RING OPENING SN2' REACTIONS OF 1,4,5,8-DIEPOXY-1,4,5,8-TETRAHYDROANTHRACENES BY ORGANOLITHIUM REAGENTS

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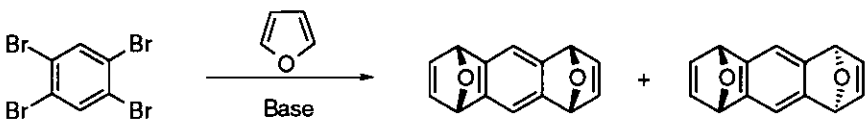
This paper is dedicated to Prof. Koji Nakanishi with occasion of his 75th birthday

Abstract - The nucleophilic S_N2' bridge opening of diepoxytetrahydroanthracenes with organolithium reagents to produce hydroanthracene derivatives shows a dependence of the excess of reagent as well as the relative stereochemistry of the oxygen bridge.

The 1,4,5,8-diepoxy-1,4,5,8-tetrahydroanthracenes (**1**) and (**2**), interesting building blocks for the synthesis of macropolycyclic derivatives[1] have been prepared by reaction of 1,2,4,5-tetrabromobenzene with furan in the presence of a strong base, usually BuLi[1] or NaH,[2] *via* the generation of the related *bis*aryne (Scheme 1).



Scheme 1

Stoddart and coworkers prepared **1** and **2** by reaction of tetrabromobenzene with BuLi and furan using a tetrabromobenzene : BuLi ratio of 1 : 8.8 [1] obtaining a mixture of **1** and **2** in 44% yield. Compound (**2**) was unambigously characterized by X-Ray analysis. We speculated that, in the presence of this considerable excess of organolithium reagent, the possibility of nucleophilic ring opening of compounds (**1**) and (**2**) by action of the organolithium reagent could not be ruled out.

Ring opening SN2' reactions of 7-oxanorbornenic derivatives [3] and 1,4-dihydro-1,4-epoxynaphthalene [4] by organolithium reagents have been previously described. However, to the best of our knowledge, this kind of ring opening has not been reported using compounds such as **1** and **2**. On the other hand, the possibility of synthesize compounds with structures like **3** (Figure 1), showing an unaltered 7-oxanorbornenic ring system, could be particularly useful since these compounds can be considered as building blocks for the synthesis of more complex, interesting molecules such as hydroanthraquinones and other hydroanthracene derivatives, *via* synthetic elaboration of both 7-oxanorbornenic and cyclohexene moieties.[5]

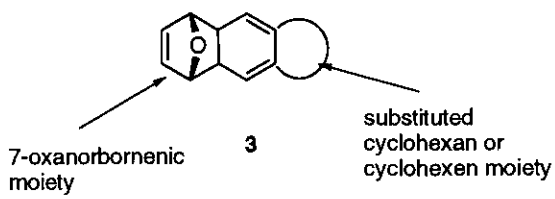
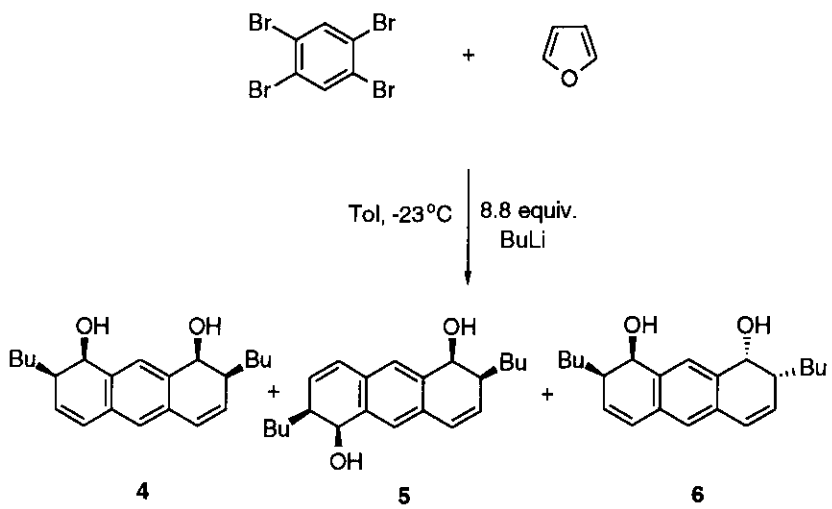


