Tetrahedron Letters, Vol.31, No.48, pp 7073-7076, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A TRANSANNULAR π-BOND PAIRING APPROACH TO THE SYNTHESIS OF 1,3-CYCLOPENTADIENE DIESTERS AND MALEIMIDO-OXEPINES AND A REPORT ON THEIR ISOMERISATION.

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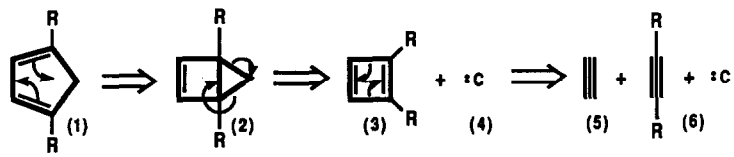
Abstract: Polycyclobutanoid compounds containing an end-fused 3-membered ring are central to the synthesis of the title target molecules: a new mode for their production is presented. Cyclopentadiene 1,3-diester is isolated and its isomerisation studied. Intermediates supporting the oxygen-walk isomerisation of maleimido-oxepines are isolated.

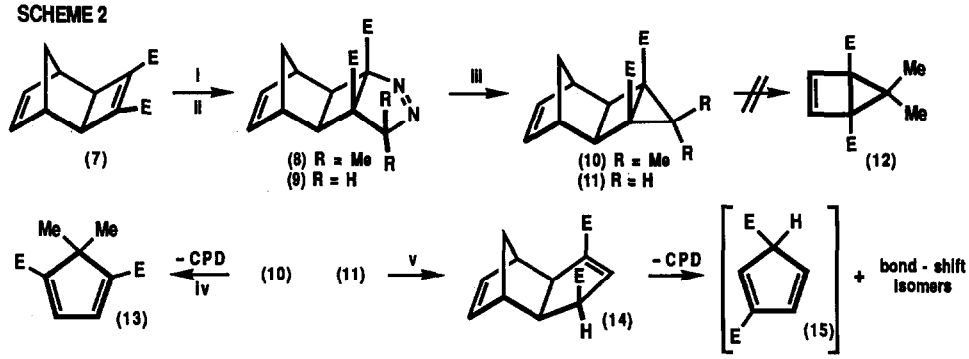
In the accompanying paper[1] we reported on a new algorithm for the retrosynthesis of unsaturated cyclic compounds. This involved transannular pairing of ring π-bonds to form a polycyclobutane which could be split into sets of acetylenic or cyclobutadiene synthons. Transfer reagents, also reported therein, are an important component of this protocol since they provide the reactive synthons in protected form. In this paper we show how this protocol can be applied to the synthesis of cyclic compounds having an odd number of ring atoms using cyclopentenes and oxepines as the illustrative examples and further discuss transfer reagents in this context.

SCHEME 1



Cyclopentadienes were selected as the carbocyclic example since they are important starting materials for the synthesis of natural products and new ways to achieve specific functionalisation in this ring-system should be useful. Application of the transannular pairing algorithm, as delineated in Scheme 1, reveals that 1,3-disubstituted cyclopentadienes should be available from coupling acetylene, a disubstituted acetylene, and a carbene. As noted earlier,[1] a transfer reagent can be used to deliver these two acetylenic synthons via the cyclobutadiene (**3**). The carbocyclic diester(**7**) was selected in this role since it is readily prepared in a reaction which accommodates several other electron-withdrawing substituents in place of the ester group,[2] thus broadening its potential. Compound (**7**) was allowed to react with dimethyl diazomethane, acting as the carbene transfer reagent, thereby producing the 1:1-adduct (**8**) by attack at its under face.[3] Efficient elimination of dinitrogen occurred upon ultraviolet irradiation to produce the cyclopropane (**10**). Heating (**10**) caused loss of cyclopentadiene (CPD) to occur in a retro Diels-Alder reaction and led to the production

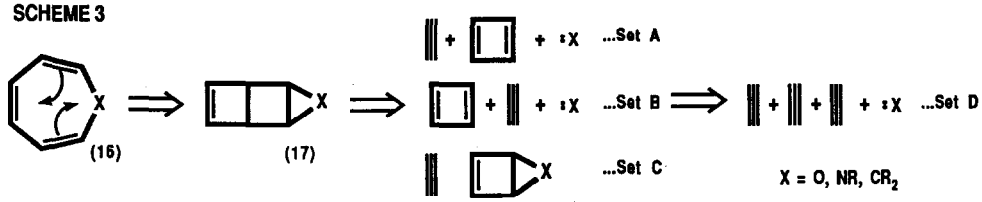
SCHEME 2



Conditions (yield);[4] I) CH_2N_2, ether, 0°C (92%); II) Me_2CN_2, ether, 0°C (92%); III) hν, benzene, 450W Hanovia lamp, (94%); IV) heat neat 160°C (91%); V) 500-550°C (55% corrected).

