Synthesis of regiospecifically substituted 2-hydroxybenzocyclobutenones

Yvonne Lear and Tony Durst

Abstract: Regiospecifically substituted 2-hydroxybenzocyclobutenones were synthesized from the corresponding TBS protected 2-bromo-mandelate esters via halogen–metal exchange, cyclization, and subsequent deprotection.

Key words: 2-hydroxybenzocyclobutenones, halogen–metal exchange, benzocyclobutenediones, 2-bromomandelate esters.

Résumé : Opérant à partir des esters correspondants de l'acide 2-bromomandélique protégés par du «TBS» et procédant par le biais d'un échange halogène–métal, d'une cyclisation et d'une déprotection subséquente, on a réalisé la synthèse de 2-hydroxybenzocyclobuténones régiospécifiquement substituées.

Mots clés : 2-hydroxybenzocyclobuténones, échange halogène–métal, benzocyclobutènediones, esters de l'acide 2-bromomandélique.

[Traduit par la réduction]

Introduction

Benzocyclobutenediones have been shown to be useful intermediates in the synthesis of polycyclic natural products, in particular naphtha- and anthraquinones (1, 2) (Scheme 1). In general, the benzocyclobutenedione **1** is treated with a Grignard reagent to generate a 2-hydroxybenzocyclobutenone **2**. The thermal opening of the 2-hydroxybenzocyclobutenone **2** occurs at about 110°C and is governed by the torquoselectivity rules described by Houk and co-workers (3). This results exclusively in the formation of the intermediate **3** in which the aryl or vinyl substituent is suitably placed for an intramolecular acylation process. Thus anthraquinones or naphthaquinones are obtained, depending on whether an aryl or a vinyl Grignard reagent is used in the addition reaction. The regioselectivity of the addition of Grignard reagents to **1** is difficult to control except when R in **1** is a large *ortho* substituent (4). To have a general synthesis of specifically substituted anthraquinones **4**, based on such a reaction sequence, access to unsymmetrically substituted benzocyclobutenediones with one of the carbonyl moieties masked is needed. Ideally, such compounds would allow for the addition of an organometallic reagent at one of the carbonyl groups, followed by unmasking of the second carbonyl group, and the thermolysis reactions described above.

Previous efforts in this group involved the synthesis of 2-benzylidene-benzocyclobutenone **5** as an unsymmetrical benzocyclobuten-1,2-dione equivalent (5) (Scheme 2). Addition of organolithiums or Grignard reagents occurred exclusively by a 1,2 pathway to give **6** (R′ = aryl). The usefulness of **6** as a synthetic intermediate to anthraquinones suffered greatly since it was oxidized to **7** in only poor yields. Furthermore, thermolysis of **6**, prior to oxidation of the benzylidene group to a carbonyl function, led to a variety of ring enlargement products. The possibility of first protecting the ketone in **5** as a ketal to give **8**, then ozonolyzing the benzylidene group to reveal the other carbonyl group to give **9**, was also considered; again the oxidation step proceeded in only poor yield (6).

Since it had already been shown that benzocyclobutenols could be made by halogen–metal exchange in *o*-bromophenylacetone followed by cyclization (7), it was envisioned that this method could also be applied to the synthesis of benzocyclobutenones. It was necessary to generate a substrate that had a halogen *ortho* to a "functionalized arm" containing two oxygen functionalities: one as an ester to serve as an electrophile in the cyclization process and generate the benzocyclobutenone and the other a potential carbonyl group, for example, a protected hydroxy group (Scheme 3). The realization of such a process is described below.

Results and discussion

The known 6-bromopiperonal **12a** (8) (Scheme 4) was converted to the cyanohydrin **13a** using trimethylsilyl cyanide in dichloromethane with catalytic zinc iodide (9). Further treatment with hydrochloric acid in refluxing ethanol for 1 h afforded the hydroxy ester **14a**. The changes described were easily followed by NMR spectroscopy.

Gallagher and Beak have shown that, under halogen–metal exchange conditions, acidic protons are removed before the exchange reaction takes place (10). To avoid this complication, the hydroxy ester **14a** was protected using *tert*-butyldimethylsilyl chloride in DMF using imidazole as base. When the protected ester **15a** was treated with 2 equivalents of *tert*-

Received November 22, 1996.

This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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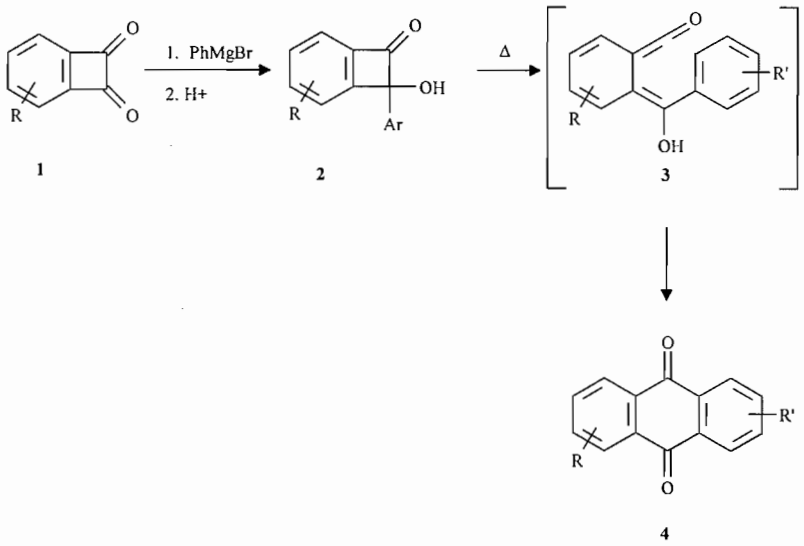
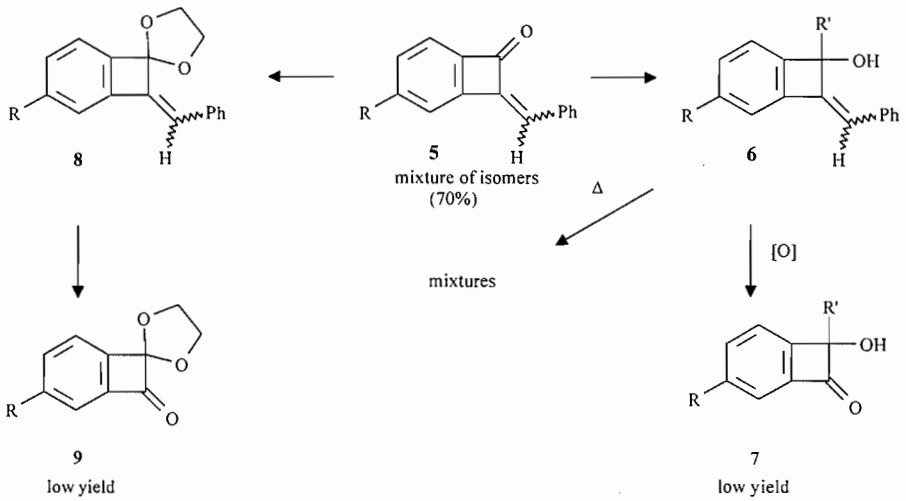
Scheme 1.



