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Efficient, Direct Synthesis of Novel Racemic Trimethoxy-Substituted [6] and [7]Metacyclophanes and Their Transannular Ring Closure *via* an $S_{RN}Ar$ Reaction Process

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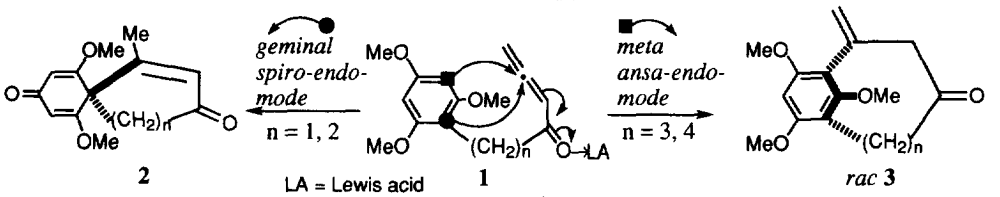
Abstract: Allenyl (2,4,6-trimethoxyphenyl)alkyl ketones **1** (n = 3,4) were treated with $B(CF_3SO_3)_3$ in CH_2Cl_2 to give racemic [6]and [7]metacyclophanes **3** (n = 3,4) in good yields. The structures of these strained compounds **3** (n = 3,4) were established by X-ray crystallographic analyses. The reaction of **3** (n = 3,4) with NaH in THF under reflux readily proceeded to give the corresponding β-naphthols **4** (n = 3,4) *via* an $S_{RN}Ar$ reaction pathway.

When von Braun and Neumann[1] first synthesized the remarkable compounds bearing one *meta*-bridged benzene in 1919, synthetic chemists challenged to develop a methodology for constructing [*n*]metacyclophanes. In later decades, various methods for synthesizing [*n*]metacyclophanes with one bridged aromatic ring have been independently reported by Prelog,[2a] Nozaki,[2b,c] Bickelhaupt,[2d,e] Effenberger,[2f] and Shea[2g] groups. Recently, Bickelhaupt and his coworkers have extensively studied the reactivity of dihalo[5]metacyclophanes, and reported interesting and unusual transannular reactions occurring *via* the $S_{RN}Ar$ mechanism.[3] In this communication, we describe the first endo-mode type intramolecular cyclization at the phenyl moiety brought about by a conjugated allenyl ketone system to give a new type of racemic(*rac*) trimethoxy-substituted [6] and [7]metacyclophanes, and their transannular reactions *via* an $S_{RN}Ar$ mechanism.

