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Note

Carbohydrate functionalization using cationic iron carbonyl complexes

Anders Bergh,[a] Henrik Gradén,[a] Núria Parera Pera,[a] Thomas Olsson,[b] Ulf J. Nilsson[c,*] and Nina Kann[a,*]

[a]*Organic Chemistry, Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-41296 Göteborg, Sweden*
[b]*AstraZeneca R&D Mölndal, SE-43183 Mölndal, Sweden*
[c]*Organic Chemistry, Lund University, PO Box 124, SE-22100 Lund, Sweden*

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Abstract—Cationic iron carbonyl cyclohexadiene complexes were employed in the derivatization of the 3-OH position of unprotected and protected methyl β-D-galactopyranosides using two different approaches, giving access to galactopyranosides with an aromatic or cyclohexadienoic functionality in this position.
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Cationic iron carbonyl complexes of both cyclic and acyclic dienes are highly reactive towards many different types of nucleophiles, providing a means for the derivatization of such compounds.[1,2] Amongst the precursor dienes, the cyclohexadiene structure has been the most studied and was the first cationic complex of this type prepared by Fischer in 1960.[3] Complexation of the diene is generally effected by heating with $Fe(CO)_5$ or $Fe_2(CO)_9$, and subsequent treatment with a strong acid such as triphenylmethyl tetrafluoroborate then generates the stabilized cation.[1] The scope of nucleophiles that react with this type of cation is wide, and includes alcohols,[4] amines,[5] phosphines and phosphites,[6] hydride,[5] and activated carbon nucleophiles such as silyl enol ethers,[1] enamines[7] and electron rich aromatics,[8] thus providing methodology for both carbon–carbon and carbon–heteroatom formation. The reaction proceeds under mild conditions, and is generally highly regioselective, the selectivity determined by the initial substitution pattern on the cyclohexadiene structure.[9,10]

As part of a study aimed at preparing potential galectin inhibitors, we wished to investigate if cationic iron carbonyl dienyl complexes could be applied in the derivatization of carbohydrate structures,[11] galactose derivatives, in particular. Galectins are a family of proteins that share a similar carbohydrate recognition domain (CRD).[12] They can have both intra- and extracellular activities, and a majority of their functions are associated with carbohydrate–protein interactions. Galectin-1, for example, possesses immunomodulatory effects[13,14] and displays increased expression in cancer cells compared to normal cells and has thus been the focus of much cancer research in the last years.[15] Moreover, studies on Galectin-3 had demonstrated its expression in cancer[16] and inflammation processes.[17–19] Ample information is available concerning structures of galectins in complexes with lactose or Lac*N*Ac and all show extended binding pockets close to the 3-hydroxy group of the galactose residue.[20–25] That has allowed the study and design of new potential galectin inhibitors and it is known that replacing the 3-hydroxyl group from

* Corresponding authors. Tel.: +46 31 7723070; fax: +46 31 7723657 (N.K.); e-mail addresses: ulf.nilsson@organic.lu.se; kann@chalmers.se

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D-galactose with different functionalities enhances binding and improves affinity to the galectin compared to lactose or Lac*N*Ac.[26–30]

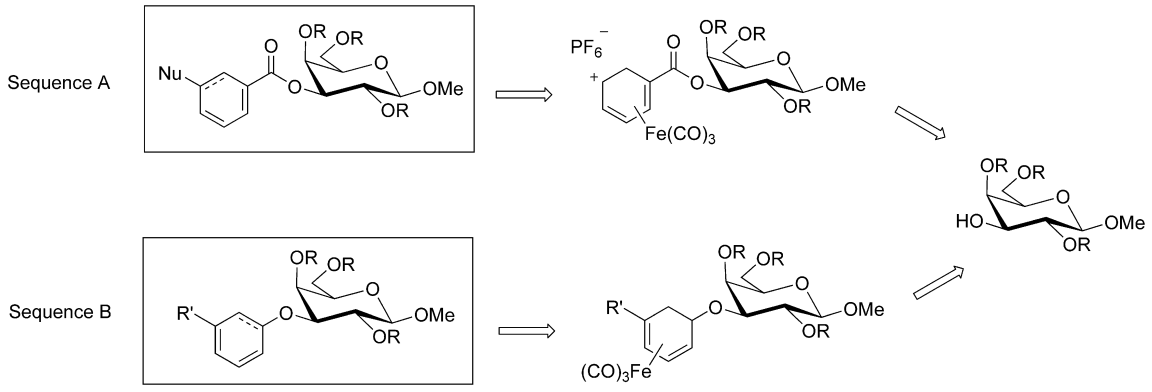
Two different strategies were envisioned for the derivatization of the carbohydrate scaffold. The galactoside could be attached to the cationic iron carbonyl cyclohexadienyl scaffold in the form of an ester (Scheme 1, sequence A), allowing the use of different carbon or heteroatom nucleophiles in the reaction with the cation, giving access to a wide variety of derivatives. Alternatively, the protected galactoside could be used directly as the nucleophile in the reaction with the cationic salt of the iron carbonyl cyclohexadienyl complex (sequence B). In theory, both approaches could give access either to cyclohexadiene derivatives as the final products, or the corresponding aromatic compounds if an oxidation reaction was applied as the final step.

