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Two Fascinating Rearrangements Through Selective Placement of Bromine Substituents. Photochemical Synthesis of 3-Bromo-7-(bromomethyl) tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-10(12)-ene-9,11-dione and its Rearrangement with Amines

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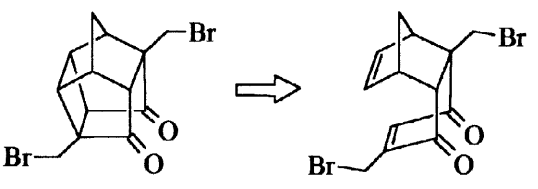
Abstract

A novel entry into 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undec-10(12)-ene-9,11-dione, which readily undergoes further rearrangement with primary amines, has been developed through photolysis of 2,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione.

Key words: Cage compounds, rearrangement, photochemistry, radical and radical reactions

Studies towards the synthesis and rearrangement of polycyclic cage compounds continue to be a fascinating area of research [1]. The facile formation of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane system through [$_{\pi}2_s$+$_{\pi}2_s$] photocycloaddition first reported by Cookson [2] has been used extensively for enriching the chemistry of polycyclic cage compounds by Mehta [3], Eaton [4] and Marchand [5]. Through careful placement of substituents on the pentacyclic system and using selective ring cleavage techniques, Mehta et.al. have shown the exceptional versatility of such compounds for the rapid synthesis of natural and unnatural tricyclopentanoids [3c, d]. Attracted by the various methods by which bromomethyl substituted pentacyclic cage system such as **1** could be triggered to undergo rearrangement leading to uncaged systems useful in natural product synthesis, we initiated a study towards the synthesis of **1** through the [$_{\pi}2_s$+$_{\pi}2_s$] photocycloaddition of its logical precursor **2**.



1 **2**

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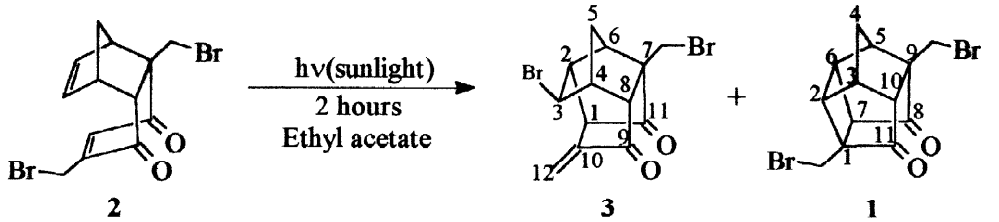
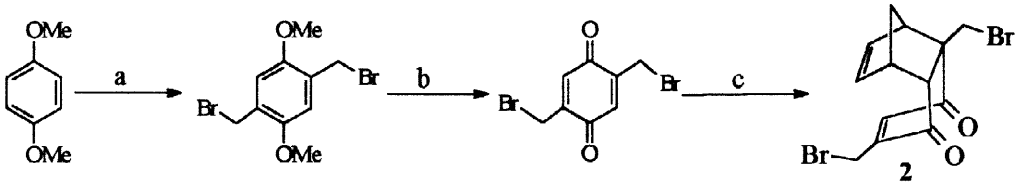
This has led to the unravelling of a novel photochemically initiated bromine radical mediated cascade rearrangement leading to 3-bromo-7-(bromomethyl)tetracyclo [5.3.1.$0^{2,6}$.$0^{4,8}$]undec-10(12)-ene-9,11-dione **3** along with the required pentacyclic dione 1,9-bis(bromomethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undec-8,11-dione **1** as shown below. We delineate here the details of the synthesis of **1**, **2** and **3**; and further rearrangement of **3** in the presence of primary amines.