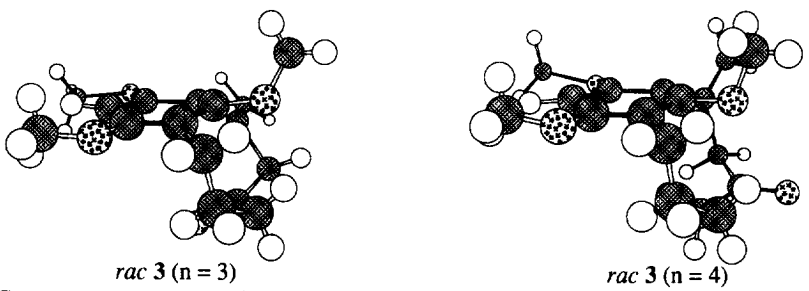


Scheme 1

We have been developing intramolecular carbocyclic and heterocyclic endo-mode cyclization reactions using high electrophilicity of the Lewis or Brønsted acid-generated cationic sp carbon atom of the conjugated allenyl ketone moiety toward a substituted benzene or nucleophilic hetero atom.[4] Recently, however, we have achieved an intramolecular *geminal spiro-endo-mode* ring closure of allenyl (2,4,6-trimethoxyphenyl)alkyl ketones **1** (n = 1,2) to give the corresponding bicyclic spiro compounds **2** (n = 1,2) in fairly good yields.[5] This successful cyclization of **1** (n = 1,2) prompted us to attempt an intramolecular *meta ansa-endo-mode* ring closure of the allenyl (2,4,6-trimethoxyphenyl)alkyl ketones **1** having more CH_2 groups (n = 3,4) as shown in Scheme 1. The details of this *meta ansa-endo-mode* cyclization with high yields are as follows. To a solution of $B(CF_3SO_3)_3$ which was prepared by stirring a mixture of BH_3•THF (1M solution in THF) (434 μl, 0.43 mmol) with CF_3SO_3H (115 μl, 1.30 mmol) in CH_2Cl_2 (10 ml) at 0 ℃ for 15 min was added a solution of compound **1** (n = 3)[6] (100 mg, 0.36 mmol) in CH_2Cl_2 (10 ml) at -78 ℃. After being stirred at -78 ℃ for 5 min,

the reaction mixture was treated as usual[4,5] to afford *rac* [6]metacyclophane **3** (n = 3) [80 mg, colorless prisms, mp 131 °C (CH_2Cl_2-hexane)] in 80% yield (Schemes 1 and 2). Similar treatment of **1** (n = 4)[6] with 1.2 mol eq. of $B(CF_3SO_3)_3$ in CH_2Cl_2 as described above gave *rac* [7]metacyclophane **3** (n = 4) [colorless prisms, mp 123-124 °C (CH_2Cl_2-hexane)] in 79% yield. This cyclization of **1** (n = 3,4) also proceeded in the presence of 1.2 mol eq. of BF_3•OEt_2 in CH_2Cl_2 at -78 ~ -20 °C over 2h to give the corresponding *rac* [6] and [7]metacyclophanes **3** (n = 3,4) in 77% (n = 3) and 86% (n = 4) yields, respectively.

The structures of these new strained molecules **3** (n = 3,4) were established by X-ray crystallographic analyses (*vide infra*).[7] In these cyclization reactions, spiro compounds **2** (n = 3,4) were not obtained.[8] Suitable location of two reaction centers, the electrophilic sp cationic carbon atom and the electron-rich carbon atom on the substituted benzene ring, depending on the carbon chain length (n value of **1**) should account for the selectivity of the cyclization mode leading to the spiro compound or the metacyclophane.[8] X-ray analyses of the new *rac* [6] and [7]metacyclophanes **3** (n = 3,4) revealed the nonplanarity of the trimethoxy-substituted benzene ring, which adopted a boat conformation with bow [C(2)-C(1)-C(6)] and stern [C(3)-C(4)-C(5)], as demonstrated by their χ^2-test, the torsion angle, and inspection of the side view of their crystallographic structures (Fig. 1).[7] Our *meta ansa-endo-mode* cyclization method is the first example of the direct ring closure at the aromatic moiety in order to furnish the strained [*n*]metacyclophanes bearing one bridged phenyl group. This particular *ansa-endo-mode* cyclization can readily lead to the formation of medium-sized (9- and 10-membered) carbocyclic molecules in high yields without employing a conventional high dilution procedure. One can synthesize optically active functionalized [6] and [7]metacyclophanes on the basis of our method by utilizing a suitable asymmetric induction procedure.[9]



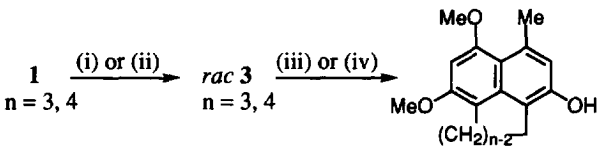
rac **3** (n = 3) *rac* **3** (n = 4)

Fig. 1. Computer-generated drawing (side view) of *rac* **3** (n = 3,4) derived from the X-ray coordinates.

