Efficient Synthesis of Unsaturated Seven-membered Rings by an Entropy/Strain Reduction Strategy: 2,7-Dihydro-1*H*-azepines, -oxepines, -thiepines, -1*H*-phosphepine and 1,3-Cycloheptadienes

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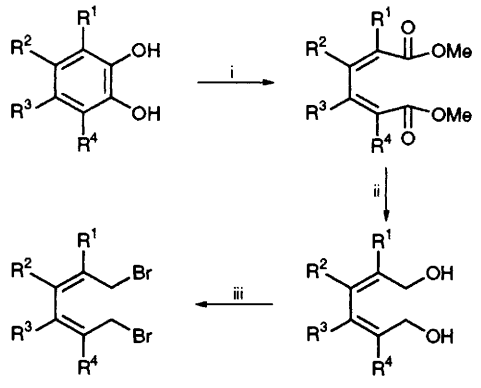
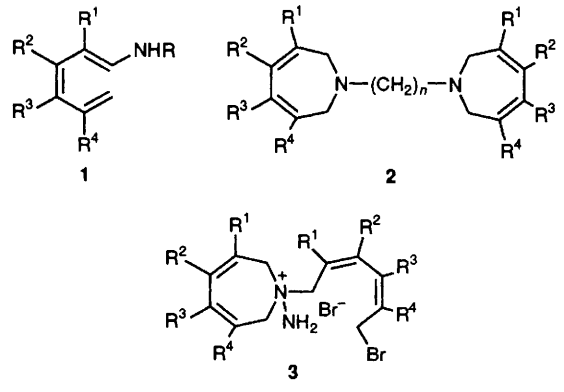
Substituted (*Z,Z*)-1,6-dibromohexa-2,4-dienes, obtained from substituted catechols *via* the corresponding diols, react with primary amines, lithium sulfide, sodium phenylphosphide and malonic ester enolate under mild conditions to give efficient syntheses of 2,7-dihydro-1*H*-azepines, 2,7-dihydrothiepines, 2,7-dihydro-1*H*-phosphepine and cyclohepta-1,3-dienes respectively while the precursor diols yield the 2,7-dihydrooxepines on treatment with toluene-*p*-sulfonyl chloride.

Compounds containing medium and large rings are important theoretically,[1] synthetically[2] and therapeutically[3] but their synthesis has always been a challenging problem[4] and remains a topic of current interest.[4–7] Although many synthetic approaches to these molecules have been described including cycloaddition, cyclisation and rearrangement reactions,[2] direct cycloaddition strategies are poorly represented despite the fact that often they are among the most logical disconnections of the target molecules.[7,8] This is undoubtedly because of the low yields usually associated with medium and large ring synthesis.[2b,c] A strategy which can be employed to overcome these low yields is the replacement of methylene groups in the acyclic chain by double or triple bonds. This has the effect of reducing the degrees of freedom in the chain and, if the appropriate double bond stereoisomer (*e.g. Z* in the case of disubstituted alkene) can be used, a further entropy advantage can be gained because the ends of the chain are brought within reacting distance in certain conformations. Furthermore, if the multiple bonds are appropriately located they may also reduce or eliminate eclipsing and transannular steric interactions in the product. This concept is not new,[9] for example 1,2-substituted benzene rings have long been used to similar



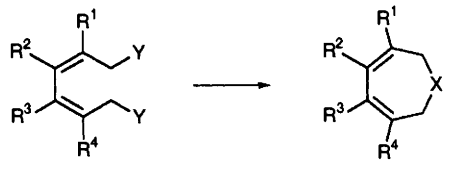
Scheme 1 *Reagents and conditions*: i, $Pb(OAc)_4$, MeOH, C_7H_8, 25 °C, 67–98%; ii, diisobutylaluminium hydride, C_7H_8, 25 °C, 67–80%; iii, PBr_3, Et_2O, 0 °C, 60–95%



effect,[10] but it appears to have been first stated explicitly and formalised by Deslongchamps[4] and successfully utilised by his group in the generation of ten- to fourteen-membered carbocycles by direct cyclisation of triple bond-containing chains without the need for high dilution techniques.[5a] There have also been a number of similar recent examples in heterocyclic synthesis.[5b,c] However there have been fewer examples of the use of double bonds,[5b] probably because of the lack of routes to suitable starting materials.[8b] Therefore as an example of the power of this entropy/strain reduction strategy we describe below an efficient route for the construction of unsaturated seven-membered rings from appropriately substituted dienes.