2 **3** **1**

Results and Discussion

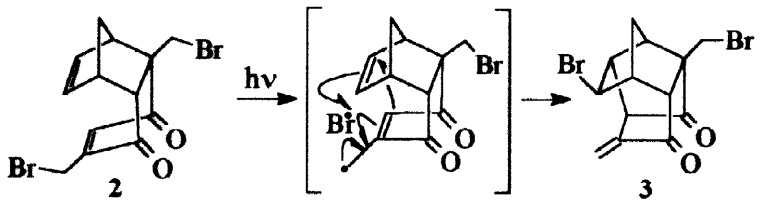
Synthesis of 2,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **2**, was achieved in 88% yield through the Diels-Alder cycloaddition of cyclopentadiene and 2,5-bisbromomethyl-1,4-benzoquinone. The latter was synthesised rapidly in two steps *viz.* bisbromomethylation of 1,4-dimethoxybenzene using a sonicated version of Gates method [6] recently developed by us [7] followed by oxidation [8]. (Scheme 1)



Conditions : a) 3 eq. paraformaldehyde, 3 eq. 33% HBr in glacial acetic acid, glacial acetic acid, sonication, 1 hour, 65%. b) concentrated nitric acid, glacial acetic acid, RT, 1 hour, 37%. c) cyclopentadiene, dry benzene, ~10 °C-RT, 15 hours, 88%.

Scheme 1

A solution of **2** in degassed dry ethyl acetate was irradiated with sunlight for 2 hours. The major product was found to be UV active. After chromatographic separation using 10% ethyl acetate in petroleum ether, the major product **3** was obtained in 63% yield as white crystals from petroleum ether - ethyl acetate. Its infra-red spectrum, which showed absorption at 1715 and 1613cm^{-1}, as well as the ^{1}H NMR spectrum, which showed signals at δ 6.21 and δ 5.49, indicated the presence of an enone moiety having an exocyclic double bond. The structure was confirmed as **3** after obtaining ^{13}C NMR and DEPT-135 as well as 2D ^{1}H-^{1}H COSY spectra. The formation of **3** can be explained through the initial photolytic cleavage of the bromine-allylic carbon bond followed by radical reorganisation and final bromine radical capture as depicted in Scheme 2.



Scheme 2

The formation of a single bromine isomer and our further observation that irradiation in the presence of isopropanol also leads to the same compounds but in a slightly different ratio suggest that the bromine radical is still within the solvent cage and is recaptured immediately resulting in bromine at the C-3 position in **3**. The final proof of the structure of **3** was obtained through X-ray crystal structure determination (Figure 1). This photochemical transformation of **2** to **3** is especially interesting because Mehta et.al. have shown that the corresponding bischloromethyl derivative on irradiation leads to 75% yield of the corresponding pentacyclic diketone with no trace of rearranged product [9].

The minor product from the reaction obtained in 18% yield as pure white crystals (mp 95-96°C) was readily identified as the 1,9-bis(bromomethyl)pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione **1** based on the spectral data.