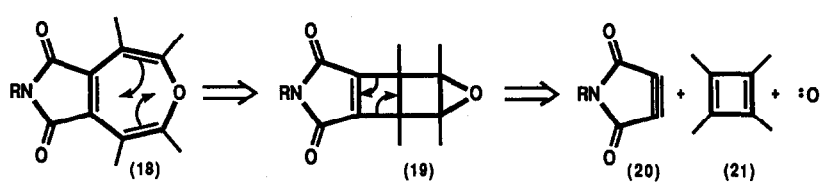
of the substituted cyclopentadiene (**13**). No evidence for the production of bicyclopentene (**12**) was observed in this reaction and it is likely that the retro Diels-Alder reaction of (**10**) occurs with concommitant σ-bond participation to produce cyclopentadiene (**11**) directly. There is a strong propensity for the σ-bond to break in these systems even prior to the retro Diels-Alder reaction occurring. Thus heating the H-containing cyclopropane (**11**), formed in a similar way from (**7**) and diazomethane, initiates an isomerisation of the starting material to produce the *exo*-fused cyclopentene (**14**) together with its C5 epimeric ester (ratio 88:12 at 180°C).[5] Once again fragmentation occurs under more vigorous thermal conditions, in this case to produce dimethyl cyclopentadiene 1,3-dicarboxylate (**15**), isolated in crystalline form for the first time. This compound exists in solution as a mixture of bond-shift isomers.[6] While the yield of the last FVP step is low, the sequence has synthetic value as the precursor reactions are high yielding and the route short.

SCHEME 3

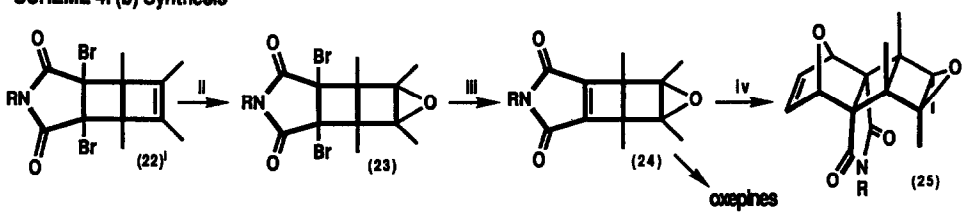


The synthesis of oxepines (**16**; **X=O**) can be approached via Dewar-benzene epoxides (**17**; **X=O**) using the transannular pairing algorithm to produce four sets of synthons as shown in Scheme 3 . The maleimido-oxepine (**18**), selected as the target molecule and conducted at the methyl-substituted level to satisfy other objectives,[7] is based on sets B/D and provides an elegant example of the synthetic potential of this new protocol. Thus reaction of *N*-methyl 3,4-dibromo maleimide with tetramethyl cyclobutadiene, generated *in situ* by treatment of the aluminium halide complex of permethylcyclobutadiene with DMSO,[8] formed 1:1-adduct (**22**)(Scheme 4). Reaction of this adduct with mCPBA yielded a single epoxide (**23**), debromination of which occured on treatment with zinc/silver couple to produce the Dewar-benzene monoepoxide (**24**). which is readily trapped as its furan adduct (**25**). In the absence of trapping agent (**24**), isomerises($t_{0.5}$ = 77 min