Table 1 shows the yields of carbocyclic and various

Table 1 Yields of 2,7-dihydroheterepines and cyclohepta-1,3-dienes from reaction of (*Z,Z*)-1,6-dibromohexa-2,4-dienes with various nucleophiles



Method[a]	R^1	R^2	R^3	R^4	X	Yield (%)[b]
A	H	H	H	H	NCH_2Ph	55
A	Bu^t	H	Bu^t	H	NBu^n	41
A	Bu^t	H	Bu^t	H	NCH_2Ph	71
A	Bu^t	H	Bu^t	H	$NSO_2C_6H_4Me$	49
A	Bu^t	H	Bu^t	H	$NCH_2CH(OMe)_2$	56
A	H	H	Bu^t	H	NBu^n	66
A	H	H	Bu^t	H	$NSO_2C_6H_4Me$	56
A	H	H	Bu^t	H	$NCH_2CH(OMe)_2$	74
A	Cl	Cl	Cl	Cl	$NSO_2C_6H_4Me$	48
A	Cl	Cl	Cl	Cl	NBu^n	51[c]
A	Br	Br	Br	Br	NBu^n	60[c]
A	Br	Br	Br	Br	NCH_2Ph	45[c]
A	Br	Br	Br	Br	$NCH_2CH(OMe)_2$	39[c]
B	H	H	H	H	S	50[d]
B	Bu^t	H	Bu^t	H	S	82
B	H	H	Bu^t	H	S	81
B	Cl	Cl	Cl	Cl	S	66
C	Bu^t	H	Bu^t	H	O	83
C	H	H	Bu^t	H	O	87
D	Bu^t	H	Bu^t	H	P(O)Ph	10[e]
E	H	H	H	H	$C(CO_2Me)_2$	40[f]
E	Bu^t	H	Bu^t	H	$C(CO_2Me)_2$	52
E	H	H	Bu^t	H	$C(CO_2Me)_2$	60

[a] A: H_2NR–K_2CO_3–THF, room temp., Y = Br; B: Li_2S–neutral Al_2O_3–THF, room temp., Y = Br; C: Bu^nLi–HMPA–$MeC_6H_4SO_2Cl$–Et_2O, room temp. Y = OH; D: Na_2PPh–toluene–reflux–H_2O_2, Y = Br; E: $H_2C(CO_2Me)_2$–NaOMe–THF, room temp., Y = Br. [b] Unoptimised, isolated after chromatographic purification, no other product formed, except where noted otherwise. [c] Secondary enamine also formed. [d] The 1,1-dioxide previously reported (ref. 8*a*,*b*). [e] Two other products also formed. [f] One other product also formed.