Figure 1

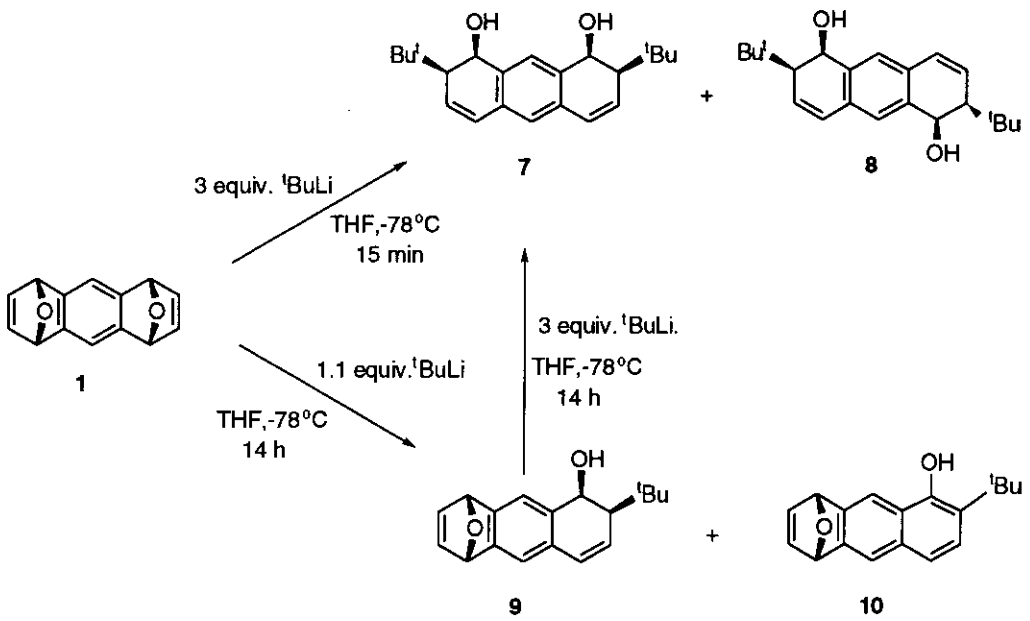
In our hand, the reaction of 1,2,4,5-tetrabromobenzene with furan in the presence of 8.8 equiv. of BuLi under the conditions previously described by Stoddart,[1] afforded a mixture of three compounds that were isolated and identified as derivatives (**4**), (**5**) and (**6**) with isolated yields of 10, 14 and 10% respectively (Scheme 2).



Scheme 2

The identification of these compounds was determined on the basis of criteria described below. This result confirmed our previous assumption and then we proceed to perform a more detailed study of this reaction considering as starting material compounds (**1**) and (**2**) prepared following the Hart's procedure.[1] Thus, the reaction of the *syn* isomer (**1**) with 3 equiv. of ^{t}BuLi in THF at -78°C over a period of 15 min afforded a 1:1 mixture of compounds (**7**) and (**8**) in 76% yield (Scheme 3). The stereochemistry of the reaction was assumed considering the invariable *exo* attack of nucleophiles on this compound.[3] On the other hand, the regiochemistry was determined taking in account that in compound (**7**) the signals corresponding to the aromatic protons H-9 and H-10 are two apparent singlets (^{1}H-NMR 300 MHz, δH-9 = 7.20 ppm, δH-10 = 6.92 ppm) whereas in compound (**8**) only one singlet was observed for both protons due to the symmetry of the compound (δH-9 = δH-10 = 7.07 ppm).

