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Regio- and Stereo-selective Intermolecular Interceptions of a Conjugated *N*-Acylhydrazonium Ion

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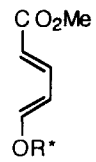
Abstract: A notable stereoinduction accompanies the 1,2-addition of nucleophiles to a cyclic *N*-acyl-hydrazonium ion.

Recently, we noted that the diene **1** showed an excellent diastereofacial reactivity towards a range of acyclic[1] and cyclic aza dienophiles.[2] For example, it reacted with 4-phenyl-1,2,4-triazoline-3,5-dione to give the cycloadduct **2**, isolated in 70% yield after crystallisation.[2] As part of an exploration of the synthetic utility of such cycloadducts, we sought to generate the conjugated *N*-acylhydrazonium ion[3] **3** from the cycloadduct **2** and to define its reactivity. We hoped that the intermediate **3** would undergo interception by nucleophiles in a regio- and stereo-selective manner,[4] in preference to experiencing loss of a proton (to give **4**). We now report findings that justify this expectation.



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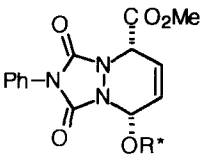

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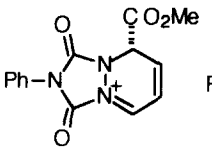

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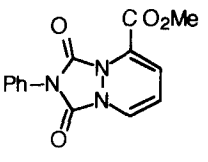

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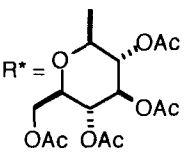
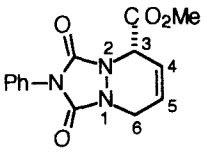


When treated overnight with triethylsilane and trifluoroacetic acid[5] in dichloromethane, the cycloadduct **2** was transformed into a 1:1 mixture of compound **5** and the tetra-acetate **6**. The mixture was stirred in methanol containing *p*-toluenesulfonic acid (to convert **6** into D-glucose) and the product was partitioned between dichloromethane and water. Work-up of the organic phase gave compound **5**[6] (67% yield after crystallisation[7]), m.p. 105–107 °C, $[\alpha]_D$ –398 (*c* 0.2, CH_2Cl_2). ^1H NMR Spectroscopy left little doubt that the product was represented by the structure indicated rather than its regioisomer **7**. Evidently, assuming that a kinetically controlled reaction is involved, the conjugated *N*-acylhydrazonium ion **3** undergoes a highly regioselective reduction.



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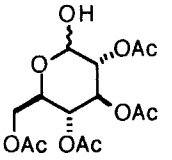

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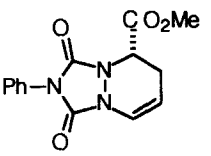


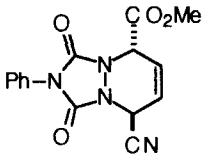
7

Compound **2** underwent reaction with trimethylsilyl cyanide and $BF_3.OEt_2$[8] in dichloromethane at 0 °C (5 h) to give a mixture of the nitrile **8** and the tetra-acetate **6**. After treatment of the mixture with methanol containing *p*-toluenesulfonic acid, the nitrile **8**[9] (63% yield after crystallisation[7]), m.p. 166–168 °C, $[\alpha]_D$ –536 (*c* 0.28, CH_2Cl_2), was isolated. That the nitrile **8** possessed the *trans*-configuration, rather than the *cis*-configuration, was deduced from its reaction with hot methanolic hydrochloric acid. The diester, which could only be obtained (in low yield) when a small-scale reaction was employed, was optically active {$[\alpha]_D$ –468 (*c* 0.07, CH_2Cl_2)}, indicating that it possessed the *trans*-geometry **9**.[10]

In dichloromethane containing allyltrimethylsilane and trifluoroacetic acid,[11] compound **2** was transformed overnight into mainly a 1:1 mixture of the allyl derivative **10** and the tetra-acetate **6**. After the usual work-up with acidic methanol and subjection of the product to silica-gel chromatography, the allyl derivative **10**[12] was obtained in 66% yield (47% after crystallisation), m.p. 132–133 °C, $[\alpha]_D$ –489 (*c* 0.44, CH_2Cl_2). Chromatography was unnecessary when $BF_3.OEt_2$ was used in place of trifluoroacetic acid in the allylation reaction. Methanolysis (MeOH, *p*-TsOH) of the product then gave compound **10** in 88% yield (56% after crystallisation).[13] The *trans*-geometry of compound **10** was inferred by analogy with the configuration of the nitrile **8**, an inference that was supported by the large negative optical rotations of both compounds {by contrast, the cycloadduct **2** showed $[\alpha]_D$ +13 (*c* 0.5, CH_2Cl_2)[2]}.

In the presence of methanol and *p*-toluenesulfonic acid, the cycloadduct **2** was converted overnight into the methoxy derivative **11**[14] (64% yield after crystallisation[15]), m.p. 155–157 °C, $[\alpha]_D$ –399 (*c* 0.21, CH_2Cl_2). Again, the *trans*-configuration of compound **11** was inferred by analogy with that of the nitrile **8** and supported by the large negative optical rotation of the compound.