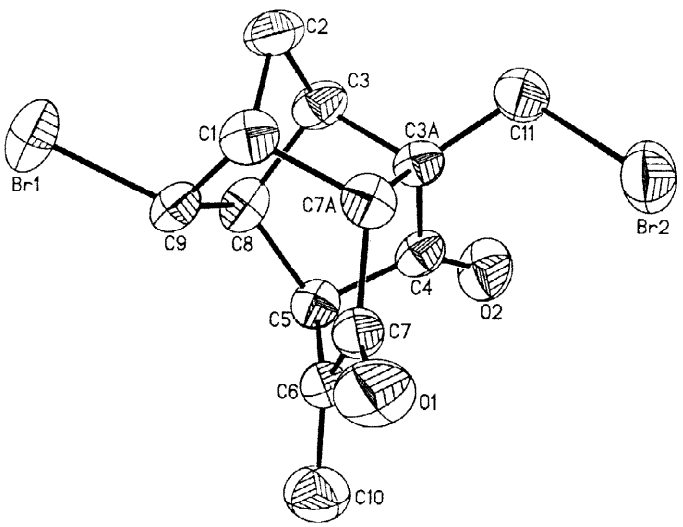


Figure 1
Compound **3**

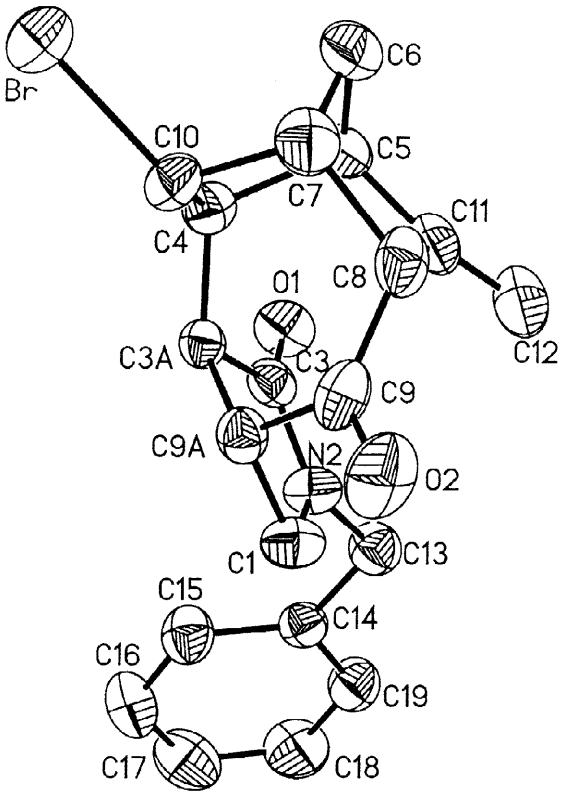
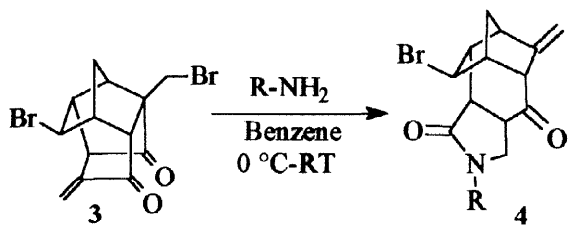


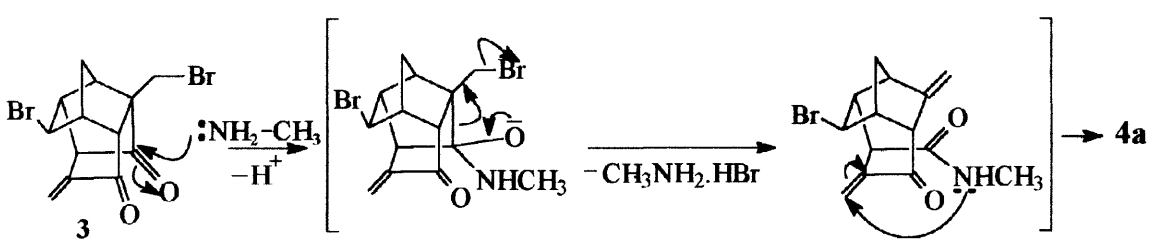
Figure 2
Compound **4c**

We then examined the reaction of **3** with primary amines. Treatment of **3** in benzene with an excess of methylamine at 0 °C-rt furnished a product in 82% yield. The mass spectrum of the product clearly indicated the loss of one bromine atom and the addition of one equivalent of amine. Salient features in the spectral data include (i) signals at δ 5.03 and 4.70 in ^{1}H NMR (one proton each) and δ 145.66 and 109.06 in ^{13}C NMR indicative of an exocyclic methylene group. (ii) signal at δ 209.36 in ^{13}C NMR and λ_{max} 1708cm^{-1} in IR spectrum suggestive of carbonyl group. (iii) signal at δ 2.68(singlet, 3H) in ^{1}H NMR and λ_{max} 1681cm^{-1} in IR spectrum suggestive of -NCH$_3$ group and amide linkage. The ^{13}C NMR spectrum and the DEPT experiments conducted provided conclusive evidence with which we arrived at structure **4a** for the rearranged product. We suggest the mechanism shown in Scheme 3 for the formation of the product.



Amine	Time and Yield
4a - R = Me	1 h, 82.4%
4b - R = $(CH_2)_3CH_3$	48 h, 72.2%
4c - R = CH_2Ph	38 h, 82.2%
4d - R = homoveratryl	48 h, 50.3%

The rearrangement of **3** was generalised using other primary amines. **3** was reacted with a large excess (~20 equivalents) of the amine for 1-2 days giving the corresponding lactam (reaction was more sluggish on treatment with lesser amount of amine), and the products were fully characterised based on their spectra. Final confirmation of the structure was obtained from X-ray diffraction studies on the product **4c** obtained by the reaction of **3** with benzylamine (Fig 2).



Scheme 3

Thus we have shown that selective placement of bromine atoms can trigger fascinating rearrangements in polycyclic cage compounds. Studies on the rearrangement of the bischloromethyl and bisbromomethyl pentacyclic diketones are in progress.

