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Enhanced Discrimination by Aza Dienophiles over their Olefinic Counterparts for the Diastereotopic Faces of Methyl (*E*,*E*)-5-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)penta-2,4-dienoate

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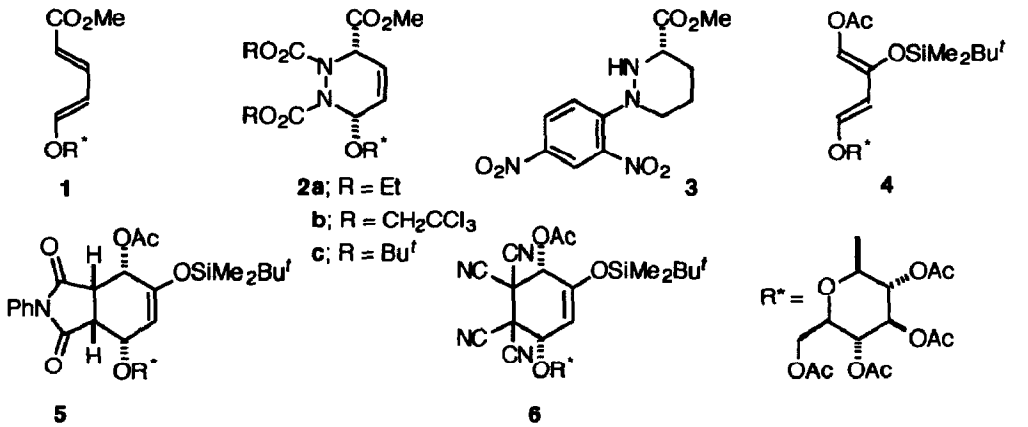
Abstract: The title diene displays a notably higher diastereofacial selectivity towards 4-phenyl-1,2,4-triazoline-3,5-dione, pyridazine-3,6-dione and phthalazine-1,4-dione than toward *N*-phenylmaleimide, 1,4-benzoquinone and 1,4 naphthoquinone.

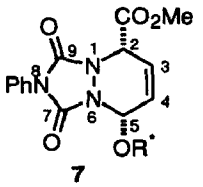
Recently, we prepared the diene **1** and showed that it reacted with diethyl, bis(2,2,2-trichloroethyl) and di(*tert*-butyl) azadicarboxylates to give the cycloadducts **2a–c** in an essentially diastereopure state.[1] Whilst the absolute stereochemistry of the products—established by the conversion of the cycloadduct **2c** into compound **3**—was in accord with our expectations,[2] the high degree of stereoselectivity was a surprise. For example, in earlier work[3] we noted that the diene **4** afforded mixtures of cycloadducts with *N*-phenylmaleimide (89:11) and tetracyanoethylene (71:29) in benzene at ambient temperature, the major products being assigned the stereostructures **5** and **6**. We now report that cyclic aza dienophiles show a notably higher degree of stereodiscrimination towards the diene **1** and two relatives than their olefinic counterparts.



The diene **1** reacted with 4-phenyl-1,2,4-triazoline-3,5-dione[4] [generated *in situ*[5] from 4-phenylurazole (1.1 mol equiv.) by oxidation with $Pb(OAc)_4$ in a 3:1 mixture of CH_2Cl_2 and HOAc] to give the cycloadduct **7** as a single diastereomer according to 300 MHz ^1H NMR spectroscopy; following crystallisation, compound **7**,[6]

m.p. 151–152 °C, $[\alpha]_D$ +13 (0.5% in CH_2Cl_2), was isolated in 70% yield. A similar outcome resulted when the reaction was conducted using the purified aza dienophile in dichloromethane and in toluene. To induce the cycloaddition of the diene **1** with *N*-phenylmaleimide in an effective manner, it was necessary to use an excess of the dienophile (~3 mol equiv.) and to heat the mixture (boiling PhMe, 3 days). Under these conditions, a 75:25 mixture of the cycloadducts **8** and **9** resulted, from which the major cycloadduct **8**,[7] m.p. 188–190 °C, $[\alpha]_D$ –28 (0.5% in CH_2Cl_2), was isolated in 60% yield after crystallisation. Subjection of the mother liquor to silica-gel chromatography (to remove *N*-phenylmaleimide) and semi-preparative HPLC provided the minor cycloadduct **9**,[8] m.p. 172–174 °C, $[\alpha]_D$ –40 (0.5% in CH_2Cl_2), in 6% yield after crystallisation.

The diene **1** reacted with pyridazine-3,6-dione[9] [generated *in situ*[10] from 3,6-dihydroxypyridazine (2 mol equiv.) by oxidation with $Pb(OAc)_4$ in a 3:1 mixture of CH_2Cl_2 and HOAc at ~40 °C] to give, after chromatography, the cycloadduct **10**, $[\alpha]_D$ –23 (0.7% in CH_2Cl_2), as an amorphous solid in 73% yield; there was no evidence for a diastereomeric cycloadduct in the crude or the chromatographed product. An 85:15 mixture of the cycloadducts **11** and **12** emerged from the reaction of the diene **1** with 1,4-benzoquinone (1 mol equiv.) in boiling toluene (4 days); crystallisation provided the major cycloadduct **11**, m.p. 201–203 °C, $[\alpha]_D$ +132 (0.5% in CH_2Cl_2), in 58% yield.



