_2$, 0 °C, 16 h) produced one diastereoisomer of the product, (**3b**), to the virtual exclusion of the other three possibilities, (**3a,c,d**) (>97% by h.p.l.c. analysis) in 42% isolated yield.†‡

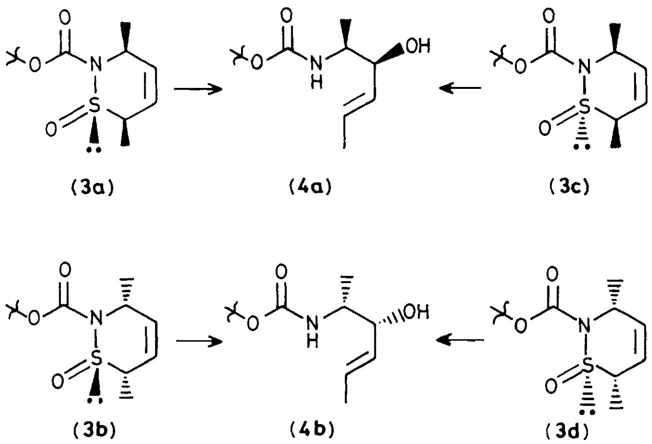
The degree of stereochemical control observed in the presence of a Lewis acid was in marked contrast to that of a strictly thermal reaction (room temp., 24 h, toluene) where four diastereoisomers of the products [(**3a**—**d**); 2 : 1 : 2.5 : 9, listed in order of their elution] were formed as a readily separated (h.p.l.c.) mixture.§ It is also interesting to note that the least abundant component from the thermal reaction, (**3b**), was identical to the dominant diastereoisomer obtained in the presence of SnCl$_4$. A complete, single crystal *X*-ray structure determination¶ was used to establish the stereochemistry of (**3d**).


(1) R = H

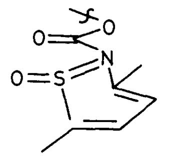
(2) R = CONSO

(3)

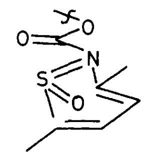
The relative and absolute configurations of the other three diastereoisomers were then assigned as follows. Reaction of each of (**3a**—**d**) separately with phenylmagnesium bromide[5] resulted in four phenyl sulphoxides, and these four diastereoisomers in turn underwent smooth 2,3-rearrangement–desulphurization (trimethylphosphite at reflux in MeOH) forming only two carbamate alcohols, (**4a**) and (**4b**). Since it has been established[5,6] that the stereochemistry in the 2,3-rearrangements of allylic sulphoxides is controlled by the stereochemistry of the carbon which bears sulphur, not by that


(3a) (4a) (3c)

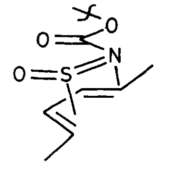
(3b) (4b) (3d)


(5a) → (3a)

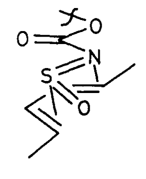
exo, syn


(5c) → (3c)

exo, anti


(5b) → (3b)

endo, syn


(5d) → (3d)

endo, anti

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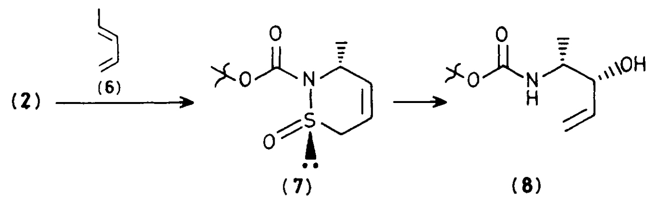
† Substantial quantities of the carbamate resulting from hydrolysis of the sulphinyl group are obtained, and the material balance for these reactions is quite high.

‡ In the presence of Lewis acids, the *N*-sulphinylcarbamate (**2**) undergoes ene reactions with simple alkenes with high levels of stereochemical control, opening the avenue to simple allylic sulphoxides and the wide range of functionalities that can be derived from them. These results will be communicated separately.

§ It is also interesting to compare our results for the thermal reaction of the *N*-sulphinylcarbamate of 8-phenylmenthol with those obtained by Weinreb (ref. 5) for the benzyl alcohol derivative where a single diastereoisomer was obtained.

¶ We are grateful to Dr. Steve Larsen of the University of Texas at Austin for this analysis. Full details will be reported in due course.

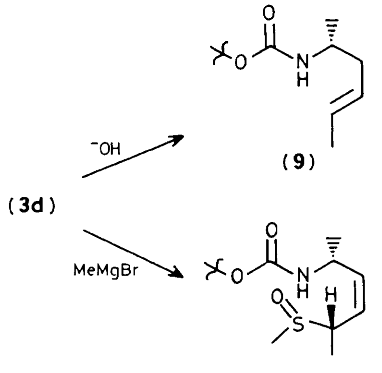


of the sulphur itself when both carbon and sulphur are chiral, the stereochemistry for the other three 3,6-dihydro-1,2-thiazine 1-oxides then follows by correlation since the configurations at both C-3 and C-6 must be the same in (**3b**) as in (**3d**) [since they form the same carbamate alcohol, (**4b**)] while the stereochemistry at both of these centres is inverted in the pair (**3a**) and (**3c**). It is interesting to note that the dominant stereoisomers from the thermal and the acid catalysed reactions have the same configuration at C-3 and C-6 but differ at sulphur.[7] Presumably, (**3b**) is the result of an *endo, syn* transition state (**5b**) while (**3d**) is produced *via* the *endo, anti* arrangement (**5d**), and the influence of the Lewis acid is to inforce by chelation the *syn* relationship of the carbonyl and sulphinyl moieties.

With the unsymmetrical diene (**6**), cycloaddition occurred to form one regio- and stereo-isomer, (**7**) to the extent of at least 98 : 2. The regiochemistry of (**7**) could be easily established by conversion, as above, into (**8**) as an 11 : 1 mixture of diastereoisomers in 39% isolated yield.‖ The stereochemistry of the major isomer of (**8**) is tentatively assigned as shown based on an analysis of the possible, diastereoisomeric transition states for the 2,3-rearrangement process.

Numerous possibilities exist for the transformation of dihydrothiazines such as (**3**) into useful derivatives. For example, reaction of (**3d**) with aqueous base[5] (NaOH, H_2O/MeOH/tetrahydrofuran) afforded the carbamate (**9**). Substitution of methyl- for phenyl-magnesium bromide (above) afforded *cis*-sulphoxide (**10**) as a single stereoisomer that did not undergo 2,3-rearrangement when treated under the same conditions as the phenyl analogue.

Clearly, the realization of high levels of asymmetric induction in the formation of 3,6-dihydrothiazines through Lewis acid mediated cycloaddition reactions opens new avenues for the synthesis of nitrogen containing, chiral molecules with control of both relative and absolute stereochemistry.



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‖ A high degree of selectivity in the transfer of chirality from sulphur to the COH carbon is expected in the 2,3-rearrangement of a (*Z*)-allylic sulphoxide, ref. 6d,e.