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Intramolecular hetero-Diels–Alder reactions of a tethered triene possessing a carboxynitroso dienophilic group

Donald Craig* and Mónica Yáñez López

Centre for Chemical Synthesis, Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW 7 2AY, UK

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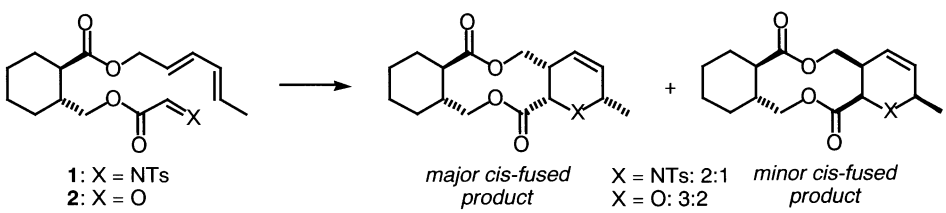
Abstract—Intramolecular hetero-Diels–Alder reaction of a tethered alkoxycarbonylnitroso-containing triene proceeds with complete stereoselectivity. Cleavage of the tethering group and further synthetic elaboration of the cycloadduct is described.

Previous studies from this laboratory have looked at the intramolecular Diels–Alder (IMDA) reactions of trienes in which the diene and dienophile are tethered using a temporary covalent linkage. We and others pioneered the use of silaketal tethers,[1] and we introduced tertiary and benzylic ether linkages to serve this purpose.[2] Many of the IMDA reactions were highly stereoselective, and methods for tether cleavage were developed which delivered the overall products of regio- and stereoselective intermolecular [4+2] cycloadditions. More recently, we looked at ester tethers so as to assess whether the normally deleterious effect on IMDA reactivity of this moiety could be overcome by the inclusion of two such groups in a medium-ring linking chain. This hope was realised using chiral diester spacers between the diene and dienophile, which in some cases gave stereoselective cycloadditions, and this chemistry was adapted to include hetero-Diels–Alder reactions (Scheme 1).[3] These findings encouraged us to look for further IMDA substrates of this type, with the goal of identifying systems which would allow the synthesis of a range of nitrogen heterocycles. This letter reports our preliminary results.

We elected to study IMDA reactions of **3** with three major factors influencing our choice. First, we were keen to use 2,4-hexadienyl as the dienophilic grouping, since our previous studies[1,3] had revealed a marked preference for *cis*-fused IMDA products arising from the more favourable 'inside' orientation of the oxygen atom tethering the diene. Secondly, the *trans*-cyclohexane-1,2-dicarboxyl linkage was established as a chiral spacer group which conferred optimum reactivity upon diene–dienophile combinations tethered by it, on account of its unambiguous 1,2-diequatorial conformation. Also, its chiral nature is such that enantiomerically enriched products would be available from optically pure substrates. Finally, alkoxycarbonylnitroso seemed an ideal choice of dienophilic partner, combining ease of accessibility from the hydroxamic acid-like precursor, high reactivity[4] and amenability to a variety of sequences post-cycloaddition. Russell and



Scheme 1.

Keywords: Diels–Alder; intramolecular; nitroso; stereoselective; tether.
* Corresponding author. Fax: +44 20 7594 5868; e-mail: d.craig@ic.ac.uk