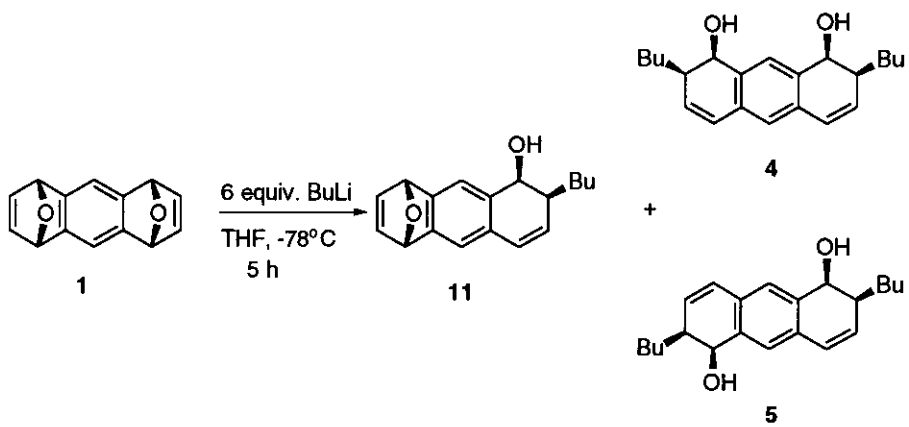
When the reaction of **1** was performed with 1.1 equiv. of ^{t}BuLi at -78°C over a period of 14 h, compound (**9**) was isolated (40%) together with 25% of **10**, 5% of the mixture of **7** and **8** and 18% of starting material (Scheme 3) .



Scheme 3

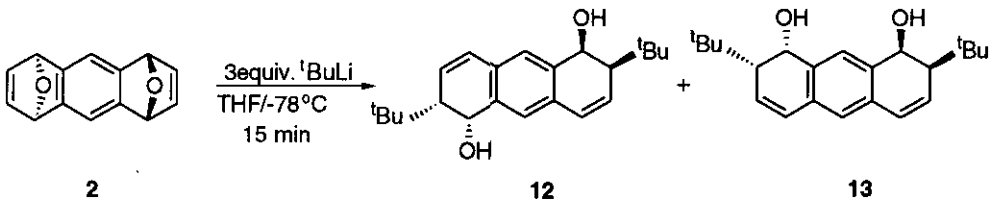
The regioselective transformation of **9** in **7** was possible by reaction of **9** with 3 equiv. of ^{t}BuLi (THF, -78°C, 14 h, 40% yield).[6] No traces of compound **(8)** were detected in the crude reaction mixture. From these results, we can deduce that the ring opening of **1** is not sequential even though the regiochemistry of the reaction of the second 7-oxanorbornenic ring in **9** appears to be controlled by the first ring opening.

It should be pointed out that the synthesis of analogue of **9** using BuLi **11** needed 6 equiv. of organolithium reagent and a reaction time of 5 h at the same temperature. Under these conditions, 37% of **11** was obtained, together with 20% of the mixture of **4** and **5** in a ratio 2:1 (Scheme 4).



Scheme 4

The behaviour of the *anti* isomer (**2**) under the same reaction conditions was different. Thus, reaction of **2** with 3 equiv. of ^{t}BuLi (THF, -78°C, 15 min) yielded a mixture of compounds (**12**) and (**13**) in a ratio 1:2.3 and 64% yield (Scheme 5).



2 **12** **13**

Scheme 5

However, the reaction of **2** with 1.1 equiv of ^{t}BuLi under the same conditions as above, was significantly slower compared to the same reaction performed on **1** and only after two days of reaction time at room temperature, a complex reaction crude was obtained, from which 10% of mixture **12** and **13** and 30% of starting material could be isolated.

In summary, the ring opening S_N2' reactions of diepoxytetrahydroanthracenes depend on the amount of the organolithium reagent as well as the relative stereochemistry of the oxygen bridge and permit the access to hydroanthracene derivatives starting from furan.

EXPERIMENTAL

General Methods. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran was distilled from sodium and benzophenone; toluene from calcium hydride; all other solvents were reagent grade. Commercial BuLi (1.6 M solution in hexane) and ^{t}BuLi (1.7 M solution in pentane) were purchased from Aldrich. Flash chromatography was performed using Merck 230-400 mesh silica gel. Analytical TLC was carried out on Merck (Kiesegel 60F-254) silica gel plates with detection by UV light and acidic vanillin solution in ethanol. Melting points were determined on a Büchi 512 apparatus and are uncorrected.