Acknowledgments

M. S. Nair thanks Prof. G. Mehta for suggestions and for providing facilities to initiate the programme in his laboratory at the University of Hyderabad and Prof. M.V. George for providing high resolution mass spectra. US and SJ thanks the CSIR for Research Fellowship.

Experimental Details

All experiments were carried out in oven dried glass-ware. Analytical thin layer chromatography was performed on silica gel GF_{254} TLC plates. Purification by gravity column chromatography was carried out using silica gel (100-200 mesh). Mixtures of ethyl acetate and petroleum ether were used as eluent. Melting points were recorded on Aldrich Meltemp-II and are uncorrected. IR spectra were recorded on a Nicolet (impact 400D FT-IR) spectrophotometer. NMR spectra were obtained using chloroform-d as solvent on Bruker AC-200, Bruker DPX 300 and Bruker 500 MHz NMR spectrometers. Chemical shifts are given in δ scale with TMS as internal reference.

Procedure for the preparation of 2,5-bis(bromomethyl)tricyclo[6.2.1.$0^{2,7}$]undec-4,9-diene-3,6-dione **2**

A solution of 2,5-bisbromomethyl-1,4-benzoquinone (0.85g, 2.9 mmol) in dry benzene (20 mL) was cooled in an ice-water bath (~ 10 °C) and freshly cracked cyclopentadiene (0.50 mL, 6.1 mmol) was added dropwise. The reaction mixture was left stirring at room temperature for 15 hours, TLC then indicated that the starting material had been completely consumed. The reaction was worked up by removing the solvent and the residue was purified by silica gel column chromatography using 5% ethyl acetate in petroleum ether as the eluent which afforded **2** as a pale yellow solid (0.92 g, 88%). This was recrystallised from CH_2Cl_2-petroleum ether giving large pale yellow crystals (m.p. 110-112 °C).

Spectral data for **2**

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72(s, 1H), 6.14-6.07(m, 2H), 4.27-4.23(m, 1H), 4.04-3.98(m, 2H), 3.46(s, 1H), 3.29-3.20(m, 2H), 3.10(s, 1H), 1.61(s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 196.3, 148.8, 140.1, 136.7, 136.4, 59.9, 55.9, 54.2, 49.9, 47.2, 39.9, 25.3. UV(CH_2Cl_2) (λ_{max}) = 243 nm (ε = 140759). FT-IR(KBr, ν_{max}/cm^{-1}) : 3036, 2982, 1674, 1620, 1243. Anal. Calcd. for $C_{13}H_{12}O_2Br_2$: C, 43.37; H, 3.36. Found : C, 43.65; H, 3.56.

Procedure for the photolysis of **2**

The Diels-Alder adduct **2** (0.48 g, 1.3 mmol) was dissolved in 100 mL of dry ethyl acetate, degassed with argon gas and exposed to bright sunlight for two hours. TLC at the end of this period showed the complete consumption of starting material along with the formation of two products. The reaction was worked up by removing the solvent and the residue was separated using silica gel column chromatography. Elution with 10% ethyl acetate in petroleum ether afforded **3** (0.30 g, 63%), which was crystallised from ethyl acetate-petroleum ether giving white crystals (m.p. 136-137 °C). Further elution gave **1** (0.08 g, 18%) which readily recrystallised from ethyl acetate-petroleum ether as pure white crystals (m.p. 95-96 °C).

Spectral data of **3**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21(s, 1H), 5.49(s, 1H), 4.41(s, 1H), 3.56(½ABq, J = 10.6 Hz, 1H), 3.47(d, J = 8.8 Hz, 1H), 3.28(½ABq, J = 10.6 Hz, 1H), 3.25-3.22(m, 1H), 3.10(d, J = 4.9 Hz, 1H), 2.97-2.96(m, 1H), 2.81(½ABq, J = 11.9 Hz, 1H), 2.68(d, J = 5.5 Hz, 1H), 1.98(½ABq, J = 11.9 Hz, 1H). ^{13}C NMR (75 MHz): δ 205.0, 194.7, 141.5, 124.8, 62.6, 59.1, 53.2, 52.2, 49.5, 45.8, 45.6, 36.6, 30.3. UV(CH_2Cl_2) $(\lambda_{max})_1$ = 230 nm (ε = 6354), $(\lambda_{max})_2$ = 251 nm (ε = 4125) and $(\lambda_{max})_3$ = 309 nm (ε = 1031). FT-IR(KBr, ν_{max}/cm^{-1}) : 2989, 1762, 1715, 1613. HRMS (EI) found for (M^+) 359.9184; $C_{13}H_{12}O_2Br_2$ requires 359.9183.