Scheme 2.



butyllitium at −78°C,[2] the desired cyclobutenone **16a** was formed but was accompanied by the tertiary alcohol **18a** (Scheme 5). Use of 1.1 equivalents of *tert*-butyllithium afforded a crude reaction mixture whose ^{1}H NMR spectrum indicated that approximately 60% of the starting material had been converted to the desired benzocyclobutenone. Reaction of **15a** with 1.5 equivalents of *tert*-butyllithium at −78°C for 15 min, followed by quenching of the reaction mixture with saturated ammonium chloride at that temperature, led to a 95% yield of the desired benzocyclobutenone. The compound could be purified by silica gel chromatography, or by simple recrystallization from hexanes – ethyl acetate. The ^{1}H NMR spectrum showed the disappearance of the ethyl group of the ester and the shift of the benzylic proton from 5.48 to 5.56 ppm in going from **15a** to **16a**. The ^{13}C NMR peak at 187.5 ppm and the IR absorbtion at 1757 cm^{-1} are values associated with the carbonyl group in other benzocyclobutenones (5). Deprotection using tetra-*n*-butylammonium fluoride in THF afforded the hydroxybenzocyclobutenone **17a** in 80% yield.

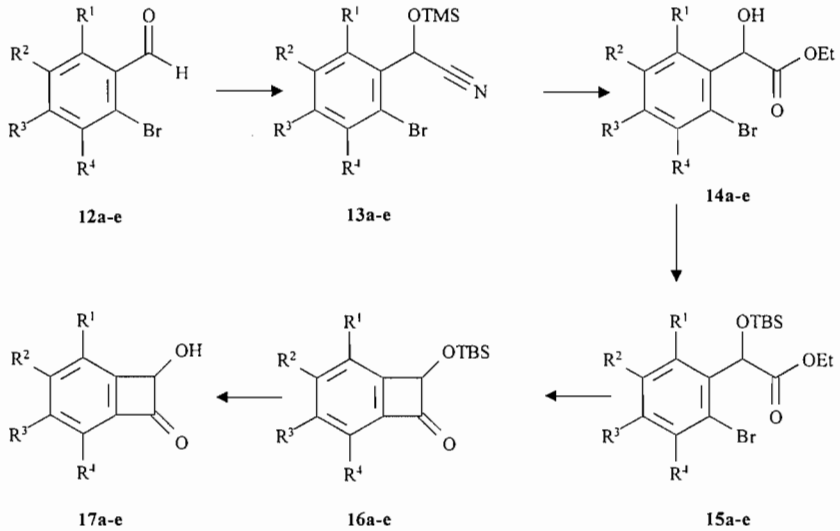
Scheme 3.

P=protecting group, L=leaving group, X=halogen

The starting materials for the remaining cyclization precursors were the commercially available 2-bromobenzaldehyde, *m*-anisaldehyde, *p*-anisaldehyde, and 3-bromophenol. *m*-Anisaldehyde was brominated at the 2 position using the same method as for piperonal to give **12d**. *p*-Anisaldehyde was

[2] Halogen–metal exchange reactions are generally carried out using two equivalents of butyllithium, one to do the exchange reaction and the other consumed as base, causing an elimination from the butyl bromide formed from the reaction (11).

Scheme 4.



a $R^1=R^4=H$ $R^2,R^3=OCH_2O$

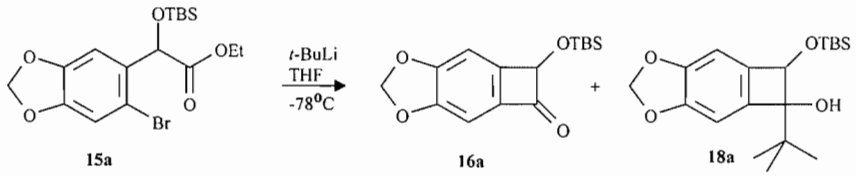
b $R^1=R^2=R^3=R^4=H$

c $R^1=OCH_3$ $R^2=R^3=R^4=H$

d $R^2=OCH_3$ $R^1=R^3=R^4=H$

e $R^3=OCH_3$ $R^1=R^2=R^4=H$

Scheme 5.



halogenated using Comins' procedure to afford **12e** (12, 13). *m*-Bromophenol was formylated under Reimer–Tiemann conditions (14) and methylated using potassium carbonate and methyl iodide in acetone to give **12c**.