SCHEME 4: (a) Retrosynthesis



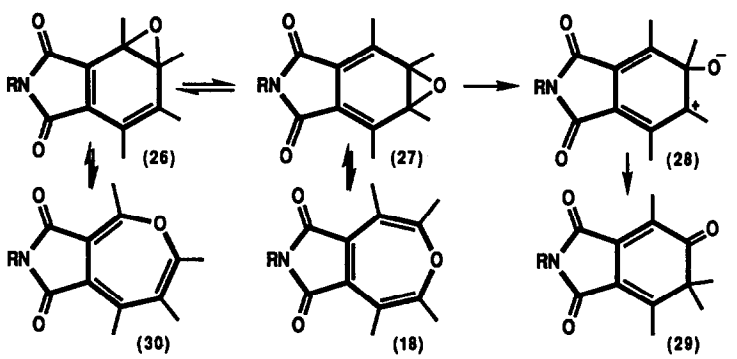
SCHEME 4: (b) Synthesis



Conditions (yield)[4]: I) 2-butyne, CH_2Cl_2,$AlCl_3$, 0°C , then *N*-methyl 3,4-dibromomaleimide, DMSO (82%) to form (22); II) mCPBA, CH_2Cl_2 at reflux, 15hr (93%); III) Zn/Ag couple, THF at reflux, 3 min ; IV) Zn/Ag couple, THF/furan at reflux, 4hr (93%)

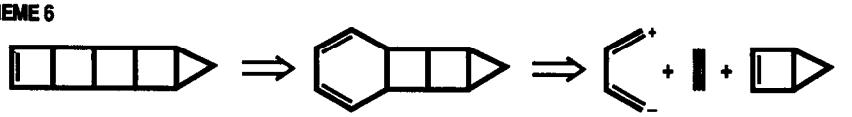
at 30°C) to the maleimido-oxepine (**18**) which exists in solution as an equilibrium mixture with the benzene epoxide form (**27**); NMR studies confirm the C_2 symmetry of all these products, a factor which became important given the following results. A more complex equilibrium mixture was produced when (**24**) was generated via pyrolysis of the furan adduct (**25**); chromatography yielded the isomeric maleimido-oxepines (**18**) and (**30**), each in equilibrium with its valence-isomer, benzene epoxides (**27**) and (**26**) respectively, as well as the cyclohexadienone (**29**). An interrelationship between the products is shown in the flow diagram in Scheme 5 which involves isomerisation of the initially formed oxepine (**18**) to benzene oxide (**27**) and its oxygen walk isomeration.to (**26**).[9a] Cyclohexadienone (**29**) is considered to be formed from (**26**) or (**27**) via intermediate (**28**).[9b]

SCHEME 5



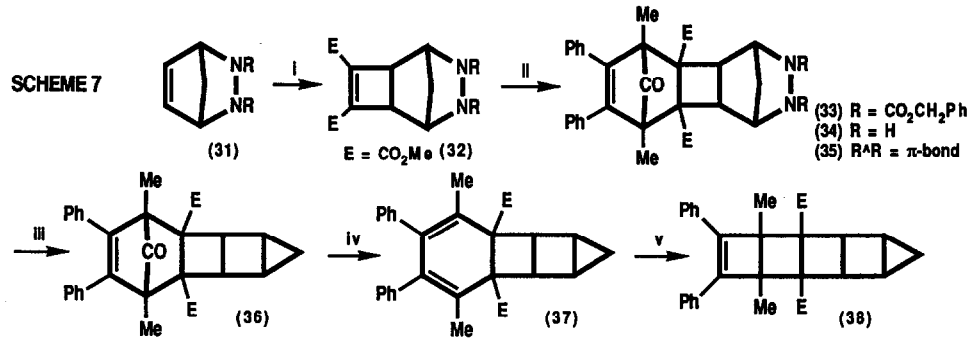
The polycyclobutane intermediate identified in the first step of transannular pairing retrosyntheses involving odd-numbered carbocycles, has a variety of cleavage pathways open to it including that leading to bicyclo[2.1.0]pentene synthons (Scheme 2, synthon set C). As this ring system is known to be unstable,[10] we sought a transfer reagent for its delivery which would not only make it more readily available, but also retain or improve its cycloaddition capabilities. The diazabicyclo[2.2.1]pentane (**31**; R = CO_2CH_2Ph) was selected as it is stable, crystalline, readily prepared from commercially available reagents and known to serve as a precursor to the bicyclo[2.1.0]pentane moiety in other contexts.[11] The synthesis of the target molecule (**38**), based on the retrosynthesis shown in Scheme 6, forms the cyclobutene (**32**) by ruthenium catalysed [2π+2π] cycloaddition of DMAD onto diazanorbornene (**31**) (Scheme 7).[12] This cyclobutene was reacted with