That the integrity of the stereogenic centre adjacent to the methoxycarbonyl group had not been compromised in either the **2**→**5** or the **2**→**11** transformation was suggested by the finding that compound **11** underwent reduction (Et_3SiH, CF_3CO_2H, CH_2Cl_2) to give compound **5** (79% yield after crystallisation), m.p. 104–106 °C, $[\alpha]_D$ –389 (*c* 0.6, CH_2Cl_2).



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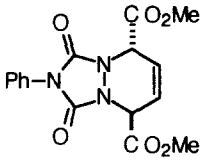

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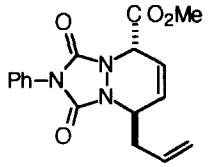

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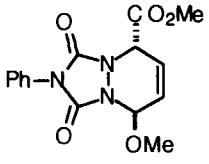
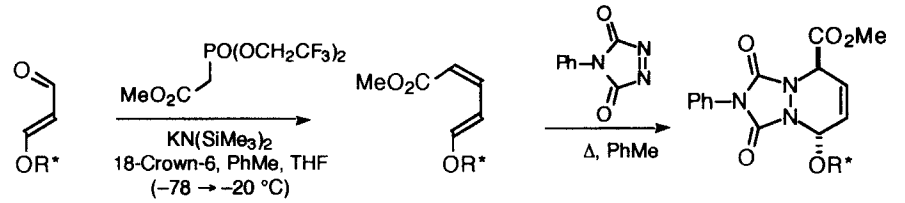


11

In principle, the inversion of configuration observed in the formation of compounds **8**, **10** and **11** from the precursor **2** might be attributed to an S_N2-like reaction pathway, rather than an ionisation process leading to

the species **3**. To shed some light on the situation, it was decided to prepare the *trans*-cycloadduct **14** and to examine the stereochemical outcome of analogous reactions.

The synthesis of the *trans*-cycloadduct **14** from the propenal **12**[16] is outlined in Scheme 1. Thus, the propenal **12** underwent a highly (*Z*)-selective olefination using the Still protocol[17] to give a 94:6 mixture of the dienes **13** and **1**. The diene **13** (36% yield after chromatography and crystallisation), m.p. 141–143 °C, $[\alpha]_D$ –12 (*c* 0.5, CH_2Cl_2), reacted with 4-phenyl-1,2,4-triazoline-3,5-dione in boiling toluene to give the *trans*-cycloadduct **14**[18] (53% yield after crystallisation), m.p. 197–199 °C, $[\alpha]_D$ +210 (*c* 0.3, CH_2Cl_2).



12 (36%) **13** (53%) **14**

Scheme 1

The *trans*-cycloadduct **14** underwent reduction (CF_3CO_2H, Et_3SiH, CH_2Cl_2) to give compound *enant*-**5** (50% yield after crystallisation[7]), m.p. 109–111 °C, $[\alpha]_D$ +382 (*c* 0.3, CH_2Cl_2), allylation (CF_3CO_2H, CH_2:$CHCH_2SiMe_3$, CH_2Cl_2) to give compound *enant*-**10** (54% yield after crystallisation[7]), m.p. 135–137 °C, $[\alpha]_D$ +482 (*c* 0.47, CH_2Cl_2), and methanolysis (MeOH, *p*-TsOH) to give compound *enant*-**11** (53% yield after crystallisation[15]), m.p. 153–155 °C, $[\alpha]_D$ +384 (*c* 0.3, CH_2Cl_2).

Since the formation of compounds **8**, **10** and **11** from the precursor **2** had occurred with an inversion of configuration at the reaction centre whereas the formation of compounds *enant*-**10** and *enant*-**11** from the precursor **14** had taken place with a retention of configuration at the reaction centre, we consider that a common ionisation process is implicated in both series of reactions. Clearly, the conjugated *N*-acylhydrazonium ions **3** and *enant*-**3** intervene in the reactions emanating from the cycloadducts **2** and **14**, respectively. Certainly in the case of the *C*-nucleophiles and probably in the case of *H*- and *O*-nucleophiles, there is a strong kinetic preference for attack of the conjugated *N*-acylhydrazonium ion to occur in a 1,2- rather than a 1,4-manner and *anti* with respect to the methoxycarbonyl group.

The aforecited results are of both synthetic and mechanistic interest. In the former context, they illustrate a simple means of effecting the reductive removal or stereoselective replacement of the sugar auxiliary from the cycloadducts **2** and **14**. As well as providing access to enantiomerically related products, the technology offers considerable potential for the synthesis of novel α-amino acids. In a mechanistic connection, the results reveal that the conjugated *N*-acylhydrazonium ion **3** displays a high degree of regio- and stereoselectivity with respect to nucleophilic attack. The notable 1,4-stereoinduction is surprising and its origin remains to be determined.

Acknowledgements

We thank the SERC for a CASE studentship (to P. M. C.) and a referee for constructive comments.

