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Transformation of [6] and [7]Metacyclophanols into New Strained Tricyclic Ethers *via* an Intramolecular Version of the S_N2 Reaction

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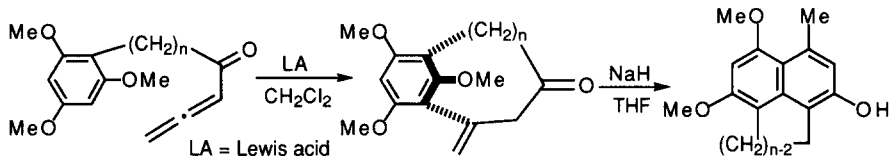
Abstract: Treatment of **2a, b** with $LiAlH_4$ gave the [6] and [7]metacyclophanols **4** and **8** in good yields. The reactions of **4** and **8** with $MeSO_2Cl$ in the presence of Et_3N in CH_2Cl_2 rapidly proceeded to give the corresponding strained tricyclic ethers **6** and **10** *via* an intramolecular version of the S_N2 reaction. This stereospecific cyclic ether formation in the mesylate molecules **5** and **9** can be rationalized in terms of a short nonbonded length between both reaction centers and a fairly rigid linear relationship between the leaving group and the nucleophilic group. © 1997 Elsevier Science Ltd.

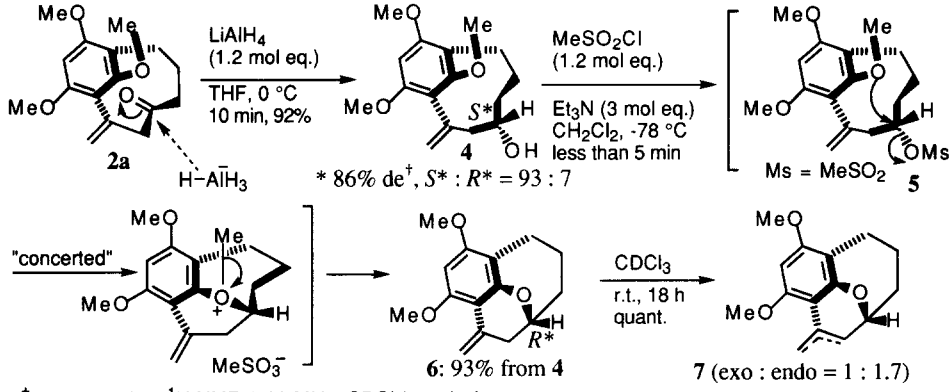
Since the discovery of [*n*]metacyclophane compounds,[1] efforts have been made to explore their unusual reactivity under various reaction conditions. The rich reactivity of [*n*]metacyclophanes has been primarily exploited in the carbon-carbon bond formation to give tricyclic products employing the compounds containing halogen substituent(s) (Cl, Br) between the bridgehead atoms.[2] Recently, we have developed a convenient synthetic method for the strained racemic [6] and [7]metacyclophanones by direct ring closure (**1a, b**→**2a, b**) of the allenyl ketones and their transannular ring closure (**2a, b**→**3a, b**) on the electron-rich benzene ring *via* an $S_{RN}Ar$ pathway (Scheme 1).[3] This paper describes the first example of an intramolecular version of a rapid S_N2 reaction on the strained trimethoxybenzene ring of [6] and [7]metacyclophanols **4** and **8**.



1a, b **a**: n = 3, **b**: n = 4 **2a, b** **3a, b**

Scheme 1

To separate each enantiomer of a racemic mixture of **2a** employing the Mosher reagent as a chiral auxiliary, **2a** was converted by reduction with $LiAlH_4$ (THF, 0 ℃, 10 min) to **4** with high diastereoselectivity (*S** : *R** = 88.6 : 11.4 ~ 93 : 7). The pure *S**-compound **4** was submitted to X-ray crystallographic analysis to determine the stereochemistry of the carbon atom bearing a hydroxyl group (Fig. 1).[4] Reaction of **4** (*S** : *R** = 88.6 : 11.4) with excess *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in pyridine at 0 ℃ for 30 min proceeded to give its ester in 79% yield as a diastereomeric mixture. However, each enantiomeric pure ester has never been obtained. Subsequently, excess *1S*-(+)-10-camphorsulfonyl chloride as a chiral auxiliary was used in the reaction with **4** (86% de) in pyridine at 0 ℃ for 1 h. Surprisingly, the reaction very smoothly proceeded to give the strained tricyclic ether **6** in 93% yield (*vide infra*).Then, reaction of **4** (*S** : *R** = 93 : 7) with $MeSO_2Cl$ (1.2 mol eq.) in the presence of Et_3N (3.0 mol eq.) in CH_2Cl_2 was tentatively examined. This reaction very quickly proceeded to afford the tricyclic ether **6** in 93% yield *via* an intramolecular version of the S_N2 reaction. The exo-methylene double bond of **6** in a NMR tube shifted to the cyclic moiety giving endo-olefinic compound **7** (exo : endo = 1 : 1.7) (Scheme 2).



