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FACILE SYNTHESIS OF A SUBSTITUTED BICYCLO[4.2.1]NONANE VIA AN ANIONIC [1,3]-SIGMATROPIC SHIFT: USE OF LONG RANGE 2D HETCOR AND DIFFERENCE NOE IN STRUCTURE DETERMINATION[1]

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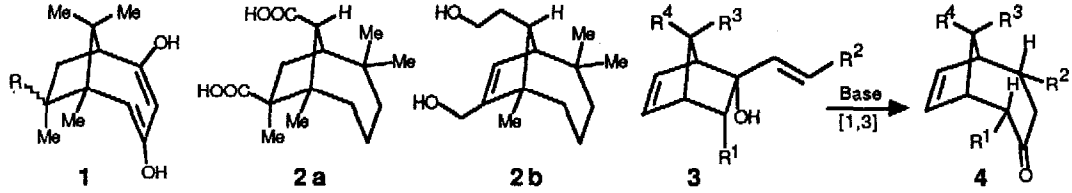
Abstract: The structure of the exo-alkenyl norbornenol **16x** (prepared in good yield from the ketone **11**) was proven by HETCOR and difference NOE of **15x**; it rearranges readily to the substituted bicyclo[4.2.1]non-7-en-3-one **17**.

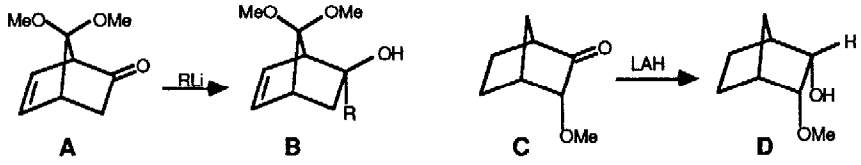
The bicyclo[4.2.1]nonane ring system is a substructure of several natural terpenoids and their metabolites, such as the mediterraneols **1**, longicamphoric acid **2a**, and secolongifolenediol **2b**.[3] Highly unsaturated derivatives of this ring system are often used as templates to study electronic effects.[4] We report here a new approach for the synthesis of bicyclo[4.2.1]nonane systems, which should be especially applicable for the preparation of multifunctional, highly substituted derivatives with defined stereochemistry, such as **4**, by the anionic [1,3]-sigmatropic shift[5] of an allylic alcohol, such as **3**.



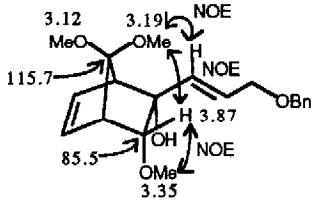
There are several routes in the literature for the preparation of bicyclo[4.2.1]nonane derivatives: a) trapping of cyclooctatetraene dianion with one-carbon bis-electrophiles (e.g., dimethylcarbamoyl chloride);[4a] b) [6 + 2] cycloadditions with cycloheptatriene;[6] c) Cope rearrangement of vinyl ketene-cyclopentadiene adducts;[7] d) rearrangements of transient tetracyclo[4.3.0.0^{2,9}.0^{5,7}]non-3-enes.[8] However most of these synthetic methods are applicable mainly for unsaturated derivatives and do not easily permit the preparation of stereochemically defined substituted derivatives. If successful, a route based on a [1,3]-sigmatropic shift of an exo 2-vinyl norbornen-2-ol would allow the preparation of functionalized derivatives with good stereocontrol. The substrate **16x** for the rearrangement was prepared by our general route[9] as shown in the Scheme.

Cycloaddition of dimethoxytetrachlorocyclopentadiene **5** with vinylene carbonate **6** (80°C/2d) afforded an 86% yield of the crystalline endo adduct **7**.[10] Basic methanolysis gave in 84% yield the diol **8** which could be monomethylated to give **9** in 91% yield.[11] Removal of the chlorine atoms was effected by our standard procedure, namely lithium in ammonia with 3 eq of ethanol as a proton source (the hydroxyl group in **9** provides the fourth proton). In this way we obtained an 89% yield of the dechlorinated alcohol **10**, which was then oxidized to give the ketone **11** in 91% yield (53% overall from **5** and **6**). This ketone presents a unique case to test the effects of the 3-endo and 7-syn methoxy groups on nucleophilic additions to 2-norbornenones. As we have shown,[9ab] the 7-syn methoxy group hinders nucleophilic attack from the exo direction so that acetylenic and aromatic nucleophiles add exclusively from the

endo direction in **A** to give **B**. On the other hand, a 3-endo methoxy group causes reduction of the 2-norbornanone **C** to occur exclusively from the exo direction, giving only **D**,[12] due either to steric hindrance of endo attack by the 3-endo methoxy group or an electronic interaction of the 3-methoxy group which favors exo attack. The addition of nucleophiles to compound **11** would allow us to determine which of the methoxy groups (7-syn or 3-endo) would have the greater directing effect, if the structures of the products could be unequivocally determined.



