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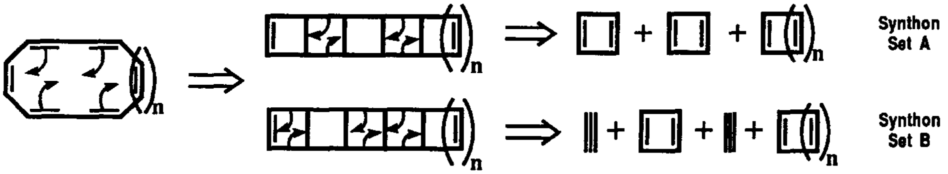
TRANSFER TECHNOLOGY III : THE SYNTHESIS OF BRIDGED CYCLIC POLYENES USING A NEW RETROSYNTHETIC ALGORITHM AS A GUIDE.

by R.N. Warrener*, J-M. Wang[1], K.D.V. Weerasuria and R.A. Russell

Graduate School of Science and Technology, Bond University, Gold Coast, Queensland 4229, Australia.

Abstract: This route to bridged [4] and [8] annulenes employs a new retrosynthetic algorithm, transannular π-bond pairing, as its basis and improved transfer reagents for substituted cyclobutadienes to achieve the synthesis.

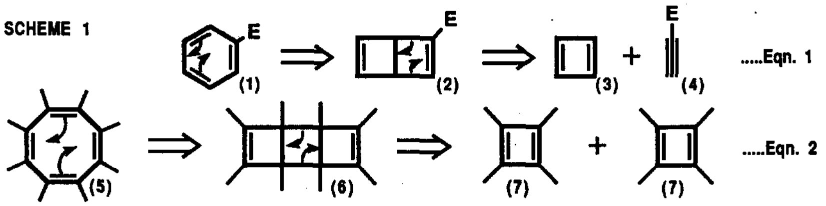
In an earlier report[2] we demonstrated the use of transfer technology in organic synthesis. This technique uses transfer reagents to deliver specific synthons in a conveniently protected form for use in the synthesis itself, such that improved reactivities and reaction selectivities can be achieved and the production of highly reactive species in their free state can be avoided. Several examples served to demonstrate the advantages of using this protocol in the synthesis of cyclic polyenes, however a severe limitation was identified in the direct synthesis of bridged bicyclo[4.2.0]octa-1,3,6-trienes(biCOTs). In this communication we show how improved transfer reagents can overcome this deficiency and be employed successfully in the direct synthesis of bridged biCOTs and how transfer technology can be applied to the synthesis of large-ring polyenes. Further, we show that these syntheses, as well as the examples described earlier, can be incorporated within a retrosynthetic algorithm which has general application to the synthesis of cyclic polyenes.



The retrosynthetic algorithm incorporates two steps: the transannular pairing of cross-ring π-bonds of the target molecule in a series of [2π+2π] electrocyclic ring-closures to produce a polycyclobutanoid intermediate,[3] followed by a series of [2σ+2σ] electrocyclic ring-fragmentations which identify a set of acetylenic and cyclobutadiene synthons, e.g. synthon set A or B.[4,5]