Scheme 2

Computational study indicated that an arbitrary molecular structure of *S**-[6]metacyclophanol mesylate **5**, generated by sulfonylation of **4**, involves a nonbonded length (3.25 Å) between O1 of the C1-MeO group and *S**-C9 carbon and an angle (141.98°) of O1···C9—O4 as illustrated in Fig. 2.[5] This result can rationalize the stereochemical outcome for an intramolecular version of the fast S_N2 reaction in the mesylate molecule to give the strained tricyclic ether **6**. The structure of the *S**-[6]metacyclophanol mesylate **5** was derived from the computational study based on the X-ray analysis of **4** (Fig. 2).[5]

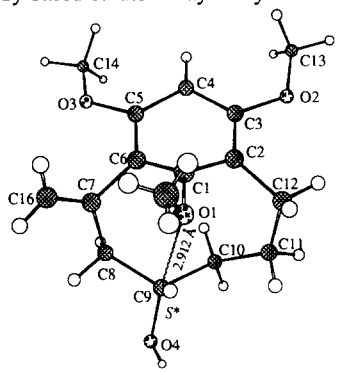


Fig. 1. Computer-generated drawing of compound **4** derived from X-ray coordinates.

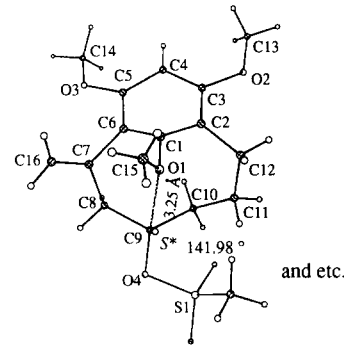
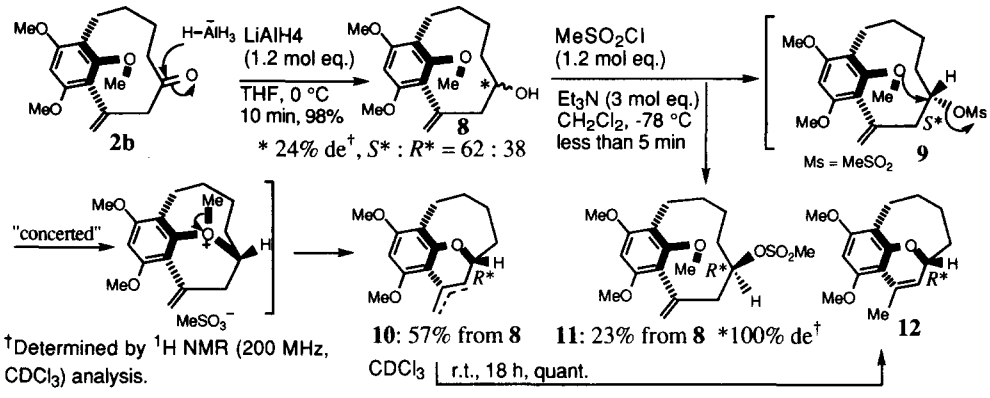


Fig. 2. Computational studies of *S**-[6]metacyclophanol mesylate **5**.

Reaction of **2b** with $LiAlH_4$ in THF at 0 °C for 10 min gave a diastereomeric mixture (*S** : *R** = 62 : 38) of alcohol **8** in 98% yield (Scheme 3). Similar treatment of the diastereomeric mixture of compound **8** with $MeSO_2Cl$ (1.2 mol eq.) in CH_2Cl_2 at -78 °C afforded the corresponding *R**-tricyclic ether **10** (57% yield) and the *R**-mesylate **11** (23% yield), respectively. The exo-methylene double bond of **10** (113.44 kcal/mol)[5] in a NMR tube readily shifted to the cyclic moiety giving the endo-olefinic compound **12** (110.00 kcal/mol)[5] in a quantitative yield (Scheme 3).

The structure of **11** was confirmed by X-ray crystallographic analysis (Fig. 3)[6] to be *R**-configuration. This X-ray analysis suggested that the S_N2-like reaction occurs at the *S**-carbon atom of only *S**-mesylate **9**. The structure of **12** was established by X-ray crystallographic analysis (Fig. 4).[7] Nonplanarity of the benzene ring in the compound **12** was confirmed by χ^2-test, torsion angles, and inspection of a side view of the crystallographic structure (Fig. 4).



Scheme 3

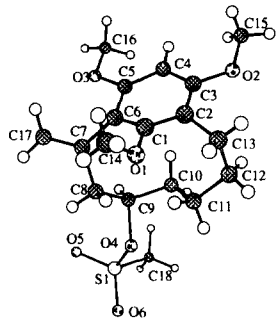


Fig. 3. Computer-generated drawing of compound **11** derived from X-ray coordinates.