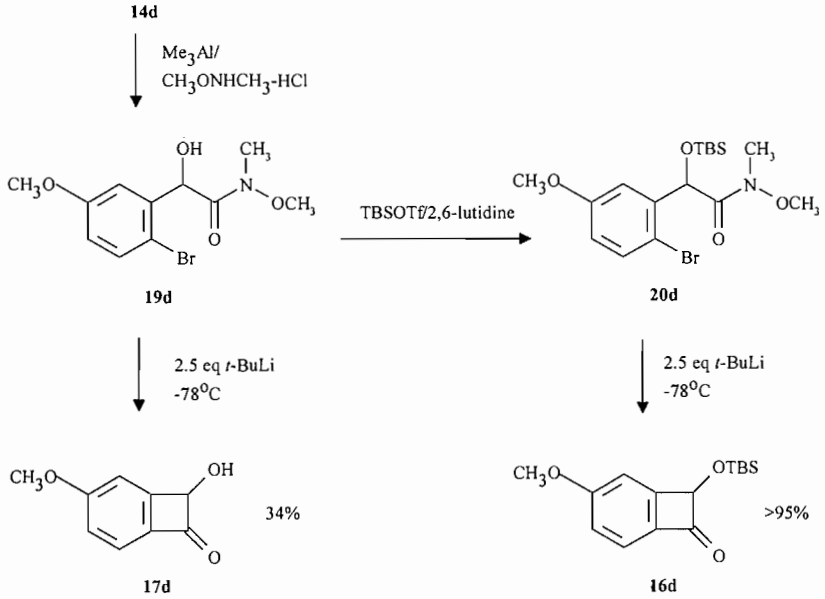
The above *ortho*-bromobenzaldehydes were converted in >95% yield to the corresponding trimethylsilyl protected cyanohydrins **13a–e** using trimethylsilyl cyanide as previously described and were then converted to the ethyl esters. The reactivities of these cyanohydrins toward ethanolysis were variable. When the cyanohydrin **13e** was reacted under the conditions previously described for the piperonal system, a 1:1 mixture of the hydroxy ester **14e** and the corresponding α-ethoxy ester was obtained. This difference in reactivity is likely due to the methoxy group *para* to the benzylic alcohol that makes the benzylic hydroxyl group susceptible to exchange with the solvent ethanol. This reaction was suppressed by using hydrogen chloride gas bubbled through anhydrous ethanol instead of concentrated aqueous hydrochloric acid. This led to the exclusive formation of the desired hydroxy ester in 87% yield. The formation of the other hydroxy esters was carried out using aqueous acid in ethanol with yields ranging from 60 to 90%. (See Experimental section)

The α-hydroxy esters were protected as *tert*-butyldimethylsilyl (TBS) ethers using either TBSCl with imidazole as base, or *tert*-butyldimethylsilyl trifluoromethane sulfonate with 2,6-lutidine as base. For the hydroxy ester **14c**, protection using TBSCl with imidazole was incomplete after 3 days, necessitating the use of the triflate, which gave **15c** in >95% yield in 30 min.

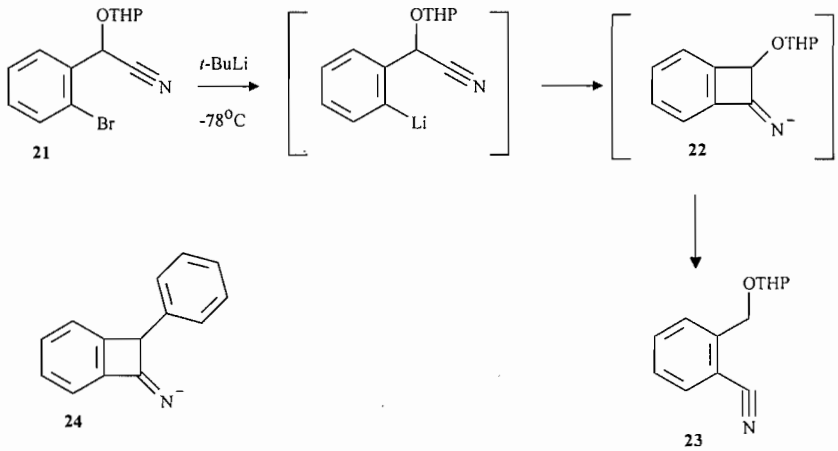
As in the case of **15a** it was necessary to determine the appropriate amount of *tert*-butyllithium for optimum yields in the cyclization of **15b–e**. When the *ortho*-bromo ester **13d** was treated with two equivalents of *tert*-butyllithium at −78°C, the cyclized product **16b** was obtained in 90% isolated yield. Compounds such as **14e–16e** bearing an aryl methoxy group required only 1.2–1.5 equivalents of *tert*-butyllithium, as did the piperonal derivative **16a**.

When cyclization reactions were carried out on mandelic esters **15d** and **15e,** the ^{1}H NMR spectrum of the crude reaction mixtures generally showed mixtures of the starting material, the desired benzocyclobutenone, and a third compound in

Scheme 6.



Scheme 7.



which *tert*-butyllithium had added to the benzocyclobutenone. This indicated that the addition of *tert*-butyllithium to the benzocyclobutenone product begins before halogen–metal exchange is complete. Slower addition of *tert*-butyllithium and (or) lowering the reaction temperature did not improve the selectivity. The reactions were optimized with yields in the 60–70% range. This problem was overcome by converting the mandelic ester **14d** to the corresponding Weinreb amide **19d** (15, 16), which was protected using TBSOTf to give **20d**. When the protected hydroxy amide **20d** was reacted with 2.5 equivalents of *tert*-butyllithium at −78°C, the desired benzocyclobutenone **16d** was produced in essentially quantitative yield (Scheme 6). Attempts to shorten the sequence by direct cyclization of the unprotected hydroxy ester **19d** using 2.5 equivalents of *tert*-butyllithium at −78°C led to the cyclized product **17d** in only 34% yield, along with four other side products that were not identified.

Deprotection of the TBS derivatives **16** using tetra-*n*-butylammonium fluoride afforded the 2-hydroxybenzocyclobutenones **17** in 65–90% isolated yields. For the preparation of benzocyclobutenone **17e**, it was necessary to add acetic acid in the deprotection step in order to avoid base-catalyzed ring opening (17).

To try to shorten the reaction sequence, cyclization was attempted directly on the protected cyanohydrin **21** rather than the hydrolyzed cyanohydrin (Scheme 7). It was anticipated that halogen–metal exchange followed by cyclization would yield the iminium ion **22** as an intermediate and the benzocyclobutenone **11** upon aqueous work-up.

The cyanohydrin **21**, when treated with 1 equivalent of *t*-BuLi at −78°C for 5 min, afforded the rearranged nitrile **23** as the major product. The expected cyclization to **22** did occur but this intermediate underwent [2+2] ring opening even at −78°C; subsequent protonation afforded **23**. Biehl and co-workers had earlier noted the instability of the iminium ion of 2–phenylbenzocyclobutenone (18). We anticipated that cycloreversion of **22** would be considerably less favourable than **24** but unfortunately were unable to intercept it prior to ring opening.