(1S*,2S*,7R*,8R*)-2,7-Di-n-butyl-1,8-dihydroxy-1,2,7,8-tetrahydroanthracene(4), (1S*,2S*,5S*,6S*)-2,6-di-n-butyl-1,5-dihydroxy-1,2,5,6-tetrahydroanthracene (5) and (1R*,2R*,7R*,8R*)-2,7-di-n-butyl-1,8-dihydroxy-1,2,7,8-tetrahydroanthracene(6). ^{n}BuLi (41.9 mL, 1.6 M, 8.8 equiv) was added dropwise over a period of 90 min to a stirred solution of 1, 2, 4, 5-tetrabromobenzene (3 g, 7.62 mmol) and furan (9.1 mL, 126 mmol) in anhydrous toluene (108 mL) at -23°C under an atmosphere of argon. Upon completion of the addition, the reaction mixture was allowed to warm to rt whilst being stirred overnight. The reaction was quenched with H_2O and stirred vigorously for 20 min. The organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated under reduce pressure. The resulting yellow-brown gum was purified by column chromatography on silica gel using EtOAc/light petroleum (1:2) as eluant to afford 500 mg of a white solid, which was subjected to

column chromatography on silica gel (CH_2Cl_2/Et_2O, 3:2) to afford, in order of elution, a white solid, characterized as **4** (165 mg, 10%), followed by a white solid, characterized as **5** (170 mg, 14%) and finally, a third white solid characterized as **6** (165 mg, 10%). Data of **4** : *Rf*=0.78 (CH_2Cl_2/Et_2O, 3:2). mp: 139-140°C (recrystallization solvent: hexane/ether). ^{1}H NMR (300 MHz): δ 7.22(s, 1H), 6.79(s, 1H), 6.41(dd, J=9.6, 2.4 Hz, 2H), 5.73(dd, J=9.6, 1.8 Hz, 2H), 4.49(d, J=4.5 Hz, 2H), 2.36(m, 2H), 1.75(br s, 2H), 1.55(m, 12H), 0.85(t, J=7.0 Hz, 6H). ^{13}C NMR (75 MHz): δ 135.8, 132.8 131.6, 127.0, 126.2, 124.5, 70.0, 40.3, 29.3, 28.7, 22.8, 14.0. IR (KBr): 3350, 2960, 1320, 900 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.72; H, 9.07. Data of **5**: *Rf*=0.71 (CH_2Cl_2/Et_2O, 3:2). mp: 142-143°C (recrystallization solvent: hexane/ether). ^{1}H NMR (300 MHz): δ 7.27(s, 2H), 6.54 (dd, J=9.6, 2.5 Hz, 2H), 5.84(dd, J=9.6, 2.1 Hz, 2H), 4.59(br s, 2H), 2.43(m, 2H), 1.80(m, 2H), 1.35(m, 12H), 0.94(t, J=7.1 Hz, 6H).^{13}C NMR (75 MHz): δ 136.9, 132.1, 131.4, 126.6, 125.9, 70.2, 40.6, 29.5, 28.8, 23.0, 14.2. IR (KBr): 3350, 2980, 1450, 1360, 1080, 900 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.05; H, 9.49. Data of **6**: *Rf*=0.67 (CH_2Cl_2/Et_2O, 3:2). mp: 141-142°C (recrystallization solvent: hexane/ether). ^{1}H NMR (300 MHz): δ 7.24(s, 1H), 6.85(s,1H), 6.48(dd, J=9.6, 2.4 Hz, 2H), 5.81(dd, J=9.5, 1.9 Hz, 2H), 4.50(d, J=4.8 Hz, 2H), 2.37(m, 2H), 2.06 (br s, 2H), 1.41(m, 12H), 0.94(t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz): δ 135.9, 133.1, 131.9, 127.3, 126.3, 124.5, 69.9, 40.5, 29.5, 28.9, 22.4, 14.1. IR (KBr): 3350, 2980, 1460, 1060, 900 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.63; H, 8.99.