heterocyclic seven-membered rings‡ resulting from reaction of substituted (*Z,Z*)-1,6-dibromohexa-2,4-dienes with various nucleophiles. All reactions were performed at room temperature and with few exceptions yielded only one main product. The major exception was the tetrahaloazepine class which were formed along with side products identified as the halosubstituted enamines **1** [R^1,R^2,R^3,R^4 = Cl, Br; R = Bu^n, $PhCH_2$, $(MeO)_2CHCH_2$] produced by elimination reaction. The key to the success of this approach was the location of a readily available source of the all important (*Z,Z*)-dienes. As is often the case, nature provided the key to a solution of laboratory problems. Thus, the enzyme pyrocatechase is known to oxidatively ring cleave catechols and *o*-quinones to give *cis,cis*-muconic acids[11] and many model systems have been investigated in an attempt to reproduce the specificity of this reaction.[12] Our initial investigations were with the Cu^I–MeOH–pyridine system developed by Tsuji and Takayanagi[12a] because it has the potential to be completely specific for catechol intradiol ring-opening but difficulties with the substituted cases led us to the less specific but more practical lead tetraacetate system developed by Wiessler.[13] This results in the corresponding (*Z,Z*)-diesters which can then be manipulated by standard room temperature reactions to give the required dibromides as shown in Scheme 1.§ Yields for each step in this sequence, which are all unoptimised, were excellent (>80%) except in the unsubstituted cases (60–70%) which are more prone to decomposition.

Particular advantages of this route compared to all others are its brevity, the mild conditions, procedural simplicity, the ready availability of starting materials and the fact that there is built-in flexibility for further elaboration of the prodcut *via* the double bonds. The (*Z,Z*)-diene dibromides also react with diamines to give the corresponding bisdihydroazepines **2** (*n* = 1, 2) but with hydrazines they give the hydrazinium salts (*e.g.* **3**), which are to be expected[15] if, as seems likely, the reaction mechanism proceeds by stepwise quaternisation/dehydrobromination. No reaction was observed under these conditions with aromatic amines, amides or urea, probably because of their relatively reduced nucleophilicity and work is ongoing to address this problem.

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Footnotes

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‡ All compounds are previously unreported (except for one case noted) and gave satisfactory spectroscopic and elemental analyses.

§ In all cases only one product was observed which was purified by short column chromatography. The stereochemistry of these precursors was confirmed by ^1H NMR comparison with literature data.[14] We also note that these substituted (*Z,Z*)-dienes are useful for purposes other than ring construction *e.g.* as substrates in the Diels–Alder or Sharpless epoxidation reactions.

References

1 D. Lloyd, *Non-Benzenoid Conjugated Carbocyclic Compounds*, Elsevier, Amsterdam, 1984; I. Murata and K. Nakasuyi, *Top. Curr. Chem.*, 1981, **97**, 33.

2 For overviews of heterocyclic medium rings see: (*a*) A. R. Katritsky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1985, vols. 1 and 5; (*b*) T. L. Gilchrist, *Heterocyclic Chemistry*, Pitman, London, 1985; for overviews of carbocyclic medium rings see: (*c*) F. J. McQuillan and M. S. Baird, *Alicyclic Chemistry*, Cambridge University Press, Cambridge, 2nd edn., 1983.

3 *Antibiotics, Chemotherapeutics and Antibacterial Agents for Disease Control*, ed. M. Grayson, Wiley-Interscience, New York, 1980; L. H. Sternbach, *J. Med. Chem.*, 1979, **22**, 1; *The Benzodiazepines*, ed. S. Garrantini, E. Mussini and L. O. Randell, Raven Press, New York, 1973.

4 P. Deslongchamps, *Aldrichimica Acta*, 1984, **17**, 59 and references cited therein.

5 (*a*) P. Deslongchamps, S. Lamothe and H.-S. Lin, *Can. J. Chem.*, 1984, **62**, 2395; D. Brillon and P. Delongchamps, *Can. J. Chem.*, 1987, **65**, 43, 56; (*b*) K. C. Nicolaou, G. Zuccarello, C. Reimer, V. A. Estevez and W.-M. Dai, *J. Am. Chem. Soc.*, 1992, **114**, 7360; K. Toshima, K. Ohta, A. Ohashi, M. Nakata and K. Tatsuta, *J. Chem. Soc., Chem. Commun.*, 1992, 1306; (*c*) R. Gleiter, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 27.