References and notes

1. Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179–1180.

2. Aspinall, I. H.; Cowley, P. M.; Stoodley, R. J.; Mitchell, G. *Tetrahedron Lett.* **1994**, *35*, 3397–3400.

3. *N*-Acylhydrazonium ions have been the subject of only a few studies (see: Rutjes, P. J. T.; Teerhuis, N. M.; Hiemstra, H.; Speckamp, W. N. *Tetahedron*, **1993**, *49*, 8605–8628 and references therein). By contrast, *N*-acyliminium ions have been extensively investigated (see: Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford; vol. 2, 1991, pp. 1047–1082; Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416; Shono, T. *Tetrahedron* **1984**, *40*, 811–850; Zaugg, H. E. *Synthesis* **1984**, 85–110 and 181–212; Zaugg, H. E. *Synthesis* **1970**, 49–73; Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52–269).

4. For related reactions involving conjugated *N*-acyliminium ions, see: Comins, D. L.; Weglary, M. A.; *J. Org. Chem.* **1991**, *56*, 2506–2512; Natsume, M.; Utsunomiya, I.; Yamaguchi, K.; Sakai, S. *Tetrahedron* **1985**, *41*, 2115–2123; Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1984**, *49*, 1674–1676.

5. Auerbach, J.; Zamore, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725–726.

6. For compound **5**: δ (300 MHz; $CDCl_3$) 3.80 (3 H, s, MeO), 4.04 and 4.42 [each 1 H, dm (separation 18 Hz), 6-H_2], 5.12–5.14 (1 H, m, 3-H), 6.07–6.16 (2 H, m, 4- and 5-H) and 7.36–7.56 (5 H, m, Ph).

7. The yield of the crude material, which was virtually pure by NMR spectroscopy, was near quantitative.

8. Asher, V.; Becu, C.; Anteunis, M. J. O.; Callens, R. *Tetrahedron Lett.* **1981**, *22*, 141–144.

9. For compound **8**: δ (300 MHz; $CDCl_3$) 3.82 (3 H, s, MeO), 5.21–5.24 and 5.28–5.30 (each 1 H, m, 3- and 6-H), 6.14 and 6.43 [each 1 H, ddd (*J* 10, 5 and 2 Hz), 4- and 5-H] and 7.40–7.57 (5 H, m, Ph).

10. For compound **9**: δ (300 MHz; $CDCl_3$) 3.81 (6 H, s, 2 x MeO_2C), 5.15 (2 H, d, *J* 3 Hz, 3- and 6-H), 6.24 (2 H, d, *J* 3 Hz, 4- and 5-H) and 7.37–7.61 (5 H, m, Ph).

11. Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1981**, *22*, 1567–1570.

12. For compound **10**: δ (300 MHz; $CDCl_3$) 2.61 (2 H, br t, separation 7 Hz, $CH_2CH{:}CH_2$), 3.79 (3 H, s, MeO_2C), 4.62–4.67 (1 H, m, 6-H), 5.12–5.20 (3 H, m, $CH{:}CH_2$ and 3-H), 5.74–5.88 (1 H, m, $CH{:}CH_2$), 6.06–6.15 (2 H, m, 4- and 5-H) and 7.35–7.54 (5 H, m, Ph).

13. We thank Dr. C. M. Raynor for performing this experiment.

14. For compound **11**: δ (300 MHz; $CDCl_3$) 3.64 (3 H, s, MeO), 3.79 (3 H, s, MeO_2C), 5.18 (1 H, dd, *J* 5 and 2 Hz, 3-H), 5.64 (1 H, br d, *J* 4.5 Hz, 6-H), 6.12 (1 H, ddd, *J* 10, 4.5 and 2 Hz, 5-H), 6.27 (1 H, ddd, *J* 10, 5 and 1 Hz, 4-H) and 7.37–7.57 (5 H, m, Ph).

15. The yield of the crude material, which contained *ca.* 10% of a contaminant (possibly, a regioisomer), was almost quantitative.

16. Gupta, R. C.; Larsen, D. S.; Stoodley, R. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 739–749; Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001–1010.

17. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

18. For compound **14**: δ (300 MHz; $CDCl_3$) 1.87, 1.98, 2.02 and 2.07 (each 3 H, s, 4 x $MeCO_2$), 3.73–3.79 (1 H, m, 5'-H), 3.79 (3 H, s, MeO), 4.15 and 4.25 [each 1 H, dd (*J* 12.5 and 2.5 Hz) and dd (*J* 12.5 and 4.5 Hz), 6'-H_2], 4.95 (1 H, dd, *J* 9.5 and 8 Hz, 2'-H), 5.07 (1 H, t, *J* 10 Hz, 4'-H), 5.16–5.24 (3 H, m, 1'-, 3'- and 3-H), 5.95 (1 H, br d, separation 4.5 Hz, 6-H), 6.08 (1 H, ddd, *J* 10, 4.5 and 2 Hz, 5-H), 6.30 (1 H, ddd, *J* 10, 5.5 and 1 Hz, 4-H) and 7.38–7.57 (5 H, m, Ph).

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