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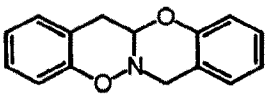
Synthesis of the First [1,3]Benzoxazino[3,2-*b*][1,2]benzoxazine and its Tandem Retro-Diels-Alder - Diels-Alder Rearrangement to a Novel [1,3]Benzoxazino[2,3-*b*][1,3]benzoxazine.

Zeev Goldschmidt,* Shlomo Levinger and Hugo E. Gottlieb

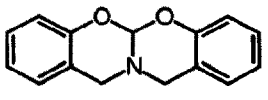
Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel

Abstract: Thermolysis of 3-methyl-4*H*-1,2-benzoxazine gave the tetracyclic 12a-methyl-7*H*,12a*H*,13*H*-[1,3]benzoxazino[3,2-*b*][1,2]benzoxazine, which further rearranged to the isomeric 5a-methyl-5a*H*,11*H*,13*H*-[1,3]benzoxazino[2,3-*b*][1,3]benzoxazine. Thermolysis of the benzoxazinobenzoxazines gave 2-methyl-4*H*-1,3-benzoxazine, and *o*-quinone methide which was trapped by ethyl vinyl ether to give 2-ethoxy-dihydrobenzopyran.

Hetero cycloaddition reactions have recently become a powerful tool in the stereoselective synthesis of complex heterocyclic systems.[1] Here we wish to report a simple approach to two novel derivatives of bezoxazinobenzoxazines, **1** and **2**, by a sequence of tandem[2] retro-Diels-Alder-Diels-Alder (RDA-DA) reactions. Of the three possible isomers of the nitrogen-bridged linear benzoxazinobenzoxazines **1-3**, only a single analogue, imide **4**,[3] and the thio-analogue benzothiazinobenzothazine **5**,[4] have been reported before.



1
[1,3][3,2-b][1,2]



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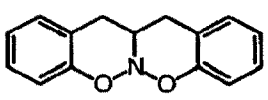

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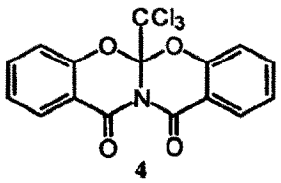
[1,2][2,3-b][1,2]



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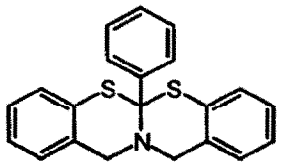
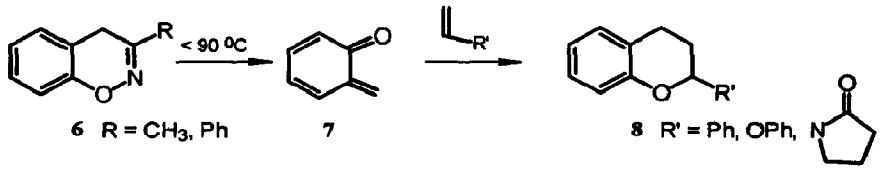
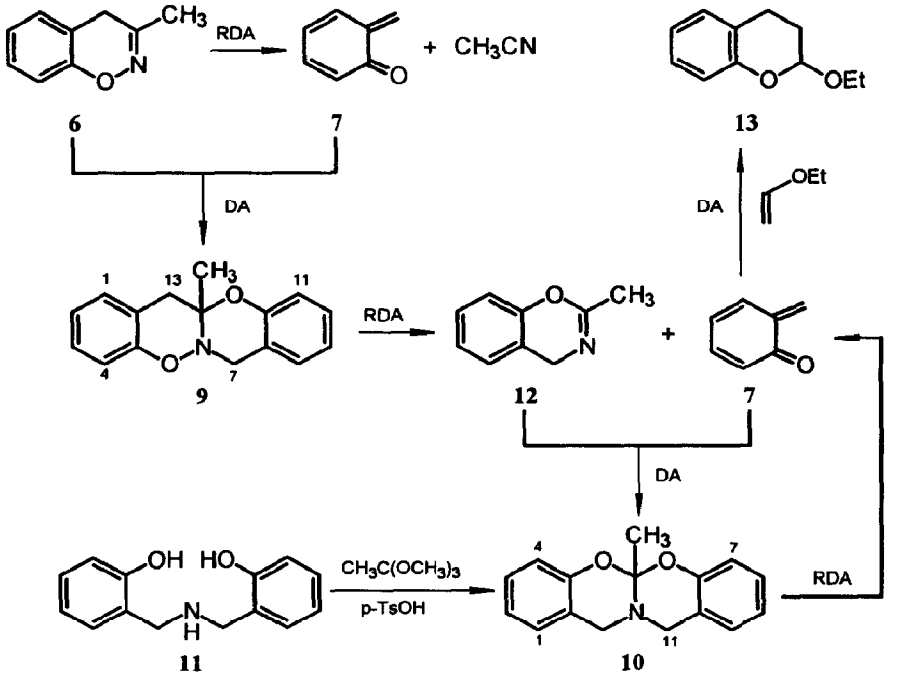