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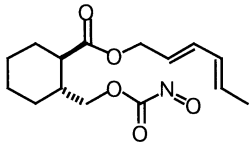
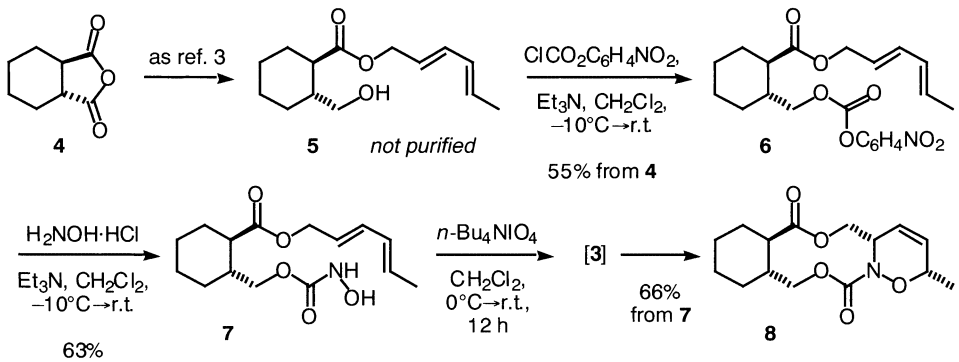
co-workers reported[5] quite recently related IMDA reactions, in which substrates with dienes tethered to an alkoxycarbonylnitroso dienophile were converted into bicyclo[4.3.0] and -[4.4.0] systems. Complete asymmetric induction was observed for the reaction of one of the latter substrates possessing a directing linking-chain stereocentre; this directing group remained in the product post-tether cleavage.



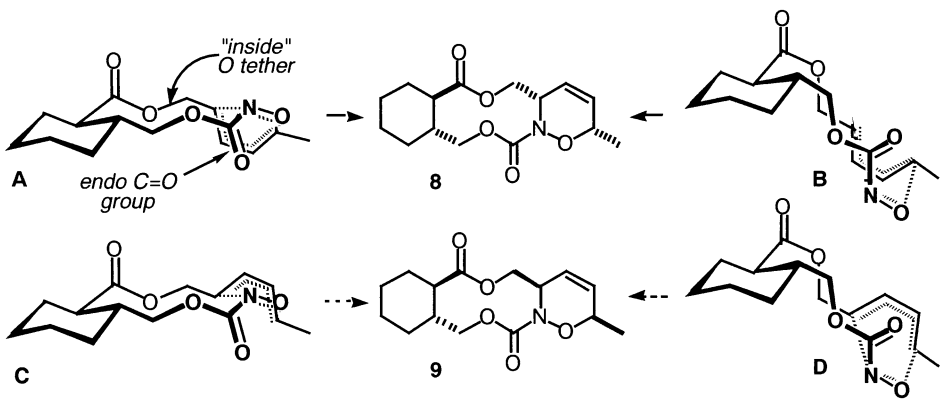
3

The synthesis of the precursor of **3** followed largely the route to the hetero-Diels–Alder substrates established in our earlier work.[3] Thus, dienyl hydroxyester **5** was prepared as before from commercially available[6] racemic anhydride **4** by reaction with sorbyl alcohol and diisopropylamine, followed by trapping with isobutyl chloroformate and removal of ammonium salts by simple filtration; treatment of the filtrate with aqueous $NaBH_4$ gave dienol **5**. Again, problems were encountered because of the tendency of **5** to undergo lactonisation with loss of sorbyl alcohol, and these were circumvented in the present work by reaction of crude **5** directly with 4-nitrophenyl chloroformate and triethylamine, giving **6** in 55% overall yield from **4**.[7] Reaction of **6** with hydroxylamine hydrochloride–triethylamine gave **7** in 63% yield; small quantities of **5** liberated during the reaction could be recycled by further reaction with 4-nitrophenyl chloroformate and triethylamine. Exposure of **7** to the established[4] tetra-*n*-butylammonium periodate[8] conditions at slightly sub-ambient temperatures gave essentially a single product in 66% yield; the structure **8** was assigned unambiguously following X-ray diffraction analysis of a single crystal.[9] The synthesis of **7** and the in situ IMDA reaction of **3** are depicted in Scheme 2.