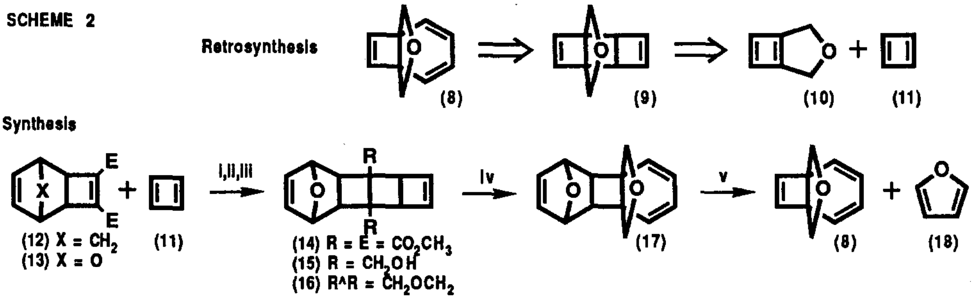
The synthesis of methyl benzoate (equation 1) and permethyl cyclooctatetraene (equation 2) based on the retrosynthetic protocol shown in Scheme 1 have already been reported in the literature.[6,7] They are selected to illustrate the two types of transannular π-bond pairing (conjugated and cross-ring respectively) used to form the cyclobutanoid intermediate and further, to show how an appropriate set of synthons is derived therefrom. The synthons identified in these examples are known reagents and can be used directly in the synthesis without ambiguity. These polycyclobutanoid intermediates have each been identified and separately converted to the polyene, however, this is not a necessary condition (*vide infra*). The syntheses of (1) and (5) are straightforward as the symmetrical cyclobutadienes avoid site selectivity problems: in the syntheses which follow this is not the case and transfer reagents are used to provide the required site and regioselectivities.

SCHEME 1



The synthesis of the bridged bicyclo[4.2.0]octa-1,3,6-trienes (**8**) can be approached via a similar polycyclobutane intermediate (**9**) (Scheme 2). Here, disconnection of (**9**) into two cyclobutadiene synthons (**10**) and (**11**), forms the basis for the present synthetic approach. This example is especially instructive as one of the cyclobutadiene synthons, the symmetrical cyclobutadiene itself, is delivered as the free reagent while the other (**10**) is provided as the corresponding transfer reagent (**13**) to ensure the required site selectivity in the linking of the two reagents. A major advance in the present work is the use of oxa-bridged transfer reagent (**13**) which provides distinct advantage over the carbocyclic counterpart (**12**), owing to the improved dienofugacity of furan relative to cyclopentadiene (CPD).

SCHEME 2

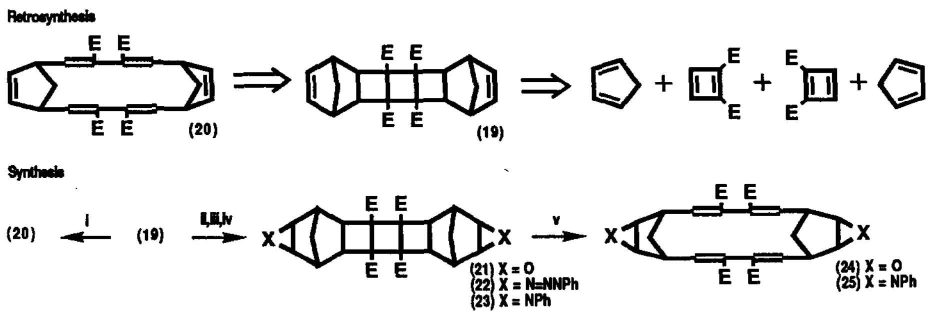


Conditions (yield): i) Fe(CO)$_3$CBD, CAN, THF (82%); ii) LAH, THF (85%); iii) PPh$_3$, dibenzyl azodicarboxylate, THF (60%); iv) FVP 450°C/0.001mm Hg (85%); v) FVP 490°C/0.004 mm Hg (48%).[8]

The synthesis of bridged biCOT (**8**) starts with the reaction of free cyclobutadiene, generated from its iron tricarbonyl complex, with transfer reagent (**13**), which occurs site specifically at the activated cyclobutene π-bond to produce a mixture of two stereoisomers (**14**). Treatment of the major isomer with LAH produced the related diol (**15**) which smoothly cyclised on treatment with the Mitsunobu reagent to form the cyclic ether (**16**). Isomerisation of (**16**) under controlled thermal conditions yielded the triene (**17**), which under more vigorous conditions formed the required oxabridged biCOT (**8**). The synthesis of (**8**) in five steps (20% overall yield) from (**13**) is considerable shorter than the ten step (9% overall yield) procedure reported in the literature.[9] Similar transformations were conducted on the minor isomer of (**14**).