SCHEME 6



hemicyclone to form the cycloadduct (**33**), which was transformed to the azo-compound (**35**) by removal of the benzyl ester group and oxidation of the resultant hydrazo-compound (**34**). Thermal ejection of dinitrogen from (**35**) ocurred smoothly upon heating to 165°C to yield the fused bicyclo [2.1.0]pentane (**36**). Further transformations on (**36**) showed that the carbonyl-bridge could be eliminated by ultraviolet irradiation and that the resultant cyclohexadiene could be ring-closed to the pentacyclic system (**38**)[13]. This sequence shows that the present methodology can provide linearly fused cyclobutanoid structures with a terminal bicyclo[2.1.0]pentane component. In keeping with transfer technology principles, the bicyclo [2.1.0.]pentene synthon has been delivered without liberating the free compound. These products have potential to provide entry into cyclic polyenes having an odd-number of ring atoms and results of this aspect of the present study will be reported in due course.

SCHEME 7



Conditions (yield)[4] **i) DMAD, $RuH_2CO(PPh_3)_3$, benzene at reflux, 6 days (63%); ii) hemicyclone, $CHCl_3$, sealed 105°C (98%); iii) 10% Pd/C, EtOAc, then stir with HgO (85%); iv) diglyme at reflux (83%); v) acetone, hv 254nm, -35°C((37)55%; (38)16%).**[12]

References and footnotes.

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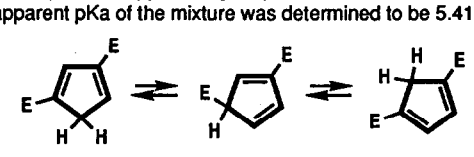
2. C.D. Smith, *J. Amer. Chem. Soc.*, 1966, **107**, 3287; U. Azzena, S. Cossu, O. De Lucchi and G. Melloni, *Gazz. Chim. Ital.*, 1989, **119**, 357.
3. D.N. Butler, R.A. Russell, R.B. Waring and R.N. Warrener, *Aust. J. Chem.*, 1984, **37**, 1293.
4. (Compound number), m.p. or b.p. °C: (**8**), 98; (**9**), 82-3; (**11**), liquid, b.p. 107-112/0.15 torr ; (**13**), liquid; (**14**), liquid, b.p. 110-114/0.15 torr ; (**18**), 164-5; (**22**), 201-7; (**23**), 227-30; (**25**), 208-10; (**29**), 101-2; (**30**), 119-20; (**32**), 117-20; (**33**), 183-4; (**35**), 166-8; (**36**), 165-6; (**37**), 133-5; (**38**), 162-3.
5. Compound (**14**) is the kinetic isomer. Epimerisation can be promoted by heating (205°C) or treatment with NaOMe (O_2 must be excluded otherwise hydroperoxides are formed). Other rigid, *exo*-fused cyclopentenes are available via this sequence, D.N. Butler and R.N. Warrener, *unpublished results.*
6. Dimethyl cyclopenta-1,3-diene exists as an equilibrium mixture of the bond-shift isomers (i) and (iii), ratio 4:1 in $CDCl_3$ solution as judged by ^1H NMR spectroscopy. A single species is formed on treatment of this product in d_8-THF solution with Na metal. The apparent pKa of the mixture was determined to be 5.41 by titration in H_2O.



7. For targets in the Dewar-furan area, see R.N. Warrener, R.A. Russell and I.G. Pitt, *Pure & Appl. Chem.*,1986,**58**,161.
8. J.B. Koster, G.J. Timmermans and H. van Bekkum, Synthesis, 1971, 139.
9. a) Oxygen walk: D.R. Boyd et al., *J. Chem. Soc., Chem. Commun.*, 1987, 1633; W.B. Jennings, M. Rutherford, D.R. Boyd, S.K. Agarwal and N.D. Sharma, *Tetrahedron*, 1988, **44**, 7551.
   b) Hydrolysis and NMR data will be discussed in the full paper.
10. $t_{0.5}$ = ca 2 hr. J.I. Brauman, L.E. Ellis and E.E. van Tamelin, *J. Amer. Chem. Soc.*, 1966, **88**, 846.
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13. Compounds (**36**) and (**37**) are in photoequilibrium; continued u.v. irradiation causes photofragmentation via (**37**) to form dimethyl 3,6-dimethyl-4,5-diphenylphthalate. Surprisingly, neither (**2**, R=H) nor (**1**) could be trapped or detected spectroscopically.

(Received in UK 24 September 1990)