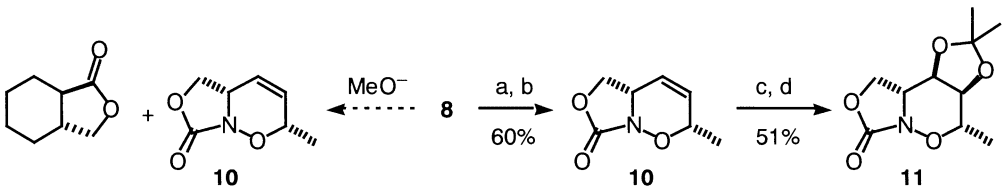
Our previous hetero-IMDA studies[3] had revealed a strong bias towards the formation of *cis*-fused cycloadducts (Scheme 1: **1**: 8:1 *cis*:*trans*; **2**: 5:1 *cis*:*trans*). It was postulated that these arose from reactive conformations having 'inside'-oriented[10] oxygen atoms tethering the diene moiety. We speculate similarly in the present study that **8** arises via the transition-state geometry depicted by structure **A** in Scheme 3. Although conformation **B** would also lead to **8**, it seems unlikely to be significant given the 'outside' nature of the diene oxygen linking atom and the *exo*-configured dienophile carboxyl group. Also worthy of note is the fact that the IMDA reaction of **3** was completely selective, whereas those of substrates **1** and **2** depicted in Scheme 1 gave predominantly *cis*-products, but with low selectivity for the major versus the minor *cis*-fused compounds. For substrate **3**, the transition-state **D** analogous to those leading to the minor *cis*-fused products from **1** and **2** would lead to compound **9**, which was not observed, in spite of its 'inside'-*endo* nature. In the reaction of **3**, the sub-ambient temperature would be expected a priori to



Scheme 2.



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) H_2O_2 (6 equiv.), NaOH (6 equiv.), MeOH, reflux, 6 h; (b) 1,1′-carbonyldiimidazole (2 equiv.), Et_3N (2.2 equiv.), CH_2Cl_2, 0°C→rt, 2 h; (c) OsO_4 (0.15 equiv.), NMO (1.5 equiv.), acetone, rt, 36 h; (d) *p*-TSA (cat.), $Me_2C(OMe)_2$ (solvent), rt, 90 min.

allow maximisation of diastereomeric excess, and we speculate that the non-involvement of conformation **D** is a consequence of its *E*-configured ester linkage and unfavourable steric interactions between the diene/dienophile-containing substituents and the cyclohexane spacer.

The final part of this investigation was directed towards establishing a method for tether cleavage, and the investigation of simple oxidation and protecting group manipulations of the monocyclic products of the cleavage reactions. Initial, unsuccessful attempts involved treatment of **8** with sub-stoichiometric through to excess quantities of NaOMe or $BnN^+Me_3{}^-OMe$, with the intention of catalysing a ring-cleavage–recyclisation reaction sequence resulting in overall fragmentation to give two bicyclic products. It was found subsequently that portionwise addition of H_2O_2 to a basic methanolic solution of **8** effected tether cleavage to give the 3,6-dihydro-2*H*-1,2-oxazine in 72% yield; this was treated with carbonyl diimidazole and triethylamine to provide the cyclic carbamate **10**[5] in 83% yield. Stereoselective dihydroxylation of **10** was accomplished by exposure to OsO_4–*N*-methylmorpholine-*N*-oxide,[11] and the product diol was protected as the acetonide **11** by treatment with 2,2-dimethoxypropane in the presence of acid (Scheme 4).[12]

In summary, we have demonstrated that substrate **3** is readily available from *trans*-1,2-cyclohexanedicarboxylic anhydride and that it enters into a sub-ambient temperature hetero-IMDA reaction with complete stereoselectivity. The facility with which this [4+2] cycloaddition takes place is especially noteworthy given the unusual nature of the ring system being formed, and is testimony to the high reactivity of the alkoxycarbonylnitroso dienophilic group. Elaboration of the product **8** into **11** follows routine synthetic steps, and clearly demonstrates the potential of the tethering strategy for the synthesis of nitrogen heterocycles. We are currently exploring the use in these transformations of alternative, enantiomerically pure substrates having dienophilic groups possessing two heteroatoms, and the results of these investigations will be reported in due course.