Extension of the transannular pairing retrosynthesis[4] to larger ring-polyenes was tested with the bridged annulene (**20**) (Scheme 3) and some related members. Thus treatment of the polycyclobutane (**19**),[10] a known photodimer of transfer reagent (**12**), under FVP conditions yielded a number of products of which the polyene (**20**) was a significant member. In this case the major biproducts were derived from competing retro Diels-Alder processes.[11] This latter concern was avoided with the bishetero-analogues (**24**) and (**25**), for which a similar approach was employed. Treatment of dimer (**19**) with mCPBA produced the bisepoxide (**21**), which yielded the related polyene (**24**) upon FVP. The starting material for the bisaza-analogue (**25**) was prepared by treating dimer (**19**) with phenyl azide to produce a mixture of isomeric triazolines (**22**) which was used directly in the photochemically induced deazetisation step to produce a single bisaziridine (**23**) with all *exo*-stereochemistry. FVP of this compound yielded the diaza-polyene (**25**) as the major product.

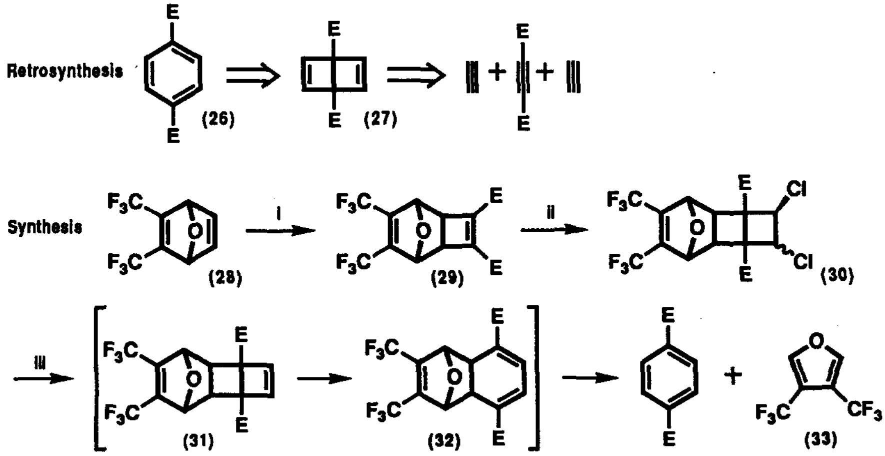
SCHEME 3



Conditions (yield): i) m-CPBA, $CHCl_3$ (82%); ii) PhN_3, reflux C_6H_6, 48 hr (79%); iii) hv, pyrex, 450W hanovia lamp, CH_2Cl_2(72%) ; iv) FVP, 500°C/0.003 mm Hg (11%); v) FVP, 500°C/0.003 mm Hg ((22)43%; (23)32%).[8]

The transannular pairing algorithm uses a polycyclobutane as an intermediate from which to produce the subsets of synthons. However the attendant synthesis does not need to proceed through such a high energy intermediate. A case in point is presented in the following synthesis of dimethyl terephthalate (Scheme 4). Here a new, readily synthesised oxa-bridged diene (**29**) is used as the transfer reagent for dimethyl cyclobutadiene 1,2-dicarboxylate and coupled with the acetylene transfer reagent. In a further variant of our earlier procedure, 1,2-dichloroethene is used as the transfer reagent for acetylene,[12] which illustrates that the required [2π+2π] cycloaddition can be achieved under photochemical conditions.[13] Reaction of the resultant mixture of cycloadducts (**30**) (chlorine stereoisomers) with zinc in ethanol at reflux effects dechlorination and initiates a series of

SCHEME 4



Conditions (yield): i) DMAD, $RuH_2CO(PPh_3)_3$ reflux C_6H_6,16 hr (91%); ii) hv, 1,2-dichloroethene as solvent, PhCOPh, pyrex filter (72%); iii) Zn, reflux, EtOH.[8]

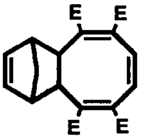
reactions culminating in the formation of dimethyl terephthalate (**26**) in high yield.[14,15] Model studies on adducts related to intermediate (**31**) show that they do not thermally eject furan (**33**) under these reaction conditions supporting that formation of dimethyl terephthalate most likely occurs via fragmentation of triene (**32**), thereby avoiding the Dewar-benzene (**27**) as an intermediate.