(1S*,2S*,7R*,8R*)-2,7-Di-*tert*-butyl-1,8-dihydroxy-1,2,7,8-tetrahydroanthracene (7) and (1R*,2R*,5R*,6R*)-2,6-di-*tert*-butyl-1,5-dihydroxy-1,2,5,6-tetrahydroanthracene (8). To a cold solution (-78°C) of **1** (35 mg, 0.16 mmol) in THF (0.9 mL), ^{t}BuLi (0.58 mL, 1.7 M, 3.0 equiv) was added under argon. The solution was stirred at-78°C for 15 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The crude mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1), to afford, in order of elution, a white solid, which was subsequently characterized as **8** (18 mg, 39%), followed by a white solid, which was characterized as **7** (17 mg, 37%). Data of **7**: *Rf*=0.10 (CH_2Cl_2/Et_2O, 20:1). mp: 91-93°C (recrystallization solvent: hexane/ether). ^{1}HNMR (300 MHz): δ 7.20(s, 1H), 6.92(s, 1H), 6.63(dd, J=9.6, 3.0 Hz, 2H), 6.05(d, J=9.6 Hz, 2H), 4.74(s, 2H), 2.17(s, 2H), 1.59(s, 1H), 1.53(s,1H), 1.17 (s, 18H). ^{13}C NMR (75 MHz): δ 136.5, 132.8, 129.5, 127.4, 127.1, 124.5, 69.8, 50.5, 32.5, 28.7. IR (CCl_4): 3300, 2980, 1450, 1360 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.81; H, 9.17. Data of **8**: *Rf*=0.21(CH_2Cl_2/EtO_2, 20:1). mp: 154-155°C (recrystallization solvent: hexane/ether). ^{1}H NMR (300 MHz): δ 7.07(s, 2H), 6.64(dd, J=9.6, 3.3 Hz, 2H), 6.03(d, J=9.6 Hz, 2H), 4.75(br s, 2H), 2.19(s, 2H), 1.50(s, 1H), 1.47(s, 1H), 1.95(s, 18H).^{13}C NMR (75 MHz): δ 137.5, 131.7, 128.9, 127.3, 126.0, 70.1, 50.5, 32.5, 28.7. IR (CCl_4): 3380, 2960, 1465, 1400, 1360 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.25; H, 9.20.

(1S*,2S*,7R*,8R*)-2,7-Di-*tert*-butyl-1,8-dihydroxy-1,2,7,8-tetrahydroanthracene (7). To a cold solution (-78°C) of **9** (15.5 mg, 0.06 mmol) in THF (0.5 mL), ^{t}BuLi (0.15 mL, 1.7 M, 3.0

equiv) was added under argon. The solution was stirred at rt for 14 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The crude mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated under reduce pressure. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1), to afford 7.2 mg (40%) of **7** as a yellow oil.

(1R*,4S*,5S*,6S*)-6-*tert*-Butyl-1,4-epoxy-5-hydroxy-1,4,5,6-tetrahydroanthracene (9) and (1R*,4S*)-6-*tert*-butyl-1,4-epoxy-5-hydroxy-1,4-dihydroanthracene (10). To a cold solution (-78°C) of **1** (32.8 mg, 0.16 mmol) in THF (0.96 mL), ^{t}BuLi (0.1 mL, 1.7 M, 1.1 equiv) was added under argon. The solution was stirred at rt for 14 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The crude mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated under reduce pressure. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1), to afford 10.5 mg (25%) of **10** as a colorless oil, followed by 15.5 mg (40%) of **9** as a colorless oil. Data of **9**: *Rf*=0.16(CH_2Cl_2/Et_2O, 20:1). ^{1}H NMR (300 MHz): δ 7.20(s, 1H), 7.06(s, 1H), 7.00(s, 2H), 6.56(dd, J=9.9, 3.3 Hz, 1H), 6.03(d, J=9.9 Hz, 1H), 5.72(s, 2H), 4.66(d, J=4.8 Hz, 1H), 2.20(d, J=2.4 Hz, 1H), 1.61(br s, 1H), 1.21(s, 9H). ^{13}C NMR (75 MHz): δ 134.1, 129.8, 128.9, 127.5, 120.5, 119.0, 82.3, 82.2, 70.5, 50.7, 32.4, 28.7. IR (KBr): 3400, 2980, 1400, 1140, 870 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.62; H, 7.42. Data of **10**: *Rf*=0.19 (CH_2Cl_2/Et_2O, 20:1). ^{1}H NMR (300 MHz): δ 7.86(s, 1H), 7.51(s, 1H), 7.40(d, J=9.0 Hz, 1H), 7.27(d, J=8.4 Hz, 1H), 6.94(s, 2H), 5.80(s, 1H), 5.79(s, 1H), 5.43(s, 1H), 1.55(s, 9H).^{13}C NMR (75 MHz): δ 149.7, 143.8, 141.7, 141.6, 131.7, 128.1, 125.2, 120.4, 118.5, 111.5, 82.1, 81.8, 43.5, 30.5. IR (KBr): 3420, 2960, 1550, 1140, 870 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.05; H, 6.92.