Experimental section

General

Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone before use. Hexanes and ethyl acetate used for chromatography and distillation were routinely distilled before use. Melting points were determined using a Thomas Scientific melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Gemini 200, Varian XL-300, or Bruker AMX 500 spectrometer in deuterated chloroform unless otherwise stated. IR spectra were recorded on a Bomem Michelson FTIR as solutions in CH_2Cl_2; then the solvent spectrum was subtracted.

Preparation of 6-bromopiperonal 12a

Piperonal (15 g, 0.10 mol) was stirred with 100 mL glacial acetic acid and bromine (6 mL, 0.12 mol) for 18 h. Water (300 mL) was added to precipitate the product. The solid was collected on a Buchner funnel and recrystallized from ethanol as colorless needles of **12a** (14.3 g, 63 mmol, 63% yield), mp 126–128°C (lit. (8) mp 127–129°C). ^{1}H NMR δ: 6.10 (s, 2H), 7.13 (s, 1H), 7.35 (s, 1H), 10.15 (s, 1H).

Preparation of 6-bromo-2-methoxybenzaldehyde 12c

A mixture of *m*-bromophenol (5 g, 29 mmol), calcium hydroxide (14 g, 0.19 mol), sodium carbonate (16 g, 0.13 mol), and 100 mL water was stirred and heated to 70°C. Chloroform (7 mL, 10.4 g, 87 mmol) was added at a rate such that a gentle reflux was maintained, about 90 min. Stirring was continued for 2 h. The mixture was acidified with concentrated sulfuric acid, extracted with CH_2Cl_2, dried with $MgSO_4$, and the solvent evaporated. Chromatography on silica gel (9:1 hexane/ethyl acetate) gave 6-bromo-2-hydroxybenzaldehyde (660 mg, 3.3 mmol, 12% yield), 600 mg of the other isomer, 2-hydroxy-4-bromobenzaldehyde, and about 1.2 g of starting material; mp 50–51°C (lit. (19) mp 52.5°C) ^{1}H NMR δ: 6.92 (dt, J = 8.9, 0.8 Hz, 1H), 7.14 (dd, J = 6.7, 0.8 Hz, 1H), 7.30 (dd, 6.7, 8.9 Hz, 1H), 10.31 (s, 1H), 11.96 (s, 1H). A mixture of 6-bromo-2-hydroxybenzaldehyde (380 mg, 2 mmol), potassium carbonate (1 g, 7.2 mmol), methyl iodide (2 mL, 4.56 g, 32 mmol), and 10 mL acetone was stirred for 20 h, diluted with 20 mL water, and extracted with ether. The organic extracts were dried with anhydrous $MgSO_4$ and evaporated to afford 400 mg crystalline **12c** (2 mmol, >95% yield), which was pure by ^{1}H NMR. mp 52–53°C. IR: 1585, 1697 cm^{-1}. ^{1}H NMR δ: 3.87 (s, 3H), 6.89 (dd, J = 1.1, 8.1 Hz, 1H), 7.16–7.32 (m, 2H), 10.36 (s, 1H). ^{13}C NMR δ: 55.86, 110.71, 124.29, 126.08, 131.07, 134.58, 161.61, 190.29. HRMS, calcd. for $C_8H_7O_2Br$: 213.9629; found: 213.9631.

Preparation of 2-bromo-5-methoxybenzaldehyde 12d

The procedure was the same as that used to prepare **12a** except the starting material was *m*-anisaldehyde. Isolated yield of **12d**: 16.5 g (70% yield), mp 71–73°C (lit. (20) mp 74°C). ^{1}H NMR δ: 3.83 (s, 3H), 7.01 (dd, J = 8.8, 3.0 Hz, 1H), 7.40 (d, J = 3.0 Hz, 1H), 7.45 (d, J = 3.0 Hz, 1H), 10.29 (s, 1H).

Preparation of 2-bromo-4-methoxybenzaldehyde 12e

To a stirred solution of trimethylethylenediamine (4.6 mL, 3.7 g, 36 mmol) in 80 mL THF at −20°C was added dropwise *n*-BuLi (13 mL 2.5 M, 32 mmol). The solution was stirred for 15 min, then *p*-anisaldehyde (3.7 mL, 4.4 g, 33 mmol) was added and stirred for 15 min. *n*-BuLi (39 mL, 2.5 M, 97.5 mmol) was added and the solution stirred, then let stand in a freezer (0°C) for 22 h. The solution was cooled to −78°C, carbon tetrabromide (30 g, 90 mmol) was added, and the solution allowed to warm to 25°C. A 10% HCl solution (300 mL) was added and extraction carried out with CH_2Cl_2. The combined organic extracts were washed with sodium thiosulfate until no cloudiness was imparted to the aqueous layer, then washed with water and brine. The organic solution was dried with anhydrous $MgSO_4$ and the solvent evaporated. The product was isolated by silica gel column chromatography (9:1 hexanes/ethyl acetate) and recrystallized from ethanol to afford 350 mg **12e** (54% yield), mp 70–71°C. IR: 1595, 1686 cm^{-1}. ^{1}H NMR δ: 3.79 (s, 3H), 6.82 (dd, 1H), 7.12 (d, 1H), 7.80 (d, 1H), 10.11 (s, 1H). ^{13}C NMR δ: 55.52, 113.74, 118.13, 126.59, 128.32, 130.93, 164.13, 190.12. HRMS, calcd. for $C_8H_7O_2Br$: 213.9629; found: 213.9622.