Crystal data for **3**

$C_{13}H_{12}Br_2O_2$, colourless crystalline solid, 0.33 x 0.20 x 0.12 mm., monoclinic, Space group : $P2_1/c$. Unit cell dimensions : a = 14.2893(2) Å alpha = 90°; b = 13.5780(1) Å beta = 96.556(1)°; c = 12.9552(2) Å gamma = 90°. R indices (all data) : R1 = 0.0996, wR2 = 0.0847, Volume = 2497.13(6) Å^3, Z = 8. Density(calculated) = 1.915 Mg/m^3. F(000) = 1408. Absorption coefficient = 6.478 mm^{-1}.

Spectral data of **1**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63(½ABq, J = 10.9 Hz, 1H), 3.51(dd, J_1 = 21.8 Hz, J_2 = 10.8 Hz, 2H), 3.35(½ABq, J = 10.9 Hz, 1H), 3.21-3.18(m, 2H), 3.04-2.98(m, 2H), 2.78-2.76(m, 1H), 2.62(d, J = 4.3 Hz, 1H), 2.25(½ABq, J = 11.7 Hz, 1H), 1.94(½ABq, J = 11.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.9, 207.9, 62.6, 60.3, 52.7, 48.0, 47.4, 43.9, 42.9, 39.5, 34.9, 30.0, 29.7. FT-IR(KBr, ν_{max} / cm^{-1}) : 2975, 2874, 1755, 1431, 1236. HRMS (EI) found for (M^+) = 359.9184; $C_{13}H_{12}O_2Br_2$ requires 359.9183.

Procedure for the reaction of **3** with methylamine

58 mg of **3** (0.16 mmol) was dissolved in 15 mL of benzene and after cooling this solution in an ice-water bath (~ 5 °C), methylamine gas was passed through it for half an hour. The reaction mixture was left stirring for one hour and TLC examination at the end of this period showed the formation of a single product. The reaction was worked up by removing the solvent and the residue was chromatographed on a silica gel column affording **4a** (41 mg, 82%) as a white solid.

This was recrystallised from CH_2Cl_2-petroleum ether as white needle-like crystals (m.p. 156-157 °C).

Spectral data of **4a**

^1H NMR (300 MHz, $CDCl_3$): δ 5.03(s, 1H), 4.70(s, 1H), 4.09(s, 1H), 3.83-3.76(m, 1H), 3.42-3.17(m, 5H), 3.02-2.97(m, 1H), 2.91(d, J = 4.9 Hz, 1H), 2.68(s, 3H), 2.61(½ABq, J = 10.8 Hz, 1H), 1.56 (½ABq, J = 10.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 172.3, 145.7, 109.1, 57.7, 52.9, 52.8, 48.3, 47.8, 46.2, 44.8, 44.7, 38.9, 29.6. UV(CH_2Cl_2, λ_{max}) = 228 nm. FT-IR(KBr, ν_{max} / cm^{-1}) : 2989, 2881, 1708, 1681, 1506, 1452, 1404, 1290. HRMS (FAB) found for (M^++H) = 310.0443; $C_{14}H_{16}NO_2Br$ requires 309.0364.

General procedure for the reaction of **3** with other primary amines

To a solution of **3** (0.04 g, 0.1 mmol) in dry benzene (15 mL) , cooled in an ice bath, was added the amine (large excess, ~20 equivalents) and the reaction mixture was stirred at room temperature till all the starting material was consumed (38-48 h). The reaction was worked up by removing the solvent and the residue on silica gel column chromatography using mixtures of ethyl acetate and petroleum ether afforded the lactams in good yield. The products were recrystallised from CH_2Cl_2-petroleum ether.