In summary, we have illustrated how the transannular pairing algorithm is valuable in retrosynthesis and how improved transfer reagents extend the scope of transfer technology in organic synthesis. In future papers application to the synthesis of odd numbered ring-compounds, including heterocycles, will be addressed.[16]

Footnotes and references.

1. Work done while enrolled as an M.Sc. student at the Australian National University.
2. R.N. Warrener, R.A. Russell, R. G. Solomon, I.G. Pitt and D.N. Butler. *Tetrahedron Lett.* 1987, **28**, 6503; D.N. Butler, D.L. Officer, I.G. Pitt, R.A. Russell and R.N. Warrener, *Tetrahedron Letters,* 1987,**28** 6507.
3. The accepted retrosynthetic guidelines such as FGI, convergency, symmetry etc are retained. Symmetry considerations are important in this protocol when deciding how to arrange the pairing of the cross-ring partners in the valence-isomerisation process, and where to fragment the cyclobutanoid intermediate.
4. In odd-membered ring-systems, these synthons are accompanied by an electron-deficient species such as a nitrene or carbene. In all systems the transannular pairing protocol need only be applied to portion of the target molecule, thus allowing the fragmentation process to generate other accepted synthons eg see synthesis of (**24**) and (**25**).
5. As cyclobutadienes can be assembled from the cycloaddition of two acetylenes, this retrosynthetic protocol can be considered to be based on the head to head, tail to tail concommitant stacking of acetylenes. This concept will be discussed in more detail in the full paper.
6. J.D. Fitzpatrick, L. Watts, G.F. Emerson and R. Pettit, *J. Amer. Chem. Soc.*, 1965, **87**, 3253
7. R. Askani and M. Wieduwilt, *Chem. Ber.*, 1976,**109**, 1887.
8. Compound, m.p.°C: (**14**), 100-101(major), 124-6(minor); (**15**), 125-7(major), 135-6(minor); (**16**), 119-20(major); (**17**), 114-5; (**8**), liquid; (**21**), 306-8; (**23**), 340; (**22**), 235; (**25**), 340; (**29**), 67-69; dimer of (**29**), 230; (**30**), 125-8; (I), 149.
9. L.A. Paquette, R.K. Russell and R.L. Burson, *J. Amer. Chem. Soc.*, 1975, **97**, 6124.
10. W. Eberbach, *Chem. Ber.*, 1974, **107**, 3287.
11. Other compounds isolated in this reaction include tetramethyl prehnitate, tetramethyl COT 1,2,5,6-tetracarboxylate and its precursor (I) as well as CPD.

(I)



E=CO_2CH_3

12. For a recent example of the use of 1,2-dichloroethene as a transfer reagent for acetylene under thermal conditions see K. Shahlai and H. Hart, *J. Amer. Chem. Soc.*, 1990,**112**, 3687.
13. We have used this technique previously, see D.N. Butler, R.A. Russell, R.B. Waring and R.N. Warrener, *Aust. J. Chem.*, 1984, **37**, 1293.
14. R.B. Waring is thanked for conducting this reaction sequence.
15. U.v irradiation of (**25**) with *N*-methyl dibromomaleimide yields a [2π+2π] photoproduct, direct FVP of which leads to the corresponding *N*-methyl phthalimide in 45% overall yield. I.G. Pitt, unpublished results.
16. " A Transannular Pairing Approach to the Synthesis of Cyclopentadiene Diesters and Maleimido-oxepines" by R. N. Warrener, S. Bina, D.N. Butler, I.G. Pitt and R.A. Russell, *Tetrahedron Lett.*,1990, **31**, 0000 accompanying communication.

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