Preparation of cyanohydrins 13a–e

The cyanohydrins were prepared according to Gassman's procedure (9). The cyanohydrin was stirred for 1 h with 1.2 equivalents of trimethylsilyl cyanide in CH_2Cl_2. The product was isolated either by evaporating the solvent and using the crude product directly or by passing the reaction mixture through a short silica gel plug to remove the catalyst and then evaporating the solvent. The yield for all cyanohydrins was >95%, on scales from 100 mg to 15 g. **13a**: ^{1}H NMR δ: 0.23 (s, 9H), 5.67 (s, 1H), 6.01 (s, 2H), 6.98 (s, 1H), 7.16 (s, 1H). **13b**: ^{1}H NMR δ: 0.18 (s, 9H), 5.68 (s, 1H), 7.16 (dd, 1H), 7.32 (dd, 1H), 7.48 (d, 1H), 7.65 (d, 1H). **13c**: ^{1}H NMR δ: 0.18 (s, 9H), 3.91 (s, 3H), 6.16 (s, 1H), 6.87–6.91 (m, 1H), 7.18–7.21 (m, 2H). **13d**: ^{1}H NMR δ: 0.16 (s, 9H), 3.72 (s, 3H), 5.61 (s, 1H), 6.71 (dd, 1H), 7.15 (d, 1H), 7.34 (d, 1H). **13e**: ^{1}H NMR δ: 0.22 (s, 9H), 3.80 (s, 3H), 5.72 (s, 1H), 6.94 (dd, J = 2.6, 8.7 Hz, 1H), 7.10 (d, J = 2.6, 8.7 Hz, 1H).

Preparation of 2-bromohydroxy esters 14a–e

Procedure A

The cyanohydrin **13** in a solution of 3:2 ethanol/concentrated hydrochloric acid (1 g **13** in 15 mL acid solution) was refluxed for 1 h, the solution neutralized with sodium bicarbonate or sodium hydroxide, the ethanol evaporated, and extraction carried out with ether. The organic extracts were combined, dried with anhydrous $MgSO_4$, and the solvent was evaporated.

Procedure B

As for procedure A except reflux was continued for 20 h.

Procedure C

Anhydrous hydrogen chloride was bubbled through a solution of **13** in absolute ethanol for 30 min. Work-up was as for procedure A.

The crude product was generally clean by ^{1}H NMR, but could be purified by silica gel column chromatography (9:1 hexanes/ethyl acetate). The reactions were carried out on scales from 100 mg to 15 g with no decrease in yield.

14a: The compound was prepared by procedure A starting with 7.2 g **13a** (22 mmol); the yield of **14a** was 4.9 g

(16 mmol, 73% yield), mp 56–58°C. IR: 1731, 3528 cm^{-1}. ^1H NMR δ: 1.22 (t, J = 7.1 Hz, 2H), 3.49 (d, J = 4.7 Hz, 1H), 4.21 (m, 2H), 5.47 (d, J = 4.7 Hz, 1H), 5.96 (s, 2H), 6.82 (s, 1H), 6.99 (s, 1H). ^{13}C NMR δ: 14.0, 62.5, 72.1, 102.0, 108.0, 112.9, 114.4, 131.0, 147.7, 148.5, 173.3. HRMS, calcd. for $C_{11}H_{11}O_5Br$: 301.9789; found: 301.9779.

14b: This compound was prepared by procedure A starting with 1.42 g **13b** (5 mmol); the yield of **14b** was 1.13 g (4.3 mmol, 87% yield), oil. IR: 3693, 1703 cm^{-1}. ^1H NMR δ: 1.11 (t, J = 7.1 Hz, 3H), 3.40–3.60 (br, 1H), 3.95–4.25 (m, 2H), 5.45 (s, 1H), 7.06–7.11 (m, 1H), 7.15–7.35 (m, 2H), 7.46 (dd, J = 8.7 Hz, 1H). ^{13}C NMR δ: 13.6, 62.0, 72.0, 123.2, 127.4, 128.4, 129.5, 132.8, 137.5, 172.8. HRMS, calcd. for $C_{10}H_{11}O_3Br$: 257.9891; found: 257.9890.

14c: The compound was prepared by procedure B from 540 mg **13c** (1.7 mmol); the yield of **14c** was 280 mg (0.97 mmol, 57% yield), mp 102–103°C. IR: 1737 cm^{-1}. ^1H NMR δ: 1.19 (t, J = 7.6 Hz, 3H), 3.62 (d, J = 1.7, 6.8 Hz, 1H), 3.79 (s, 3H), 4.21 (q, J = 7.6 Hz, 2H), 5.66 (d, J = 6.8 Hz, 1H), 6.81 (dd, J = 1.7, 7.7 Hz, 1H), 7.10–7.24 (m, 2H). ^{13}C NMR δ: 14.1, 55.9, 61.8, 70.7, 110.4, 125.5, 127.2, 130.4, 158.3, 173.2 (two of the aromatic carbon signals apparently overlap). LRMS (CI,M+1), calcd. for $C_{11}H_{13}O_4Br$: 289.0; found: 288.9

14d: The compound was prepared by procedure A from 13.9 g **13d** (44 mmol); the yield of **14d** was 10.9 g (38 mmol, 86% yield), mp 60–62°C. IR: 3517, 1732 cm^{-1}. ^1H NMR δ: 1.19 (t, J = 7.1 Hz, 3H), 3.70 (br, 1H), 3.73 (s, 3H), 4.09–4.31 (m, 2H), 5.60 (s, 1H), 6.70 (dd, J = 3.0, 8.8 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H). ^{13}C NMR δ: 13.6, 55.1, 62.1, 72.0, 113.4, 113.5, 115.7, 133.4, 138.3, 158.8, 172.7. HRMS, calcd. for $C_{11}H_{13}O_2Br$: 287.9997; found: 287.9998.

14e: The compound was prepared by procedure C from 100 mg **13e** (0.32 mmol); the yield of **14e** was 81 mg (0.28 mmol, 88% yield), mp 58–59°C. IR: 3519, 1732 cm^{-1}. ^1H NMR δ: 1.23 (t, J = 7.1 Hz, 3H), 3.48 (d, J = 5.0 Hz, 1H), 3.78 (s, 3H), 4.21 (m, 2H), 5.46, (d, J = 5.0 Hz, 1H), 6.84 (dd, J = 2.7, 8.7 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H). ^{13}C NMR δ: 13.6, 55.2, 61.9, 71.6, 113.4, 117.9, 129.0, 129.6, 159.6, 173.1, 190.3. HRMS, calcd. for $C_{11}H_{13}O_2Br$: 287.9997; found: 287.9985.