Data for **4b**

mp : 106-108°C. ^1H NMR(300 MHz, $CDCl_3$): δ 5.03(s, 1H), 4.70(s, 1H), 4.10(s, 1H), 3.78-3.74(m, 1H), 3.41-3.15(m, 4H), 3.07-3.02(m, 2H), 2.91-2.85(m, 2H), 2.61(½ABq, J = 10.8 Hz, 1H), 1.71(s, 1H), 1.55(½ABq, J = 10.8 Hz, 1H), 1.43-1.25(m, 4H), 0.93-0.88(m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.3, 171.9, 145.3, 109.9, 57.8, 53.1, 50.9, 48.2, 47.8, 46.0, 45.1, 44.6, 42.9, 39.0, 28.7, 20.2, 13.7. FT-IR(KBr, ν_{max}/cm^{-1}) : 2989, 2962, 2928, 2874, 1701, 1499. HRMS (FAB) found for (M^++H) 352.0928; $C_{17}H_{22}NO_2Br$ requires 351.0834.

Data for **4c**

mp : 155-156°C. ^1H NMR(200 MHz, $CDCl_3$) δ 7.32–7.20(m, 5H), 4.85(s, 1H), 4.61(d, J=14.4 Hz, 1H), 4.51(s, 1H), 4.09(s, 1H), 3.95(d, J=14.1 Hz, 1H), 3.70–3.59(m, 1H), 3.46–3.24(m, 3H), 3.19–2.87(m, 2H), 2.61(½ABq, J=10.8 Hz, 1H), 1.62(s, 1H), 1.55(½ABq, J=10.8 Hz, 1H), 1.26(s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 171.9, 145.1, 135.0, 128.9(2 carbons), 128.7(2 carbons), 127.9, 109.8, 57.7, 53.1, 50.6, 48.2, 47.7, 47.3, 46.3, 45.1, 44.4, 39.0. FT-IR(KBr, ν_{max}/cm^{-1}) : 2982, 2881, 1694, 1506, 1452. HRMS (FAB) found for (M^++H) 386.0748; $C_{20}H_{20}NO_2Br$ requires 385.0677.

Crystal data for **4c**

$C_{20}H_{20}BrNO_2$, colourless crystalline solid, 0.40 x 0.20 x 0.10 mm., monoclinic, space group : $P2_1$ /n. Unit cell dimensions : a = 11.1648(2) Å alpha = 90°; b = 6.8268(1) Å beta = 100.6140(10)°; c = 22.6147(3) Å gamma = 90°. R indices (all data) : R1 = 0.0703, wR2 = 0.0851, Volume =

1694.20(5) $Å^3$, Z = 4. Density(calculated) = 1.514 Mg/m^3. F(000) = 792. Absorption coefficient = 2.438 mm^{-1}.

Data for 4d

mp : 98-100°C. ^1H NMR(300 MHz, $CDCl_3$) δ 6.80-6.70(m, 3H), 5.01(s, 1H), 4.68(s,1H), 4.08(s, 1H), 3.87-3.85(m, 6H), 3.71-3.65(m, 2H), 3.40-3.26(m, 3H), 3.11-3.02(m, 3H), 2.90-2.89(m, 1H), 2.71-2.69(m, 2H), 2.60(½ABq, J= 10.8 Hz, 1H), 1.55(½ABq, J = 10.8 Hz, 1H), 1.26(s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.17, 172.13, 149.06, 147.78, 145.32, 130.76, 120.49, 111.73, 111.36, 109.93, 57.84, 55.93(2 carbons), 52.99, 51.24, 48.22, 47.78, 45.93, 44.99, 44.60, 44.50, 38.98, 32.64. FT-IR(KBr, ν_{max}/cm^{-1}) : 2948, 2840, 1694, 1593, 1526. HRMS (FAB) found for (M^++H) 460.1126; $C_{23}H_{26}NO_4Br$ requires 459.1045.

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[7] The results will be published elsewhere. Typical experimental procedure for bisbromomethylation consisted of sonicating *p*-dimethoxy benzene in glacial acetic acid with three equivalents of paraformaldehyde and three equivalents of 33% HBr in glacial acetic acid for one hour. This gave the 2,5-(bisbromomethyl)-1,4-dimethoxybenzene in 65% yield. Similarly by using concentrated hydrochloric acid instead of HBr we obtained 2,5-(bischloromethyl)-1,4-dimethoxybenzene in 68% yield.

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