The Nozaki[2c] and Bickelhaupt[3] groups independently investigated transannular ring closure of [5] and [6]metacyclophanes bearing halogen(s) (Cl, Br) in the presence of *n*-BuLi or complex reducing agents (NaH/$Ni(OAc)_2$/*tert*-amyl alcohol) or under photolytic conditions. Bickelhaupt[3] postulated the $S_{RN}Ar$ mechanisms for such a transannular reaction. Semmelhack and Bargar[10] examined photostimulated intramolecular coupling reactions between halogen (Br, I)-substituted benzenes and enolate anions *via* an $S_{RN}Ar$ process on the basis of the earlier independent studies by the Bunnett[11] and Wolfe[12] groups. There has never been any report, however, on the transannular ring closure between the strained benzene with electron-donating groups (*e.g.*, MeO) and enolate anion. To this end, compounds **3** (n = 3,4) were treated with 1.2 mol eq. of NaH in THF under reflux to give the corresponding tricyclic β-naphthols **4** (n = 3) [97%, yellow prisms (EtOAc), mp 166-167 °C] and **4** (n = 4) [76%, yellow prisms (CH_2Cl_2-hexane), mp 110-111 °C], as we expected (Scheme 2).

The structures of **4** (n = 3,4) were confirmed by X-ray analysis (Fig. 2)[13] of **4** (n = 3) and the similar spectroscopic data of both β-naphthols **4** (n = 3,4). Similar treatment of **3** (n = 4) with NaH in the presence of 1.0 mol eq. of a radical scavenger, galvinoxyl[14] or 1,4-dinitrobenzene[15] in THF under reflux for 40 min resulted in 91% or 90% recovery of **3** (n = 4). Treatment of **3** (n = 4) with 1.2 mol eq. of NaH in THF at room

temperature for 2h also resulted in quantitative recovery of the starting compound. Similar treatment of **3** (n = 4) with NaH under irradiation with a Pyrex-filtered high-pressure mercury lamp at room temperature, however, caused the desired exothermic radical-promoted cyclization to give the β-naphthol **4** (n = 4) in 48% yield. 1,4-Dinitrobenzene inhibited even this photostimulated transannular reaction, resulting in 94% recovery of compound **3** (n = 4). Thermal or photostimulated treatment of **3** (n = 3) without NaH in THF resulted in 60% or 30% recovery of the starting compound with the remainder as decomposition products. Attempts at intramolecular thermal and photostimulated $S_{RN}Ar$ cyclization of a nonbridged ketone **11** with NaH in THF under reflux or at room temperature resulted in 94-100% recovery of the starting compound. With the experimental facts described above, this particular transannular reaction may be rationalized in terms of an $S_{RN}Ar$ pathway (Scheme 3: **5**→**6**→**7**→**8**→**9**→**4**) initiated by single electron transfer (SET) from the attacking enolate to the most strained aromatic carbon followed by rapid abstraction of a hydrogen with the resultant radical from the solvent, THF, leaving methoxide anion. Thus, we can neglect the plausible alternative S_NAr pathway *via* **10**. The new radical species obtained from photostimulated transannular reaction of the enolate **5** may, one hopes, be available for DNA-strand cleavage.[16]



(i) $B(CF_3SO_3)_3$, CH_2Cl_2, -78 °C, 5 min, n = 3 (80%), n = 4 (79%); (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 ~ -20 °C, 2h, n = 3 (77%), n = 4 (86%); (iii) NaH, THF, reflux, n = 3 (2h, 97%), n = 4 (40 min, 76%); (iv) NaH, THF, room temp., *hv*, 1h, n = 4 (48%)