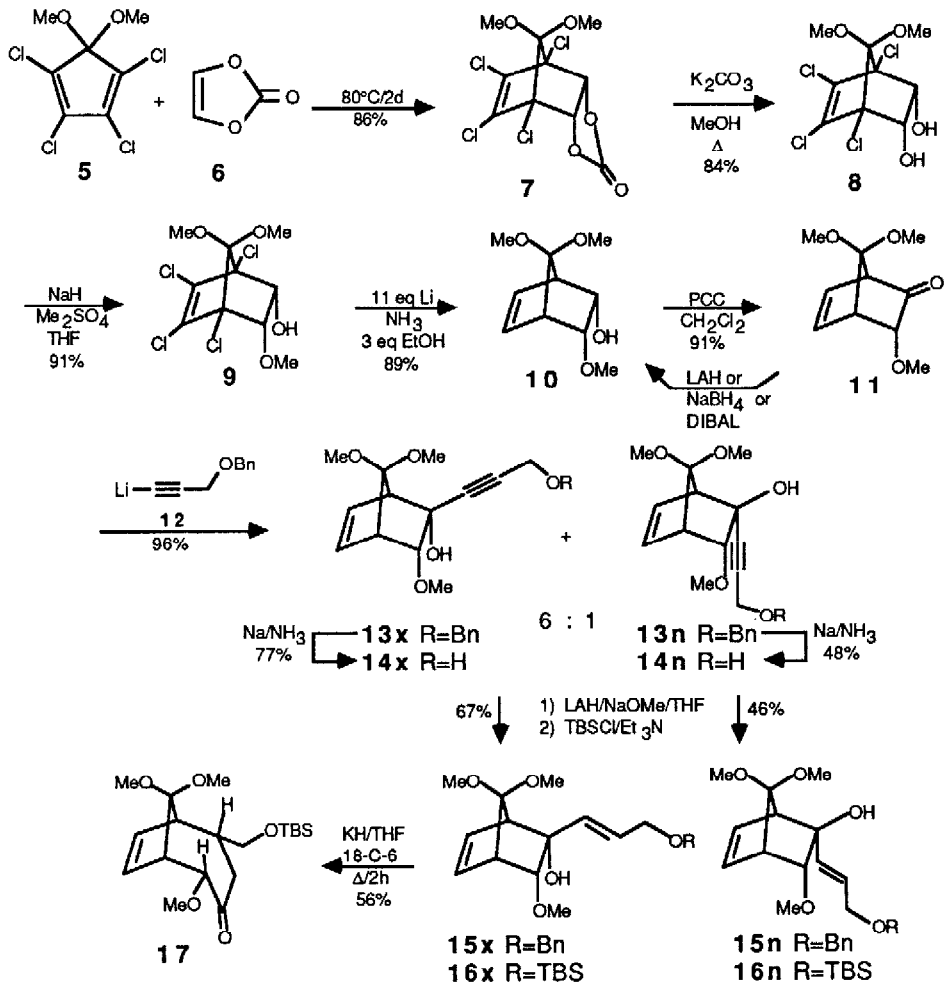
Addition to **11** of the lithium salt of 3-benzyloxypropyne **12** afforded in 96% yield a 6:1 mixture of the alcohols **13x** and **13n**, which could be readily separated by flash chromatography (R_f 1:1 ether/hexane: **13x**, 0.12; **13n**, 0.07). Reductive removal of the benzyl protecting group gave the diols **14x** and **14n** in fair yield. Although each alcohol **13** and each diol **14** had very distinct resonances in the ^1H and ^{13}C NMR spectra, there was no direct way of determining their structure. Each alcohol **13** was separately reduced to the E-allylic benzyl ether, producing **15x** and **15n** in good yields. We were able to determine the structures of **15x** and **15n** by the following process which involves the use of long range 2D heteronuclear correlated spectroscopy (2D-HETCOR) in conjunction with difference nuclear Overhauser enhancement (nOe) studies. A 2D HETCOR spectrum, optimizing long range coupling, of the major isomer **15x** allowed one to distinguish between the 3-methoxy group and the two 7-methoxy groups in the ^1H NMR spectrum, as shown below. The acetal carbon at 115.7 ppm was coupled to the two methoxy singlets at 3.12 and 3.19 ppm, while C3 (85.5 ppm) was coupled to the methoxy singlet at 3.35 ppm. Once the methoxy groups were distinguished in **15x**, we could now use difference nOe to determine the stereochemistry of each. There was an nOe between the 3-methoxy group (3.35 ppm) and the proton at C3 (3.87 ppm) but not between the 3-methoxy group and the olefinic proton on the alkenyl group. Also in **15x** there was nOe between one of the 7-methoxy groups (3.19) and the olefinic proton on the alkenyl group (6.0-6.3) as well as between this methoxy and the proton at C3 (3.87). Thus in **15x** the alkenyl group must be exo as shown since in only that stereochemistry can a 7-methoxy group show