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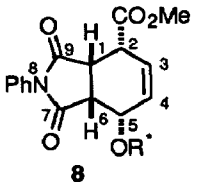

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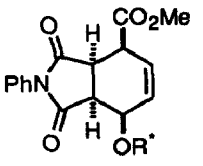

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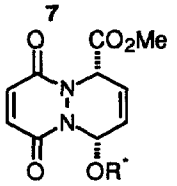

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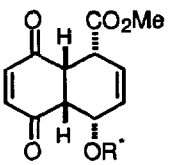

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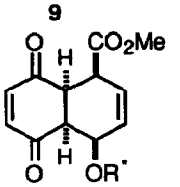

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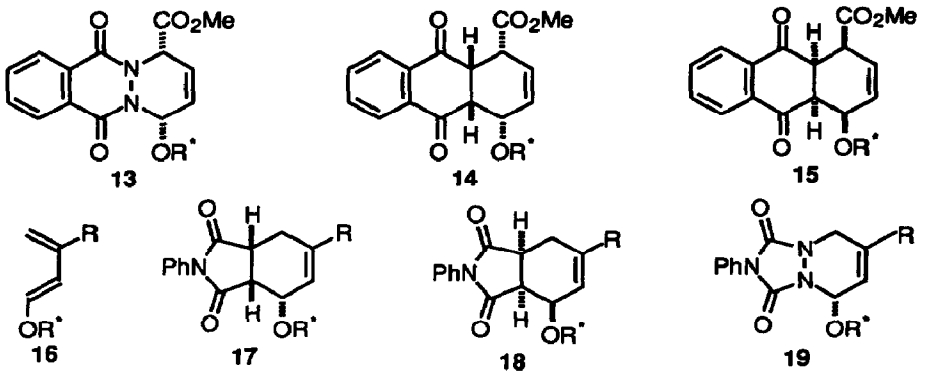
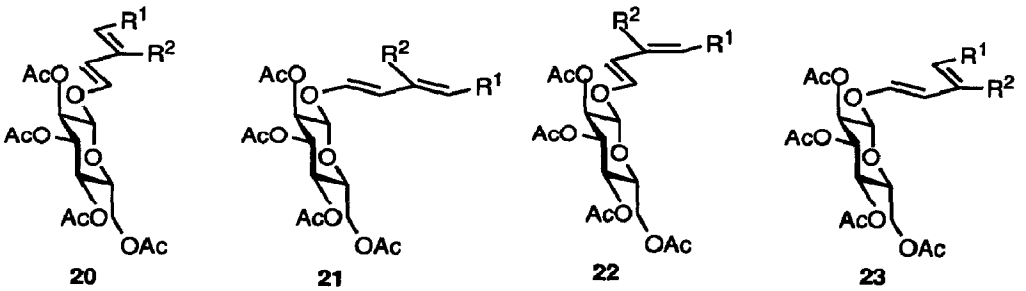
A single cycloadduct, m.p. 167–169 °C, $[\alpha]_D$ +25 (1% in CH_2Cl_2), formulated as compound **13** and isolated in 77% yield after crystallisation, was produced in the reaction of the diene **1** with phthalazine-1,4-dione[9] [generated *in situ*[10,11] by oxidation of phthalhydrazide (1.1 mol equiv.) with $Pb(OAc)_4$ in a 10:1 mixture of CH_2Cl_2 and HOAc]. By contrast, an 86:14 mixture of the cycloadducts **14** and **15** resulted when the diene **1** was heated with 1,4-naphthoquinone (5 mol equiv.) in boiling toluene (12 days). Crystallisation provided the major cycloadduct **14**, m.p. 106–108 °C, $[\alpha]_D$ +118 (0.5% in CH_2Cl_2), in 34% yield.

Earlier, it was reported[3] that the diene **16a** reacted with *N*-phenylmaleimide in benzene at ambient temperature to give an 86:14 mixture of the cycloadducts **17a** and **18a**. An essentially identical ratio of the cycloadducts **17b** and **18b** was produced in the corresponding reaction of the diene **16b**. In the present study, the dienes **16a** and **16b** were found to afford single cycloadducts with 4-phenyl-1,2,4-triazaline-3,5-dione. From the former reaction, in which the aza dienophile was generated *in situ* by oxidation of 4-phenylurazole as described earlier, compound **19a**, m.p. 151–153 °C, $[\alpha]_D$ +154 (0.1% in CH_2Cl_2), was isolated in 71% yield after crystallisation. From the latter reaction, using the purified aza dienophile in dichloromethane, the cycloadduct **19b**, m.p. 142–143 °C, $[\alpha]_D$ +103 (0.3% in CH_2Cl_2), was obtained in 45% yield after crystallisation.