6 Recent examples of medium ring synthesis include: J. Barluenga, F. Aznar, A. Martin, S. Garcia-Granda, M. A. Salvado and P. Pertierra, *J. Chem. Soc., Chem. Commun.*, 1993, 319; J. J. H. Edema, H. T. Stock, J. Buter, R. M. Kellog, W. J. J. Smeets, A. L. Spek and F. van Bolhuis, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 436; E. Lee, C. H. Yoon and T. H. Lee, *J. Am. Chem. Soc.*, 1992, **114**, 10 981; G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 5426.

7 For some previous examples of cycloaddition in the synthesis of carbocyclic medium rings see J. W. Herndon, G. Chatterjee, P. P. Patel, J. J. Matasi, S. U. Tumer, J. J. Harp and M. D. Reid, *J. Am. Chem. Soc.*, 1991, **113**, 7808 and references cited therein.

8 For previous cycloadditions in heterocyclic medium ring synthesis see: (*a*) W. L. Mock, *J. Am. Chem. Soc.*, 1967, **89**, 1281; (*b*) W. L. Mock and J. H. McCausland, *J. Org. Chem.*, 1976, **41**, 242; (*c*) A. Singh, A. Mehrotra and S. L. Regan, *Synth. Commun.*, 1981, **11**, 409.

9 'Enforced propinquity often leads on to greater intimacy'—R. B. Woodward.

10 M. Mori and Y. Ban, *Tetrahedron Lett.*, 1979, 1133; E. Schweizer, M. S. El-Bakoush, K. K. Light and K. H. Oberle, *J. Org. Chem.*, 1968, **33**, 2591; E. E. van Tamelen, G. Brieger and K. G. Untch, *Terahedron Lett.*, 1960, 14.

11 O. Hayashi, *Molecular Mechanisms of Oxygen Activation*, ed. O. Hayashi, Academic Press, New York, 1974, pp. 1–29; O. Hayashi, M. Katagiri and S. Rothberg, *J. Am. Chem. Soc.*, 1955, **77**, 5450.

12 Leading references: (*a*) J. Tsuji and H. Takayanagi, *J. Am. Chem. Soc.*, 1974, **96**, 7349; *Tetrahedron*, 1978, **34**, 641; (*b*) M. M. Rogic and T. R. Demmin, *J. Am. Chem. Soc.*, 1978, **100**, 5472; M. M. Rogic, T. R. Demmin and M. D. Swerdloff, *J. Am. Chem. Soc.*, 1981, **103**, 5795; (*c*) G. Speier and Z. Tyeklar, *J. Mol. Catal.*, 1980, 233; (*d*) A. J. Pandell and W. E. Matras, *J. Org. Chem.*, 1987, **52**, 697; (*e*) T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Tada, M. Tsuji, H. Sakamoto and S. Yoshida, *J. Am. Chem. Soc.*, 1986, **108**, 2921; (*f*) H. G. Jang, D. D. Cox and L. Que, *J. Am. Chem. Soc.*, 1991, **113**, 9200; (*g*) M. Matsumoto and K. Kuroda, *J. Am. Chem. Soc.*, 1982, **104**, 1433; (*h*) P. Barbaro, C. Bianchini, C. Mealli and A. Meli, *J. Am. Chem. Soc.*, 1991, **113**, 3181; (*i*) Y. Tatsuno, M. Tatsuda and S. Otsuka, *J. Chem. Soc., Chem. Commun.*, 1982, 1100.

13 M. Wiessler, *Tetrahedron Lett.*, 1977, 233.

14 J. W. Jaroszewski and M. G. Ettlinger, *J. Org. Chem.*, 1982, **47**, 1212; G. Schneider, T. Horvath and P. Sohar, *Carbohydrate Res.*, 1977, **56**, 43; Y. Naruta, N. Nagai, T. Yokota and K. Maruyama, *Chem. Lett.*, 1986, 1185; M. Rosner and G. Kobrich, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 741.

15 C. G. Overberger, J.-P. Anselme and J. G. Lombardino, *Organic Compounds with Nitrogen–Nitrogen Bonds*, Ronald Press Co., New York, 1966.