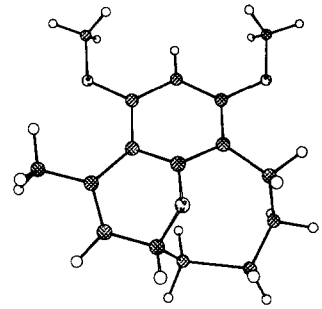


Fig. 4. Computer-generated drawing of compound **12** derived from X-ray coordinates.

Thus, the stereospecific cyclic ether formation (*S**-**8**→*R**-**10**) should be rationalized in terms of the intramolecular version of the S_N2 reaction because of the stereospecific conversion of *R**-alcohol **8** into the mesylate **11** (Scheme 3). The stereospecific conversion of *S**-**8** into *R**-**10** can be supported by exploiting the computational study as follows.[5] Namely, among numerous conformers of the mesylate *S**-**9**, a most likely one toward tricyclic ether **10** was arbitrarily adopted on the basis of X-ray analysis of *R**-mesylate **11** as shown in Fig. 5. The conformer (Fig. 5) of *S**-[7]metacyclophanol mesylate **9** involves a nonbonded length (3.25 Å) between the O1 of C1-MeO group and the *S**-C9 carbon and an angle (151.53°) of O1···C9—O4. Thus, the stereospecific intramolecular ether formation must predominantly proceed *via* this conformer (Fig. 5) to give **10**.

To realize the remarkable reactivity of *S**-[6] and [7]metacyclophanol mesylates **5** and **9**, similar intramolecular ether formation of compound **13** was attempted using $MeSO_2Cl$ (1.2 mol eq.) and Et_3N (3.0 mol eq.) in CH_2Cl_2. The reaction at -78 °C for 1 h resulted in formation of mesylate **14** in 99% yield without production of cyclic ether **15**. In general, stereospecific concerted substitution reactions of the methanesulfonyl group at the chiral carbon atom with the oxygen atom of ethers and epoxides require rigorous reaction conditions.[8] Thus, short nonbonded length [ca. 3.25 Å less than the sum (3.52 Å) of van der Waals radii (O: 1.52 Å, C: 2.0 Å)] between both reaction centers and a possibility of a fairly rigid linear relationship including the C9 atom between the leaving group (MsO) and the nucleophilic group (MeO) should be satisfactory for the intramolecular version of the fast S_N2 reaction in the *S**-[6] and [7]metacyclophanol mesylates **5** and **9**. Interestingly, *S**-[6]metacyclophanol **4** exhibited specific inhibitory activity (47% inhibitory at 100 μg/ml) against protein tyrosine kinase.

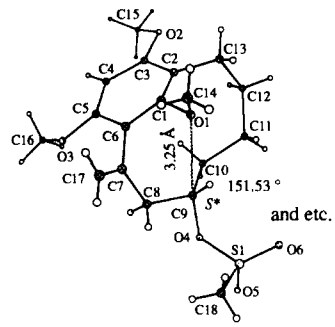
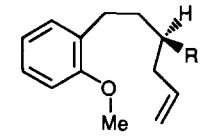
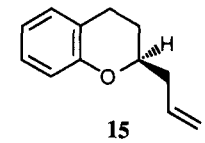


Fig. 5. Computational studies of *S**-[7]metacyclophanol mesylate **9**.



13 R = OH
14 R = $MeSO_3$



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4. The crystallographic data of compound **4** are as follows. $C_{16}H_{22}O_4$, FW = 278.35, triclinic, Space Group $P\bar{1}$(#2), a = 13.205(1) Å, b = 13.214(2) Å, c = 9.282(1) Å, α = 97.00(1)°, β = 106.854(8)°, γ = 88.568(9)°, V = 1538.4(3) $Å^3$, Z = 4, Dcalc = 1.202 g/cm^3, R = 0.062.
5. MM(Discover-CVFF) calculations were performed by using the insight II/Discover 95.0 (MSI/BIOSYM Inc., CA) program.
6. The crystallographic data of compound **11** are as follows. $C_{18}H_{26}O_6S_1$, FW = 370.46, monoclinic, Space Group $P2_1/n$(#14), a = 11.887(2) Å, b = 12.697(5) Å, c = 12.750(3) Å, β = 101.61(2)°, Z = 4, Dcalc = 1.307 g/cm^3, V = 1882.3101 $Å^3$, R = 0.047.
7. The crystallographic data of compound **12** are as follows. $C_{16}H_{20}O_3$, FW = 260.33, monoclinic, Space Group $P2_1/a$(#14), a = 9.998(4) Å, b = 8.327(3) Å, c = 34.121(4) Å, β = 97.37(2)°, V = 2817(1) $Å^3$, Z = 8, Dcalc = 1.227 g/cm^3, R = 0.059.
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