Preparation of TBS protected esters 15a–e

Procedure A

The hydroxy ester was treated with 1.2 equivalents of *tert*-butyldimethylsilyl chloride and 2.2 equivalents of imidazole in DMF and stirred at 25°C for 24 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2, and the organic extracts were washed with water until no concentration gradients were visible when water was added. The organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated. The compounds were isolated and purified by either silica gel column chromatography or reduced pressure distillation as indicated. This reaction was carried out on scales from 100 mg to 15 g with no effect on the yield.

Procedure B

The hydroxy ester was stirred with 1.5 equivalents of *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2 equivalents of 2,6–lutidine in CH_2Cl_2 at 25°C for 30 min. Water was added and extraction carried out with CH_2Cl_2. The organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated. The crude material was purified by flash chromatography on silica gel (9:1 hexane/ethyl acetate).

15a: The compound was prepared by procedure A from 2.65 g **14a** (8.7 mmol); the yield of **15a** was 3.19 g (7.5 mmol, 87% yield), oil. IR: 1743 cm^{-1}. ^1H NMR δ: 0.03 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H), 4.13 (q, J = 7.1 Hz, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.94 (s, 1H), 7.07 (s, 1H). ^{13}C NMR δ: −5.1, −5.0, 14.1, 18.2, 25.7, 25.8, 61.2, 73.4, 101.8, 108.4, 112.2, 113.0, 132.4, 148.2, 171.2. LRMS (M^+ − t-Bu), calcd. for $C_{13}H_{16}O_5BrSi$: 359.0; found: 358.8.

15b: The compound was prepared by procedure A from 2.90 g **14b** (11 mmol); the yield of **15b** was 3.74 g (9.9 mmol, 90% yield), oil. IR: 3661, 1738 cm^{-1}. ^1H NMR δ: 0.03 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H), 4.13 (q, J = 7.1 Hz, 2H), 5.57 (s, 1H), 7.15 (dd, J = 1.8, 9.4 Hz, 1H), 7.31 (m, 1H), 7.49 (d, J = 1.3, 9.4 Hz, 1H), 7.59 (dd, J = 1.8, 7.8 Hz, 1H). ^{13}C NMR δ: −4.7, −4.6, 13.6, 17.9, 25.2, 25.3, 60.8, 73.1, 122.1, 127.2, 128.5, 129.1, 132.1, 138.7, 170.8. LRMS (M^+ − t-Bu), calcd. for $C_{12}H_{16}O_3BrSi$: 315.0; found: 315.0.

15c: This compound was prepared by procedure B from 60 mg **14c** (0.2 mmol); 60 mg of **15c** (0.15 mmol, 75% yield) was isolated after flash chromatography on silica gel (9:1 hexanes/ethyl acetate as eluent), oil. IR: 1753 cm^{-1}. ^1H NMR δ: -0.05 (s, 3H), 0.14 (s, 3H), 0.85 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H), 3.77 (s, 3H), 4.16 (dq, J = 3.2, 7.1 Hz, 2H), 5.74 (s, 1H), 6.80 (dd, J = 2.0, 7.6 Hz, 1H), 7.08–7.20 (m, 2H). ^{13}C NMR δ: −4.9, −4.6,14.3, 18.3, 25.8, 56.4, 61.0, 70.1, 110.9, 125.0, 125.6, 129.2, 130.1, 158.6, 172.6. MS (CI,M^++1), calcd. for $C_{17}H_{27}O_4BrSi$: 403.1; found: 402.9.

15d: This compound was prepared by procedure A from 1.25 g **14d** (4.3 mmol), the yield of **15d** was 1.59 g (3.9 mmol, 89% yield) after silica gel column chromatography, oil. IR: 1742 cm^{-1}. ^1H NMR δ: 0.04 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H), 3.77 (s, 3H), 4.08–4.18 (dq, J = 7.1, 0.8 Hz, 2H), 5.50 (s, 1H), 6.71 (dd, J = 3.3, 8.8 Hz, 1H), 7.15 (d, J = 3.3 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H). ^{13}C NMR δ: −5.0, −5.1, 13.6, 17.9, 24.8, 25.3, 55.0, 60.8, 73.1, 112.4, 113.1, 115.7, 132.6, 139.5, 158.7, 170.6. HRMS (M^+ − t-Bu), calcd. for $C_{13}H_{18}O_4BrSi$: 345.0157; found: 345.0163.

15e: The compound was prepared by procedure B from 130 mg **14e** (0.45 mmol); the yield of **15e** was 180 mg (0.45 mmol, >95% yield) after flash chromatography on silica gel, oil. IR: 1722 cm^{-1}. ^1H NMR δ: 0.01 (s, 1H), 0.10 (s, 3H), 0.88 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H), 3.77 (s, 3H), 4.12 (q, J = 7.1 Hz, 2H), 5.50 (s, 1H), 6.86 (dd, J = 2.6, 8.8 Hz, 1H), 7.04 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H). ^{13}C NMR δ: −4.9, −4.7, 14.0, 18.2, 25.5, 25.6, 55.4, 61.0, 73.0, 113.8, 117.4, 122.7, 129.4, 131.1, 159.7, 171.4. MS calcd. for $C_{17}H_{27}O_4SiBr$: 402.1(M^+), 345.0 for M^+−t-Bu; found CI (M^++1): 403.0; EI (M^+−t-Bu): 345.0.

Preparation of 2-tert-Butyldimethylsilyloxybenzocyclobutenones 16a–e

General method

tert-Butyllithium (equivalents as indicated for each compound) was added to a solution of ester **15** in THF under nitrogen atmosphere at −78°C and stirred for 15 min. The solution was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. Extraction was carried out with diethyl ether, the organic extracts were dried with anhydrous $MgSO_4$, and the solvent was evaporated. Purification was carried out using flash chromatography on silica gel (9:1 hexanes/ethyl acetate as eluent). Recrystallization was carried out as noted for each compound.