Scheme 2

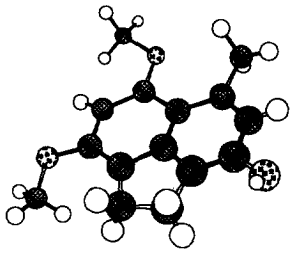
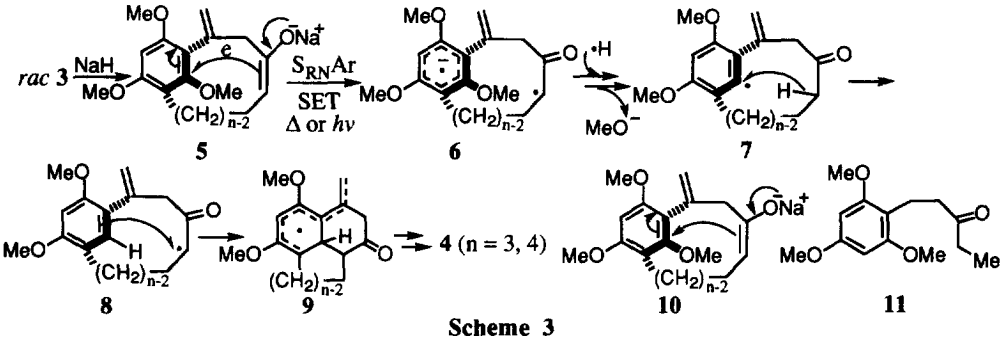


Fig. 2. Computer-generated drawing of **4** (n = 3) derived from the X-ray coordinates.



Scheme 3

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6. Allenyl ketones **1** [n = 3 : mp 46-47 °C (CH_2Cl_2-hexane), n = 4 : yellow oil] were readily prepared using the Weinreb-modified Grignard reaction[4a,b] of each corresponding key intermediate derived from commercially available 2,4,6-trimethoxybenzaldehyde *via* the several reaction steps.
7. The crystallographic data of compounds **3** (n = 3,4) are as follows. For **3** (n = 3): $C_{16}H_{20}O_4$, FW = 276.33, monoclinic, Space Group $P2_1/n$ (#14), a = 7.078(6) Å, b = 17.377(6) Å, c = 11.660(7) Å, Z = 4, Dcalc = 1.284 g/cm^3, V = 1529(1) Å^3, R = 0.066. For **3** (n = 4): $C_{17}H_{22}O_4$, FW = 290.36, monoclinic, Space Group $P2_1/n$ (#14), a = 14.326(6) Å, b = 15.922(8) Å, c = 14.634(6) Å, β = 104.95(3)°, Z = 8, Dcalc = 1.196 g/cm^3, V = 3224(2) Å^3, R = 0.074.
8. In the cyclization of **1** (n = 3,4) toward the metacyclophanes **3** (n = 3,4), a possible reaction pathway : dienone-phenol rearrangement of a spiro intermediate followed by Wagner-Meerwein type 1,2-shift must be neglected on the basis of the earlier experiments by us.[4b,5]
9. Stable existence of the chiral plane in *rac* [6] and [7]metacyclophanes **3** (n = 3,4) at room temperature was verified by HPLC analysis employing the Shimadzu LC-6A instrument equipped with an SPD-6A UV detector as follows: Compound **3** (n = 3): chiral column, Daicel A(S)MBC, 4.6 mm i.d. X 25 cm; eluent, *i*-PrOH-hexane (1 : 40); flow rate, 1.0 mL/min; detection, UV 254 nm; retention time of the racemate, 20.1 min and 22.6 min. Compound **3** (n = 4) : chiral column, Daicel CHIRALCELL OD, 4.6 mm i.d. X 25 cm; eluent, *i*-PrOH-hexane (1: 40) ; flow rate, 0.3 mL/min; detection, UV 254 nm; retention time of the racemate, 9.5 min and 10.8 min.
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13. The crystallographic data of compound **4** (n = 3) are as follows. $C_{15}H_{16}O_3$, FW = 244.29, monoclinic, Space Group $P2_1/c$ (#14), a = 12.692(2) Å, b = 4.899(1) Å, c = 19.503(1) Å, β = 106.131(6)°, Z = 4, Dcalc = 1.39 g/cm^3, V = 1164(3) Å^3, R = 0.044.
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