Acknowledgements

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7. All yields reported herein refer to isolated, pure materials which had ^1H and ^{13}C NMR, IR and elemental combustion analysis and/or high resolution MS characteristics in accord with the proposed structures.
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9. We thank Professor D. J. Williams and Dr. Andrew J. P. White of this department for this determination. Crystallographic data (excluding structural factors) for **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary data numbers CCDC 169346. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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12. **Preparation of 7**.
To a solution of the carbonate **6** (4.24 g, 9.98 mmol) in CH_2Cl_2 (200 ml) at −10°C under nitrogen was added

hydroxylamine hydrochloride (0.694 g, 9.88 mmol) and triethylamine (2.75 ml, 19.97 mmol) in four portions over 2 h. The mixture was allowed to warm to room temperature and stirred for 20 h. The reaction was quenched with water (150 ml) and the mixture extracted with EtOAc (5×100 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (50% EtOAc–petrol) gave **7** (1.86 g, 63%) as a colourless oil; R_f 0.2 (25% EtOAc–petrol); ν_{max} (film) inter alia 3294, 1727 cm^{-1}; δ_H (300 MHz) 7.31 (1H, br s, NH), 6.25 (1H, dd, *J* 15, 10.5 Hz, diene H-2), 6.03 (1H, dd, *J* 15, 10.5 Hz, diene H-3), 5.75 (1H, m, diene H-4), 5.63 (1H, dt, *J* 15, 6.5 Hz, diene H-1), 4.59 (2H, d, *J* 6.5 Hz, C*H*$_2$CH=CH-), 4.10 (1H, dd, *J* 10, 5 Hz, C*H*HOC(O)NHOH), 4.01 (1H, dd, *J* 10, 5 Hz, CH*H*OC(O)NHOH), 2.46–1.05 (10H, m, $CHCO_2$, NCO_2CH_2CH), ($(CH_2)_4$), overlapping with 1.77 (3H, d, *J* 7 Hz, -CH=CHC*H*$_3$), –O*H* not visible; δ_C (75.5 MHz) 175.5, 159.0, 135.1, 131.6, 130.4, 123.6, 69.3, 65.1, 46.5, 38.5, 29.8, 28.3, 25.1, 25.0, 18.2; *m*/*z* (CI) 315 $[MNH_4]^+$ (found: $[MH]^+$, 298.1501. $C_{15}H_{23}NO_5$ requires $[MH]^+$, 298.1654).

Preparation and in situ IMDA reaction of 3:
To a solution of **7** (0.580 g, 1.9 mmol) in CH_2Cl_2 (27 ml) at 0°C under nitrogen was added tetra-*n*-butylammonium periodate (0.687 g, 2.3 mmol). The mixture was allowed to warm to rt during 1 h and was stirred overnight. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (30 ml) and washed with brine (30 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (5% EtOAc–petrol) gave **8** (0.370 g, 66%) as a colourless solid; R_f 0.4 (15% EtOAc–petrol); ν_{max} (film) inter alia 1737 cm^{-1}; δ_H (400 MHz) 5.87 (1H, dd, *J* 10, 1.5 Hz, C*H*=CH), 5.72 (1H, ddd, *J* 10, 5, 2 Hz, CH=C*H*), 4.85 (1H, ddd, *J* 10, 5, 2.5 Hz, C*H*N(OR)CO_2R′), 4.68 (1H, m, C*H*CH_3), 4.51 (1H, dd, *J* 11, 3 Hz, $CHCO_2$C*H*H), 4.43 (1H, t, *J* 11 Hz, $CHCO_2$CH*H*), 3.90 (1H, t, *J* 11 Hz, NCO_2C*H*H), 3.80 (1H, dd, *J* 11, 3 Hz, NCO_2CH*H*), 2.10–0.84 (10H, m, $CHCO_2$, NCO_2CH_2CH), ($(CH_2)_4$), overlapping with 1.30 (3H, d, *J* 7 Hz, CH_3); δ_C (100.6 MHz) 176.0, 156.3, 133.1, 120.5, 75.5, 70.4, 62.8, 52.7, 47.4, 40.5, 28.3, 27.6, 24.5, 24.7, 24.5, 18.5; *m*/*z* (CI) 313 $[MNH_4]^+$, 296 $[MH]^+$ (found: $[MH]^+$, 296.1501. $C_{15}H_{21}NO_5$ requires $[MH]^+$, 296.1498).