16a: The compound was prepared by the general method using 1.5 equivalents of *tert*-butyllithium and 1.9 g of **15a** (4.5 mmol) as starting material; the yield of **16a** was 1.35 g (4.5 mmol, >95% yield), isolated as colorless prisms after recrystallization from hexanes – ethyl acetate, mp 104–105°C. IR: 1757 cm^{-1}. ^1H NMR δ: 0.15 (s, 3H), 0.17 (s, 3H), 0.92 (s, 9H), 5.56 (s, 1H), 6.07 (s, 2H), 6.80 (s, 1H), 6.99 (s, 1H). ^{13}C NMR δ: −4.7, −4.5, 18.3, 25.8, 83.9, 100.7, 102.2, 103.4, 140.5, 151.5, 154.4, 155.5, 187.5. HRMS, calcd. for $C_{15}H_{20}O_4Si$: 292.1131; found: 292.1108. Anal. calcd. for $C_{15}H_{20}O_4Si$: C 61.61, H 6.90%; found: C 61.48, H 6.86%.

16b: This compound was prepared by the general method using 2 equivalents of *tert*-butyllithium and 1.0 g **15b** (2.6 mmol); the yield of **16b** was 0.62 g (2.5 mmol, 96% yield) after purification by radial chromatography (9:1 hexanes/ethyl acetate), oil. IR: 1765 cm^{-1}. ^1H NMR δ: 0.20 (s, 3H), 0.22 (s, 3H), 0.96 (s, 9H), 5.78 (s, 1H), 7.44–7.68 (m, 4H). ^{13}C NMR δ: −4.8, −4.5, 18.3, 25.8, 86.2, 121.6, 123.6, 131.0, 135.4, 146.9, 158.0, 190.7. HRMS, calcd. for $C_{14}H_{20}O_2Si$: 248.1233; found: 248.1204.

16c: The compound was prepared by the general method using 1.2 equivalents *tert*-butyllithium and 750 mg **15c** (1.6 mmol), 386 mg **16c** (1.4 mmol, 88% yield) was isolated after purification by silica gel chromatography (9:1 hexanes/ethyl acetate), oil. IR: 1769 cm^{-1}. ^1H NMR δ: 0.18 (s, 3H), 0.19 (s, 3H), 0.91 (s, 9H), 4.00 (s, 3H), 5.83 (s, 1H), 7.01 (m, 2H), 7.41 (m, 1H). ^{13}C NMR δ: −4.5, −3.8, 18.8, 26.3, 57.8, 86.6, 112.9, 113.9, 121.8, 133.6, 142.6, 149.3, 157.1, 191.4. HRMS, calcd. for $C_{15}H_{22}O_3Si$: 278.1329; found: 278.1350.

16d: This compound was prepared by the general method using 1.5 equivalents of *tert*-butyllithium and 1 g **15d** (2.5 mmol); the yield of **16d** was 470 mg (1.7 mmol, 68% yield). Purification was carried out by flash chromatography on silica gel (9:1 hexanes/ethyl acetate), mp 43–44°C. IR: 1754 cm^{-1}. ^1H NMR δ: 0.18 (s, 3H), 0.21 (s, 3H), 0.95 (s, 9H), 3.91 (s, 3H), 5.68 (s, 1H), 7.00–7.08 (m, 1H), 7.05 (s, 1H), 7.36 (dd, J = 1.7, 7.5 Hz, 1H). ^{13}C NMR: δ: −4.8, −4.5, 18.3, 25.7, 55.8, 85.1, 105.9, 120.7, 123.6, 138.9, 160.4, 165.6, 188.1. HRMS, calcd. for $C_{15}H_{22}O_3Si$: 278.1329; found: 278.1315.

16e: The compound was prepared by the general method using 1.5 equivalents of *tert*-butyllithium and 120 mg **15e** (3.0 mmol); the yield of **16e** was 50 mg (1.8 mmol, 60% yield) after flash chromatography on silica gel, oil. IR: 1762 cm^{-1}. ^1H NMR δ: 0.15 (s, 3H), 0.17 (s, 3H), 0.92 (s, 9H), 3.80 (s, 3H), 5.67 (s, 1H), 6.87 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 2.0, 8.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H). ^{13}C NMR δ: −4.7, −4.5, 18.3, 25.8, 55.7, 85.0, 102.6, 124.6, 125.4, 148.3, 151.3, 162.3, 190.2. HRMS, calcd. for $C_{15}H_{22}O_3Si$: 278.1329; found: 278.1352.

Preparation of 2-hydroxybenzocyclobutenones 17a–e

General method

Tetra-*n*-butylammonium fluoride solution in THF (1 equivalent) was added to a stirred solution of the benzocyclobutenone in THF and immediately quenched with saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether, the organic extracts were dried with anhydrous magnesium sulfate, and the solvent was evaporated. The compounds were purified by flash chromatography on silica gel (1:1 hexanes/ethyl acetate as eluent).

17a: This compound was prepared by the general method using 420 mg **16a** (1.4 mmol); the yield of **17a** was 190 mg (1.1 mmol, 79% yield) after silica gel column chromatography, mp 155–157°C. IR: 1756, 3581 cm^{-1}. ^1H NMR (d_6 acetone) δ: 5.35 (br, 1H), 5.50 (s, 1H), 6.19 (s, 2H), 6.86 (s, 1H), 7.16 (s, 1H). ^{13}C NMR (d_6 acetone) δ: 84.6, 100.6, 103.5, 104.2, 141.4, 152.5, 155.3, 157.1, 188.8. HRMS, calcd. for $C_9H_6O_4$: 178.0266; found: 178.0279. Anal. calcd. for $C_9H_6O_4$: C 60.68, H 3.39%; found: C 60.49, H 3.25%.

17b: This compound was prepared by the general method using 380 mg **16b** (1.5 mmol); the yield of **17b** was 132 mg (0.99 mmol, 66% yield) after silica gel column chromatography, mp 52.5–53.5°C. IR: 1766, 3582 cm^{-1}. ^1H NMR δ: 3.05 (br, 1H), 5.79 (s, 1H), 7.49–7.62 (m, 3H), 7.75 (m, 1H). ^{13}C NMR (d_6 acetone) δ: 87.1, 121.7, 124.6, 131.8, 136.2, 148.0, 159.6, 192.2. HRMS, calcd. for $C_8H_6O_2$: 134.0368; found: 134.0379. Anal. calcd. for $C_8H_6O_2$: C 71.64, H 4.51%; found: C 71.93, H 4.29%.

