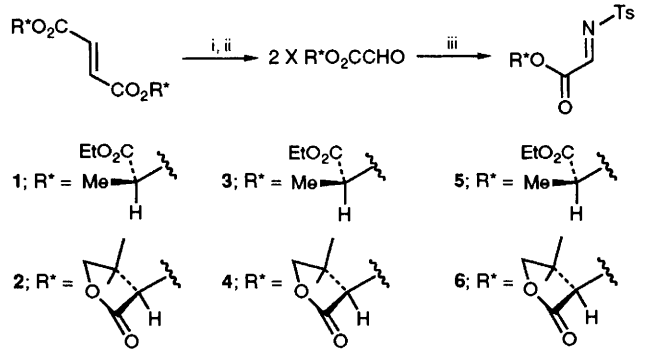
Diastereoselective Imino Ester Cycloadditions. Enantioselective Synthesis of Azabicyclo[2.2.1]heptenes

Peter Hamley,[a] Günter Helmchen,[b] Andrew B. Holmes,*[a] David R. Marshall,[c] John W. M. MacKinnon,[c] David F. Smith[a] and Joseph W. Ziller[d]

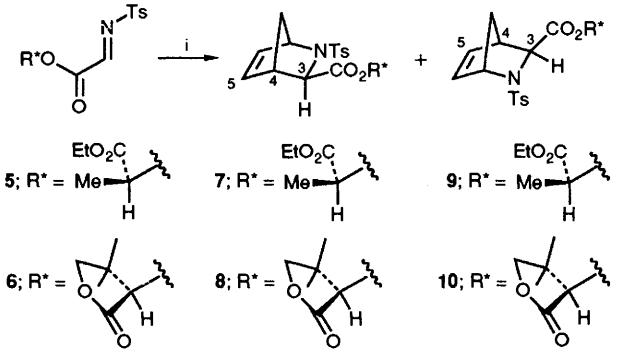
[a] *University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK*
[b] *Organisch-chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld, D-6900 Heidelberg, Germany*
[c] *Chemical Development Department, Glaxo Group Research, Ware SG12 0DP, UK*
[d] *Department of Chemistry, University of California, Irvine CA 92717, USA*

The diethylaluminium chloride-catalysed cycloaddition of cyclopentadiene to the (*S*)-lactate-derived *N*-toluene-*p*-sulfonyliminoacetate **5** gives mainly (76% diastereoisomeric excess, d.e.) the adduct **9** (X-ray structure); the (*R*)-pantolactone-derived iminoacetate **6** similarly gives (70% d.e.) the adduct **8** which is correlated *via* the methyl esters **11** with compound **9**.

The asymmetric imino Diels–Alder reaction offers significant potential for the enantioselective synthesis of alkaloids containing a six-membered ring. While two approaches employing a chiral diene partner have been reported,[1,2] the remainder have concentrated largely on attaching a chiral auxiliary to the nitrogen component of the imine. In some cases the substituent on nitrogen has been retained for subsequent synthetic transformations,[3–5] but by far the most useful class of diastereoselective aza Diels–Alder reaction is that in which the nitrogen auxiliary can be removed. Of the latter the pioneering work of Grieco,[6] using a methylene iminium species carrying the α-methylbenzyl substituent (affording moderate diastereoselectivity) has been extended by Stella[7] and Bailey[8] to include glyoxylate derivatives. Auxiliaries in which the imine nitrogen is derived from an α-amino acid[9] or an amino-sugar[10] have shown excellent diastereoselectivities, although removal of the auxiliary in the former case requires several steps. It is also difficult to remove a benzylic substituent on nitrogen without causing reduction of the adduct double bond. We report here the investigation of *N*-toluene-*p*-sulfonyl imines (which undergo efficient cycloaddition reactions[11] and whose adducts have proven easy to deprotect[12]) derived from glyoxylates carrying an ester chiral auxiliary. Bearing in mind the work of Prato[13] with 8-phenyl-



Scheme 1 Ts = *p*-$MeC_6H_4SO_2$ *Reagents and conditions*: i, O_3, CH_2Cl_2, −78 °C; ii, Me_2S, −78 °C to room temp.; iii, TsN=C=O (1 equiv.), toluene, reflux, 2 days