The afore-cited results are of both synthetic and mechanistic note. In the former context, the cycloadducts **7**, **10** and **13** are of interest as precursors of unusual amino acids; similarly, the cycloadducts **8**, **11** and **14**, incorporating four defined stereogenic centres, are of potential value in the elaboration of natural products and their relatives. In a mechanistic context, the enhanced ability of aza dienophiles compared with their olefinic counterparts to discriminate between diastereotopically related diene faces appears to be novel.[12] We believe these findings provide a clue regarding the origin of the diastereoselection process. Earlier, we established[3] that dienes such as **4**, **16a** and **16b** existed in deuteriochloroform solution as mixtures of conformers of types **20** and **21** with the former conformers being preferred. We proposed that the major cycloadducts arose by *endo* attack of cyclic dienophiles such as *N*-phenylmaleimide and 1,4-benzoquinone to the less-hindered 'top' faces of conformers of type **22** of the dienes. The minor cycloadducts were considered to arise by *endo* attack of the dienophiles to either the more-hindered 'bottom' face of conformers of type **22** or the 'top' face of conformers of type **23**. On the assumption that aza dienophiles react in a manner analogous to their olefinic counterparts but require 'more compact' transition states,[13] we favour the former pathway.



Acknowledgements

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6 For **7**: δ (300 MHz; $CDCl_3$) 1.99, 2.01, 2.02 and 2.03 (each 3 H, s, 4 x $MeCO_2$), 3.82–3.87 (1 H, m, 5'-H), 3.87 (3 H, s, MeO), 4.06 and 4.25 [each 1 H, dd (*J* 12.5 and 2 Hz) and dd (*J* 12.5 and 4 Hz), 6'-H_2], 4.96–5.30 (5 H, m, 2-, 1'-, 2'-, 3'- and 4'-H), 6.07–6.13 (2 H, m, 3- or 4-H and 5-H), 6.20–6.24 (1 H, m, 4- or 3-H) and 7.39–7.55 (5 H, m, C_6H_5).

7 For **8**: δ (300 MHz; $CDCl_3$) 1.79, 1.96, 2.01 and 2.10 (each 3 H, s, 4 x $MeCO_2$), 3.45–3.61 (3 H, m, 1-, 2- and 6-H), 3.68–3.76 (1 H, m, 5'-H), 3.76 (3 H, s, MeO), 4.15 and 4.25 [each 1 H, dd, (*J* 12 and 2.5 Hz) and dd (*J* 12 and 5 Hz), 6'-H_2], 4.64–4.69 (1 H, m, 5-H), 4.88–4.94 (2 H, m, 1'- and 2'-H), 5.07 (1 H, t, *J* 10 Hz, 4'-H), 5.16–5.23 (1 H, m, 3'-H), 6.15 (1 H, ddd, *J* 10, 4.5 and 2 Hz, 3- or 4-H), 6.42 (1 H, ddd, *J* 10, 5 and 1.5 Hz, 4- or 3-H) and 7.26–7.45 (5 H, m, C_6H_5).

8 For **9**: δ (300 MHz; $CDCl_3$) 2.00, 2.01, 2.03 and 2.09 (each 3 H, s, 4 x $MeCO_2$), 3.32–3.36 (1 H, m, 2-H), 3.60 (1 H, dd, *J* 9 and 7.5 Hz, 1- or 6-H), 3.68–3.73 (1 H, m, 5'-H), 3.75 (1 H, dd *J* 9 and 6.5 Hz, 6- or 1-H), 3.81 (3 H, s, MeO), 4.18 and 4.27 [each 1 H, dd (*J* 12.5 and 4.5 Hz) and dd (*J* 12.5 and 2.5 Hz), 6'-H_2], 4.61–4.65 (1 H, m, 5-H), 4.74 (1 H, d, *J* 7.5 Hz, 1'-H), 5.07–5.12 (1 H, m, 2'-H), 5.14 (1 H, t, *J* 9 Hz, 4'-H), 5.21 (1 H, t, *J* 9 Hz, 3'-H), 6.07 (1 H, dt, *J* 10, 3 and 3 Hz, 3- or 4-H), 6.47 (1 H, ddd, *J* 10, 4 and 2 Hz, 4- or 3-H) and 7.21–7.45 (5 H, m, C_6H_5).

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12 The greater reactivity of aza dienophiles compared with their olefinic counterparts is well established; see: Moody, C. J. *Adv. Heterocyclic Chem.* **1982**, *30*, 1–45.

13 Since the C–N bond (147 pm) is shorter than the C–C bond (154 pm), a closer approach of the aza dienophile compared with its olefinic counterpart is expected at the transition state of the reaction. For calculations on the transition-state structures involved in the reaction of diazene (diimide) and butadiene, see: Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 3673–3676; McCarrick, M. A.; Wu, Y.–D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330–3343.

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