17c: The reaction was performed on 50 mg **16c** (0.18 mmol); isolated after column chromatography was 20 mg **17c** (0.12 mmol, 67% yield), which crystallized on standing, mp 70–72°C. IR: 1767, 3575 cm^{-1}. ^1H NMR δ: 3.50 (br, 1H), 4.03 (s, 3H), 5.85 (br, 1H), 7.01–7.07 (m, 2H), 7.45 (m, 1H). ^{13}C NMR δ: 57.3, 85.7, 113.5, 121.7, 133.4, 141.3, 148.9, 156.6, 191.3. HRMS, calcd. for $C_9H_8O_3$: 164.0473; found: 164.0487.

17d: This compound was prepared using the general method on 470 mg **16d** (1.7 mmol); the yield of **17d** was 240 mg (1.5 mmol, 88% yield) after silica gel column chromatography, mp 95.0–95.5°C. IR: 1758, 3587 cm^{-1}. ^1H NMR (d_6 acetone) δ: 3.95 (s, 3H), 5.63 (s, 1H), 7.12 (dd, J = 2.0, 8.5 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 0.7, 8.5 Hz, 1H). ^{13}C NMR (d_6 acetone) δ: 56.4, 86.0, 107.1, 121.3, 123.7, 139.9, 162.2, 166.5, 189.5. HRMS, calcd. for $C_9H_8O_3$: 164.0473; found: 164.0453.

17e: TBAF (1 M, 0.16 mL, 0.16 mmol) was added to a solution of 11 mg **16e** (0.040 mmol) and 100 μL acetic acid in 5 mL THF. The solution was stirred for 1 h, washed with

saturated NH_4Cl, saturated $NaHCO_3$, and brine, then dried with anhydrous $MgSO_4$, and the solvent evaporated. Column chromatography on silica gel (ethyl acetate needed to remove **17e**) afforded approximately 2 mg of the desired hydroxy ketone **17e** (0.012 mmol, ~30% yield). ^{1}H NMR δ: 3.82 (s, 3H), 5.69 (br s, 1H), 6.88 (dd, J = 2.2, 0.4 Hz, 1H), 7.19 (dd, J = 8.3, 2.2 Hz, 1H), 7.62 (dd, J = 8.3, 0.4 Hz, 1H). ^{13}C NMR δ: 55.8, 85.1, 102.7, 124.9, 125.8, 148.8, 150.5, 162.7, 189.2. HRMS, calcd. for $C_9H_8O_3$: 164.0473; found: 164.0453.

Preparation of Weinreb amide 19d

Trimethylaluminum (4.3 mL, 2.0 M, 8.6 mmol) was added to a solution of *N,O*-dimethylhydroxylamine hydrochloride (370 mg, 3.8 mmol) in 10 mL dry CH_2Cl_2 under nitrogen atmosphere and the solution stirred for 15 min at 25°C. A solution of **14d** (1 g, 3.5 mmol) in dry CH_2Cl_2 was added and the solution refluxed for 24 h. Dilute HCl(aq) was **slowly and carefully** added dropwise through the condenser until gas evolution ceased and all remaining white precipitate had dissolved. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The organic extracts were combined, washed with water and brine, dried with anhydrous $MgSO_4$, and the solvent was evaporated. Yield: ^{1}H NMR spectrum showed 60% conversion, 450 mg isolated, 73% based on conversion of starting material; mp 71.0–71.5°C. IR: 1662, 3447 cm^{-1}. ^{1}H NMR δ: 3.20 (s, 3H), 3.29 (s, 3H), 3.73 (s, 3H), 4.28 (br, 1H), 5.71 (br, 1H), 6.68–6.76 (m, 2H), 7.44 (d, J = 8.6 Hz, 1H). ^{13}C NMR δ: 55.1, 60.5, 70.4, 89.2, 113.2, 114.3, 115.6, 133.3, 139.3, 159.0, 172.7. HRMS, calcd. for $C_{11}H_{14}NO_4$ (M^+ − Br) 224.0923; found: 224.0914.

Preparation of 20d

A solution of **19d** (135 mg, 0.44 mmol), *tert*-butyldimethylsilyl triflate (154 μL, 0.66 mmol), and 2,6–lutidine (105 μL, 0.88 mmol) in 10 mL dry CH_2Cl_2 was stirred for 30 min at 25°C. The solution was diluted with water (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated leaving 179 mg **20d** (0.43 mmol, >95% yield), a pale yellow crystalline solid that was pure by ^{1}H NMR, mp 81.0–81.5°C. IR: 1677 cm^{-1}. ^{1}H NMR δ: −0.01 (s, 3H), 0.12 (s, 3H), 0.86 (s, 9H), 3.13 (s, 3H), 3.48 (s, 3H), 3.75 (s, 3H), 5.83 (s, 1H), 6.68–6.71 (m, 1H), 7.09–7.11 (m, 1H), 7.35–7.38 (m, 1H). ^{13}C NMR δ: −4.8, −4.6, 18.2, 25.8, 32.7, 55.5, 61.0, 71.8, 113.3, 114.5, 116.3, 132.9, 140.0, 159.1, 171.9. HRMS, calcd. for $C_{13}H_{19}BrNO_4Si$ (M^+ − *t*-Bu): 360.0267; found: 360.0279.

Preparation of 23

Compound **21** (300 mg, 0.88 mmol) in 10 mL THF was cooled to −78°C and *tert*-butyllithium (550 μL, 1.7 M, 0.94 mmol) was added and stirred for 15 min. The reaction was quenched with saturated NH_4Cl solution and allowed to warm to 25°C. Extraction was carried out with CH_2Cl_2, the solvent dried with anhydrous $MgSO_4$, and the solvent evaporated. The major compound isolated after chromatography on silica gel was **23**, oil. ^{1}H NMR δ: 1.4–1.9 (m, 6H), 3.45–3.63 (m, 1H), 3.82–3.97 (m, 1H), 4.58 (d, J = 18 Hz, 1H), 4.72–4.78 (m, 1H), 4.82 (d, J = 18 Hz, 1H), 5.98 (s, 1H), 6.04 (s, 2H), 6.98 (s, 1H), 7.02 (s, 1H). HRMS, calcd. for $C_{14}H_{15}O_4N$: 261.1002; found: 261.1008.

Acknowledgements

The authors acknowledge the financial support of the Natural Sciences and Engineering Research Council of Canada (NSERC).

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