Scheme 2 *Reagents and conditions*: i, cyclopentadiene (5 equiv.), Lewis acid, toluene, −78 °C

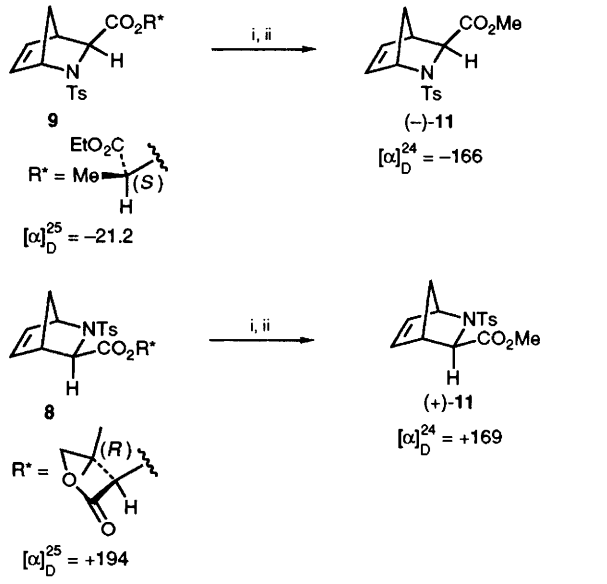
menthyl esters, which was disclosed during the course of our studies, we selected as source of the imines the glyoxylate ester derivatives of ethyl (*S*)-lactate and (*R*)-pantolactone which in the acrylate series have shown the capacity to coordinate with various Lewis acid derivatives to produce highly diastereoselective cycloaddition reactions.[14–17]

The general scheme for the preparation of the ethyl (*S*)-lactate **3** and (*R*)-pantolactone glyoxylate esters **4** is outlined in Scheme 1. Ozonolysis[18,19] of the fumarate esters **1** and **2**, respectively, gave the corresponding polymeric products which were thermally cracked to the glyoxylates by short path distillation. These were then converted in *ca.* 70–80% yield into the imino esters **5** and **6** by reaction with toluene-*p*-sulfonyl isocyanate.[11]

Cycloadditions of the imines with cyclopentadiene were studied under a range of conditions, firstly in toluene and other solvents at room temperature, and subsequently in the presence of a variety of Lewis acid catalysts (Scheme 2). In all cases only the *exo* diastereoisomers **7**, **8** and **9**, **10** (simple diastereoselectivity) were obtained, as evidenced by the absence of coupling between the 3- and 4-H protons and the presence of an NOE between 3- and 5-H in the ^1H NMR spectra.†

The induced selectivity in the uncatalysed reactions was an unremarkable 65 : 35 (for the ratio of adducts **9** : **7** and **8** : **10**), and this ratio could be reversed by switching to more polar solvents. These results parallel the experience with the corresponding acrylate ester derivatives of ethyl (*S*)-lactate

† All new compounds exhibited spectroscopic and combustion/high resolution mass spectrometric data in accord with the assigned structure.



Scheme 3 *Reagents*: i, LiOH, tetrahydrofuran–water; ii, diazomethane, diethyl ether–methanol; [yield: (−)-**11**, 70%; (+)-**11**, 77%]

and (*R*)-pantolactone in thermal cycloaddition reactions with cyclopentadiene.[14] The assignment of configuration to the four diastereoisomers follows from the X-ray crystal structure of the isomer **9** (see below). The modest diastereoselectivity of the uncatalysed reaction is in accord with our previous observations[19a] and those of Prato using the 8-phenylmenthyl analogues of the *N*-toluene-*p*-sulfonyl imino esters **5** and **6**.[13]