(1R*,4S*,5S*,6S*)-6-n-Butyl-1,4-epoxy-5-hydroxy-1,4,5,6-tetrahydroanthracene (11). To a cold solution (-78°C) of **1** (20.0 mg, 0.10 mmol) in THF (0.90 mL), ^{n}BuLi (0.24 mL, 1.6 M, 6 equiv) was added under argon. The solution was stirred at rt for 5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The crude mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated under reduce pressure. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1), to afford 9.4 mg (37%) of **11** as a colorless oil. Data of **11**: *Rf*=0.34 (CH_2Cl_2/Et_2O, 10:1). ^{1}H NMR (300 MHz): δ 7.24(s, 1H), 7.23(s, 1H), 6.99(s, 2H), 6.42(dd, J=9.3, 2.7 Hz, 2H), 5.78(d, J=9.3 Hz, 1H), 5.69(d, J=3.6 Hz, 1H), 4.46(s, 1H), 2.40(m, 1H), 1.78(m, 1H), 1.42(m, 6H), 0.92(s, 3H). ^{13}C NMR (75 MHz): δ 142.9, 142.8, 131.2, 128.3, 126.7, 120.2, 118.9, 82.3, 77.4, 70.7, 40.8, 29.5, 28.7, 22.9, 13.9. IR(CCl_4): 3380, 2980, 1380, 1250, 780 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.44; H, 7.60.

(1S*,2S*,5R*,6R*)-2,6-Di-*tert*-butyl-1,5-dihydroxy-1,2,5,6-tetrahydroanthracene (12) and (1S*,2S*,7S*,8S*)-2,7-di-*tert*-butyl-1,8-dihydroxy-1,2,7,8-tetrahydroanthracene (13). To a cold solution (-78°C) of **2** (32 mg, 0.15 mmol) in THF (0.7 mL), ^{t}BuLi (0.27 mL, 1.7 M, 3.0 equiv) was added under argon. The solution was stirred at -78°C for 15 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The crude mixture was extracted with EtOAc, dried over

$MgSO_4$ and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1), to afford, in order of elution, a white solid, characterized as **12** (11 mg, 20%), followed by a white solid, which was characterized as **13** (24 mg, 44%). Data of **12**: *Rf*=0.66 (hexane/EtOAc,1:2). mp: 164-165°C (recrystallization solvent: hexane/ether). ^1H NMR (300 MHz): δ 7.09(s, 2H), 6.66(dd, J=10.2, 3.3 Hz, 2H), 6.06(ddd, J=10.2, 3.6, 1.7 Hz, 2H), 4.77(d, J=1.2 Hz, 1H), 4.75(d, J=1.2 Hz, 1H), 2.23(m, 2H), 1.45(s, 1H), 1.43(s, 1H), 1.18(s, 18H).^{13}C NMR (75 MHz): δ 137.6, 131.9, 129.0, 127.3, 125.9, 70.1, 50.5, 32.5, 28.7. IR (CH_2Cl_2) : 3400, 3000, 1430, 1370, 900 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.05; H, 9.35. Data of **13**: *Rf*=0.60 (hexane/ EtOAc 1:2). mp: 163-164°C (recrystallization solvent: hexane/ether). ^1H NMR (300 MHz): δ 7.23(s, 1H), 6.94(s, 1H), 6.65(dd, J=9.7, 3.0 Hz, 2H), 6.07(ddd, J=9.7, 3.6, 1.8 Hz, 2H), 4.78(dd, J=3.6, 1.8 Hz, 1H), 4.76(dd, J=3.6, 1.8 Hz, 1H), 2.25(m, 2H), 1.44(m, 2H), 1.95(s, 18H).^{13}C NMR (75 MHz): δ 136.4, 132.7, 129.4, 127.3, 127.2, 124.6, 70.1, 50.4, 32.5, 28.7. IR (CH_2Cl_2) : 3580, 2970, 1460, 1370, 900 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.84; H, 9.30.

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