5

Shudo and co-workers[5] have recently shown that the mild thermolysis (< 90 ^{0}C) of 1,2-benzoxazines **6** in the presence of electron rich olefins gave chromans **8**, in a tandem RDA-DA reaction, via the highly reactive *o*-quinone methide intermediates **7**. We have found that thermolysis of **6** (R = CH_3) in refluxing chloroform, *in the absence of an external olefin source*, leads smoothly to the novel tetracyclic 12a-methyl-7*H*,12a*H*,13*H*-[1,3]benzoxazino[3,2-*b*][1,2]benzoxazine **9**.[6] None of the dimeric nor trimeric derivatives of *o*-quinone methide which are obtained in the usual pyrolytic methods[7] were detected.

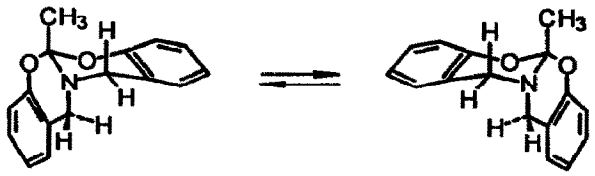


Benzoxazinobenzoxazine **9** was readily identified by its ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum which exhibits two nonequivalent AB systems for the methylene groups of the 1,2- (δ 3.14 and 3.22, J_{gem}=17 Hz) and 1,3-oxazine (δ 4.44 and 4.57, J_{gem}=18 Hz) rings. Although **9** could readily be isolated as a crystalline compound,[8] it was quite labile under the reaction conditions, undergoing further thermal rearrangement to the novel isomeric 5a-methyl-5a*H*,11*H*,13*H*-[1,3]benzoxazino[2,3-*b*][1,3]benzoxazine **10**.[6,8] Here, the two equivalent methylene groups appear in the ^{1}H NMR spectrum as a single AB system (δ 3.88 and 4.19, J_{gem}=15.8 Hz). The structure of **10** was further confirmed by its independent synthesis from bis(2-hydroxybenzyl)-amine **11**[9] and trimethyl orthoacetate.[10]



Notably, the ^{1}H and ^{13}C NMR spectra of **10** show variable temperature dependence indicating conformational dynamics about the central C-N ring fusion. At the limiting low temperature ^{1}H NMR spectrum (-114 ^{0}C, CD_2Cl_2) the methylene AB quartet is resolved into four equally populated resonances arranged in two AB quartets, whereas the angular methyl signal (δ 1.84) remains invariant. Similarly, the methylene signal (δ 48.88) in the ^{13}C{^{1}H} NMR spectrum splits at low temperature (-59 ^{0}C) into two equally populated signals while the methyl signal (δ 23.57) remains unchanged. This behavior is consistent with ring inversion of the two

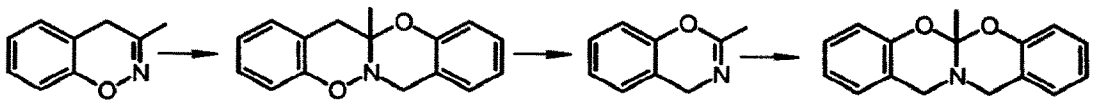
1,3-benzoxazino wings of the *cis*-fused **10**. The energy barrier to ring inversion, $\Delta G^{\#}$ = 8.7 kcal/mol, is significantly lower than that observed for *cis*-decalin ($\Delta G^{\#}$ = 12.8 kcal/mol).[11-13]