A variety of solvents were examined; toluene was found to be the best. It was considered that chelation of a Lewis acid to the imines could improve the conformational preference and simultaneously favour attack of the diene on one face. Accordingly Lewis acids in dichloromethane and toluene were studied. Strong Lewis acids such as $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}OEt_2$ caused decomposition, whereas $Ti(OPr^i)_4$ was too weak. Better induced selectivities (diastereoisomeric ratio between 64 : 36 and 85 : 15) were obtained with weaker Lewis acids such as $Al(OEt)_3$, $MgBr_2$, $ZnCl_2$, Me_2AlCl, Bu^i_2AlCl and Et_2AlCl. The best result was obtained using 0.1–0.3 equivalents of Et_2AlCl in toluene at −78 °C; for the lactate adducts the optimum ratio **7** : **9** was 12 : 88 (50–60% yield based on the glyoxylate **5**, 0.1 equiv. of Lewis acid), while for the pantolactone adducts the ratio **8** : **10** was 85 : 15 (50–60% based on **6**, 0.3 equiv. of Lewis acid). The adducts **8** and **10** were not equilibrated in the presence of Et_2AlCl. In each case the diastereoisomeric ratio could be further improved (>95 : 5) by recrystallisation.

The absolute configuration of the adduct **9** from the lactate-derived imine was determined by X-ray crystallographic analysis (Fig. 1).‡ Chemical correlation of this adduct

‡ The adduct **9** was recrystallised from ethyl acetate as colourless plates, m.p. 90–91 °C and a suitable single crystal was used in the X-ray analysis. *Crystal data*: $C_{19}H_{23}NO_6S$, M = 393.4, orthorhombic, space group, $P2_12_12_1$, a = 6.9131(11), b = 16.136(2), c = 17.319(3) Å, U = 1931.9(5) Å^3, D_c = 1.353 Mg m^{-3}, Z = 4, $F(000)$ = 832, λ(Mo-Kα) 0.71073 Å, μ(Mo-Kα) = 0.193 mm^{-1}. 1515 Intensity data ($2\theta_{max}$ = 45°) were recorded on a Siemens R3m/V diffractometer, and averaged to give 1453 unique observed reflections [$F > 4(\sigma)F$] which were used to solve the structure by direct methods, and to refine it to R = 0.044 (R' = 0.059) by full-matrix least-squares analysis (all non-hydrogen atoms anisotropic). Hydrogen atoms were placed in idealised positions and constrained to ride on the relevant C atom. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