15x

nOe with the olefinic proton on the alkenyl group. Thus the major direction of attack on the ketone **11** is from the exo face implying that the 3-endo methoxy group exerts a greater directing effect than the 7-syn methoxy. This was shown to be true for simple reduction also, with various hydride reagents converting **11** into the endo alcohol **10** in good yield.

Knowing that the major product had the desired 2-exo-alkenyl stereochemistry, we then were able to test the key reaction. Reduction of each diol **14** to the E-allylic alcohol and protection as the t-butyldimethylsilyl ether afforded the stereoisomeric alcohols **16x** and **16n**. Heating the alcohol **16x** with potassium hydride and 18-crown-6 in THF for 2h gives an 56% yield of a single product, shown by ^1H and ^{13}C NMR spectroscopy to be the desired bicyclo[4.2.1]nonanone **17**. In particular, the 500 MHz 2D ^1H COSY spectrum allowed for the determination of the stereochemistry at the silyloxymethyl group as that shown.[13] Thus an anionic [1,3]-sigmatropic rearrangement of an



Scheme

exo-2-alkenyl norbornen-2-ol leads readily to the bicyclo[4.2.1]nonane system in contrast to the thermal [1,3]-sigmatropic rearrangement in similar systems.[14]

Thus we have demonstrated the possibility of using a [1,3]-sigmatropic rearrangement of an exo 2-alkenyl bicyclo[2.2.1]hepten-2-ol to effect a 2-carbon ring expansion and lead specifically to a substituted bicyclo[4.2.1]-bicyclo[4.2.1]nonanone. These compounds are of interest in their own right and should serve as precursors, by cleavage of either the one- or two-carbon bridge, to functionalized cyclooctanes and cycloheptanes, respectively.[15]

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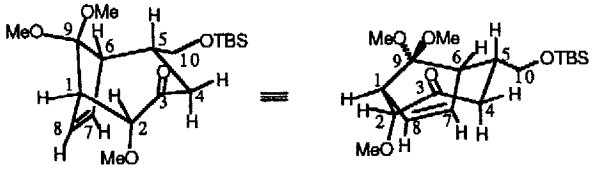
13. MM2 calculations for all the possible stable or metastable conformations of **17** indicate that the conformation shown below is the most stable by approximately 3 kcal/mole. The 500MHz proton NMR of **17**, given below,



is in agreement with this conformation, especially the triplet at δ 2.46 (H-4α) which has a large geminal coupling to H-4β and a large axial-axial coupling to H-5. ^{1}H NMR ($CDCl_3$): δ 6.01 (1H, dd, *J*=6.3, 3.4 Hz, H-8), 5.81 (1H, dd, *J*=6.3, 3.0 Hz, H-7), 3.61 (1H, d, *J*= 7.5 Hz, H-2), 3.41 (2H, m, H-10), 3.26 (3H, s, 2-OMe), 3.18 (3H, s, 9-OMe), 3.18 (1H, m, H-1), 3.15 (3H, s, 9-OMe), 3.08 (1H, dd, *J*=3.0, 2.9 Hz, H-6), 2.46 (1H, t, *J*= 11.3 Hz, H-4α), 2.04 (1H, dd, *J*=11.3, 3.1 Hz, H-4β), 2.01 (1H, m, H-5), 0.84 (9H, s), 0.00 (6H, s).
14. Berson[14a] reported that the analogous exo-2-vinyl bicyclo[2.2.2]octen-2-ol system did not undergo [1,3]-sigmatropic rearrangement on heating but rather fragmentation to the acylmethyl cyclohexene, a process seen by others in 2-alkyl norbornen-2-ols.[14b] Other similar thermal [1,3] shifts are reported to go in very poor yield.[14cd] a) J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86**, 5017 (1964). b) R. L. Snowden, *Helv. Chem. Acta*, **66**, 1031 (1983). c) W. R. Adams and D. J. Trecher, *Tetrahedron*, **28**, 2361 (1972). d) M. A. Forman and P. A. Leber, *Tetrahedron Lett.*, **27**, 4107 (1986).
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