Formation of the nonsymmetrical benzoxazinobenzoxazine **9** and its subsequent rearrangement to the symmetrical benzoxazinobenzoxazine **10** is best rationalized as a "domino cascade" of tandem RDA-DA transformations. Thus, the initial RDA generation of *o*-quinone methide **7** from 1,2-benzoxazine **6** in the absence of added olefin is rapidly followed by a *regiospecific* DA cycloaddition of **7** and another molecule of **6**, to form adduct **9** exclusively. The reaction followed first order kinetics with a free energy of activation $\Delta G^{\#}$ = 25.2 kcal/mol (at 58 ^{0}C).[12]

The second RDA-DA reaction pair leading to the Diels-Alder regiomer **10** involves regeneration of **7** and 2-methyl-4*H*-1,3-benzoxazine **12**[14] by RDA cleavage of the 1,2-benzoxazine wing of **9**, followed by a regiospecific inverse DA recombination. This rearrangement pathway could be verified by running the reaction in the presence of an excess of ethyl vinyl ether, which traps **7** *in situ*, to give the DA adduct 2-ethoxy-dihydrobenzopyran **13**[15] and the thermally stable benzoxazine **12**. The rearrangement rate is ca. one order of magnitude slower than the decomposition rate of **6** to **9**, yielding a higher reaction barrier, $\Delta G^{\#}$ = 26.2 kcal/mol (at 58 ^{0}C).[12]

Furthermore, benzoxazinobenzoxazine **10**, like its counterpart **9**, is capable of undergoing the RDA reaction regenerating once again **7** and **12**, yet this time by cleavage of the more stable 1,3-benzoxazine ring. This was again demonstrated by conducting the thermolysis in benzene with an excess of ethyl vinyl ether (100 ^{0}C, 4 days, sealed tube, 65% yield) to yield as above a 1:1 mixture of **12** and **13**, thus completing a third RDA-DA sequence. The barrier for cleavage of the 1,3-benzoxazine ring of **10**, $\Delta G^{\#}$ = 31.2 kcal/mol (at 108 ^{0}C), is considerably higher than that observed for 1,2-benzoxazines **6** and **9** (*vide supra*).[12]



In conclusion, we have demonstrated the power of sequential tandem RDA-DA reactions in the synthesis and interconversion of novel benzoxazinobenzoxazines, and have discovered *inter alia*, two mild *o*-quinone methide generators, and a convenient approach to the rare 4*H*-1,3-benzoxazine system. We are presently extending this strategy to synthesis and exploration of related novel heterocycles.

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8. **Typical procedure**: A solution of **6** (R = Me) (220 mg, 1.5 mmol) in dry $CHCl_3$ (10 ml) was refluxed for 2 h. The solvent was removed, and the residue chromatographed on silica (hexane-CH_2Cl_2) to give **9** (130 mg, 69% yield, from hexane), m.p. 116-117 ^{0}C. When reflux is continued for additional 15 h and the reaction mixture worked up as above, **10** was isolated in 60% yield, m.p. 97-98 ^{0}C.
   9: ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.59 ($3H_{Me}$), 3.14, 3.22 ($2H_{13}$, $J_{13,13'}$ = 17 Hz), 4.44, 4.57 ($2H_7$, $J_{7,7'}$ = 18 Hz), 6.7-7.4 (8H, aromatic); ^{13}C NMR ($CDCl_3$, 300 MHz, TMS) δ 23.48 (C_{Me}), 37.48 (C_{13}), 49.86 (C_7), 86.68 (C_{12a}), 114.35, 117.18, 117.31, 118.19, 121.02, 121.49, 126.84(x2), 128.10, 128.73, 151.62, 154.68 (12C, aromatic).
   10: ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.84 ($3H_{Me}$), 3.88, 4.19 (4H, J = 15.8 Hz), 6.7-7.4 (8H, aromatic); ^{13}C NMR ($CDCl_3$, 300 MHz, TMS) δ 23.57 (C_{Me}), 48.88 (C_{11}, C_{13}), 106.29 (C_{5a}), 116.73, 118.18, 121.46, 126.77, 128.19, 150.61 (12C, aromatic).
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10. **Typical procedure**: A mixture of **11** (100 mg, 0.44 mmol), trimethyl orthoacetate (2 ml) and p-TsOH (5 mg) was refluxed until all the aminediol dissolved. Excess orthoacetate was evaporated and the residue crystallized from CH_2Cl_2-hexane to give **10**.[8]
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   (b) **12**: ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.08 (3H, s), 4.53 (2H, s), 6.8-7.2 (4H, m).
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