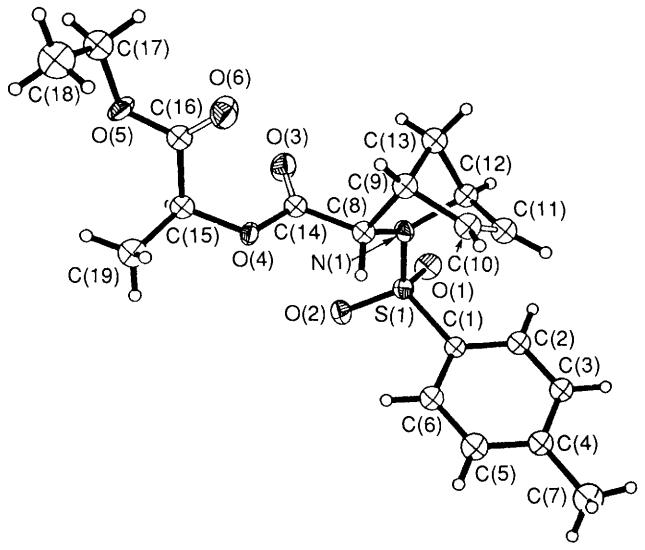


Fig. 1 The molecular structure of the adduct **9** including the atom numbering scheme adopted. Bond lengths (Å): S(1)–O(1) 1.434(3), S(1)–N(1) 1.628(4), O(3)–C(14) 1.195(5), O(4)–C(15) 1.434(5), O(5)–C(17) 1.457(6), N(1)–C(8) 1.473(5), C(1)–C(2) 1.391(6), C(2)–C(3) 1.393(6), C(4)–C(5) 1.397(7), C(5)–C(6) 1.385(6), C(8)–C(14) 1.517(6), C(9)–C(13) 1.532(6), C(11)–C(12) 1.529(6), C(15)–C(16) 1.514(6), C(17)–C(18) 1.494(7), S(1)–O(2) 1.433(3), S(1)–C(1) 1.764(4), O(4)–C(14) 1.352(5), O(5)–C(16) 1.330(5), O(6)–C(16) 1.205(6), N(1)–C(12) 1.518(6), C(1)–C(6) 1.394(6), C(3)–C(4) 1.386(7), C(4)–C(7) 1.516(7), C(8)–C(9) 1.565(6), C(9)–C(10) 1.509(6), C(10)–C(11) 1.311(6), C(12)–C(13) 1.529(6), C(15)–C(19) 1.518(7). Bond Angles (°): O(1)–S(1)–O(2) 121.0(2), O(2)–S(1)–N(1) 105.1(2), O(2)–S(1)–C(1) 108.3(2), C(14)–O(4)–C(15) 115.9(3), S(1)–N(1)–C(8) 119.9(3), C(8)–N(1)–C(12) 107.4(3), S(1)–C(1)–C(6) 119.5(3), C(1)–C(2)–C(3) 119.3(4), C(3)–C(4)–C(5) 119.2(4), C(5)–C(4)–C(7) 120.4(4), C(1)–C(6)–C(5) 118.8(4), N(1)–C(8)–C(14) 112.1(3), C(8)–C(9)–C(10) 104.5(4), C(10)–C(9)–C(13) 100.7(4), C(10)–C(11)–C(12) 107.2(4), N(1)–C(12)–C(13) 96.4(3), C(9)–C(13)–C(12) 93.7(4), O(3)–C(14)–C(8) 126.5(4), O(4)–C(15)–C(16) 109.8(4), C(16)–C(15)–C(19) 110.1(4), O(5)–C(16)–C(15) 109.5(4), O(5)–C(17)–C(18) 110.2(4), O(1)–S(1)–N(1) 106.4(2), O(1)–S(1)–C(1) 107.3(2), N(1)–S(1)–C(1) 108.1(2), C(16)–O(5)–C(17) 117.9(4), S(1)–N(1)–C(12) 122.4(3), S(1)–C(1)–C(2) 119.5(3), C(2)–C(1)–C(6) 120.9(4), C(2)–C(3)–C(4) 120.6(4), C(3)–C(4)–C(7) 120.3(4), C(4)–C(5)–C(6) 121.1(4), N(1)–C(8)–C(9) 101.0(3), C(9)–C(8)–C(14) 111.6(4), C(8)–C(9)–C(13) 100.2(3), C(9)–C(10)–C(11) 108.1(4), N(1)–C(12)–C(11) 107.8(4), C(11)–C(12)–C(13) 100.0(4), O(3)–C(14)–O(4) 124.2(4), O(4)–C(14)–C(8) 109.3(3), O(4)–C(15)–C(19) 107.5(4), O(5)–C(16)–O(6) 125.6(4), O(6)–C(16)–C(15) 124.9(4).

was achieved by saponification and esterification to the ester (−)-**11** whose specific rotation was, within experimental error, equal to that of the ester (+)-**11** obtained by similar conversion of the major adduct **8** derived from the pantolactone imino ester (Scheme 3). Thus the steric course corresponds to that observed for complexes of the acrylate lactate and pantolactone esters with monodentate Lewis acids.[14]

According to the current model[17] to rationalise Diels–Alder reactions of the acrylate of ethyl (*S*)-lactate, (*i*) the conformation of the R*OCO fragment is as shown in Fig. 2(*a*); (*ii*) the complex with monodentate Lewis acids adopts the s-*trans* conformation; (*iii*) approach of the diene at the less hindered face results in *Re* attack.

As stated above the imine **5** shows the same steric course as the corresponding acrylate, although this is *Si* attack according to the Cahn–Ingold–Prelog rules [Fig. 2(*b*)]. Further work on the scope of these reactions is in hand.

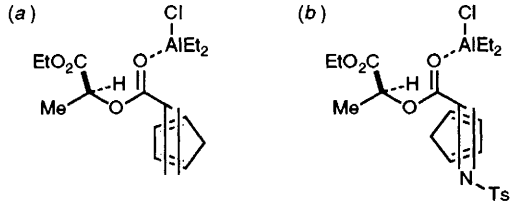


Fig. 2

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