To test the concept of sequence A, benzyl-protected methyl β-D-galactopyranoside (**2**, Scheme 2) was converted to the corresponding cyclohexadienyl carboxylic ester **4** via reaction with acid chloride **3**, prepared in situ from carboxylic acid **1**. Subsequent complexation with diiron nonacarbonyl afforded **5**, which was then converted to the cationic salt **6** upon treatment with triphenylcarbenium hexafluorophosphate. Electron rich aromatics can function as nucleophiles in the reaction with cationic iron carbonyl dienyl, and trimethoxybenzene was selected for the test sequence, allowing the formation of a carbon–carbon bond under mild conditions.

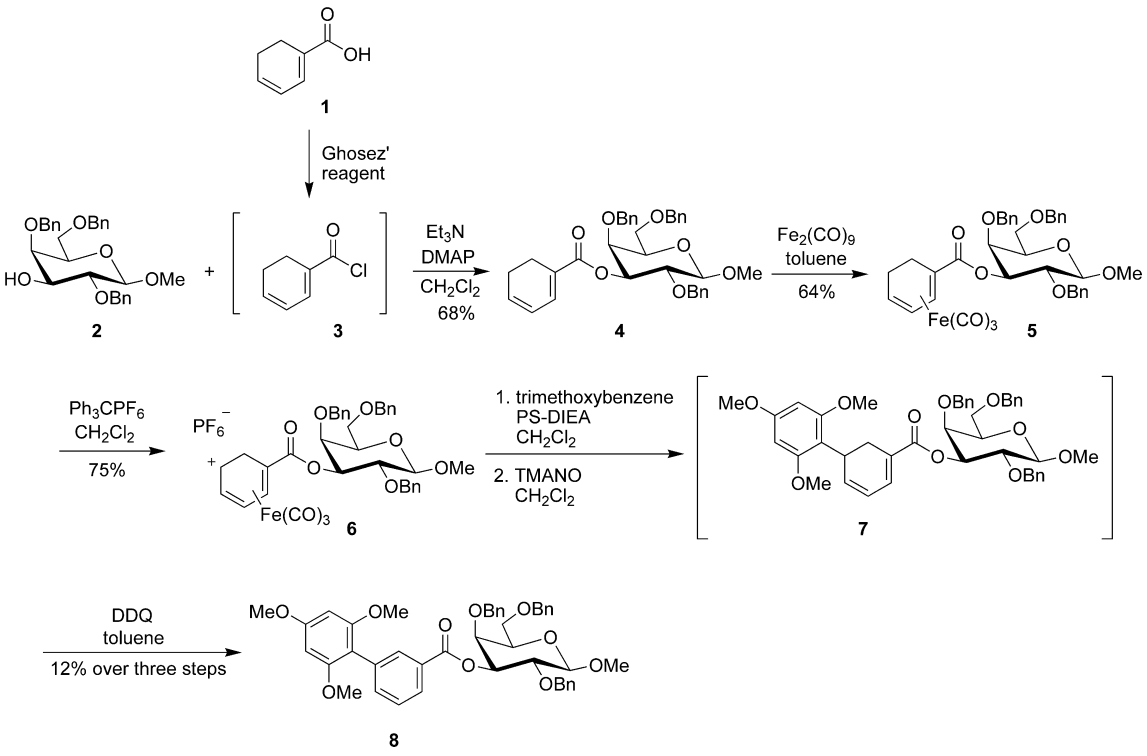
Thus, compound **6** was reacted with trimethoxybenzene in the presence of a polymer-supported base (PS-DIEA) in dichloromethane at room temperature. To remove the iron carbonyl still tethered to the product diene, the crude product was then treated with a mild oxidant, trimethylamine *N*-oxide (TMANO). Although we had anticipated being able to isolate diene **7** at this stage, ^{1}H NMR analysis of the crude product revealed that a mixture of **7** and the corresponding aromatic product **8** had been formed. We thus subjected this mixture to oxidation with DDQ to convert all material to the aromatized product. Purification of the material formed from this reaction then allowed the isolation of pure **8**, in a 12% yield calculated over three steps from the cationic complex **6**. Although this particular product could also be formed via a Suzuki reaction on a halogenated aromatic substrate, our method has the advantage that no functional group such as a halogen is necessary on the cyclohexadiene moiety, and that the application of cationic iron methodology allows the introduction of a variety of nucleophiles, both carbon and heteroatom, onto the scaffold, that is, the method is not limited to the formation of biarylic structures. By introducing the nucleophile at a late stage rather than tethering pre-prepared aromatic esters to a carbohydrate scaffold, the methodology allows for facile diversification of the scaffold and preparation of a variety of target compounds in a library format.

An alternative method to prepare methyl β-D-galactopyranosides derivatized at the C3-position could be to employ the carbohydrate as the nucleophile in a direct reaction with a cationic iron carbonyl dienyl complex (Scheme 1, sequence B). We thus studied the reaction of acetyl protected galactoside **9** (Scheme 3) in a reaction with the known cationic complex **10**.[31] The reaction produced a mixture of regioisomers of **11a**, indicating that the migration of acetyl groups had taken place under the reaction conditions, exposing alternative positions on the carbohydrate moiety to reaction with the cationic complex. A number of other bases (collidine, $(i\text{-Pr})_2$NEt, 2,3-di-*t*-butylpyridine, Cs_2CO_3) and solvent systems (toluene, acetonitrile, DMF) were tested but with the same disappointing results. We then switched to the benzyl protected galactoside **2** (used in sequence A) instead, to avoid the problem of migrating protecting groups. No reaction occurred in this case, however. Most likely, the benzyl protected carbohydrate is too sterically hindered to function in a direct reaction with the cationic complex.

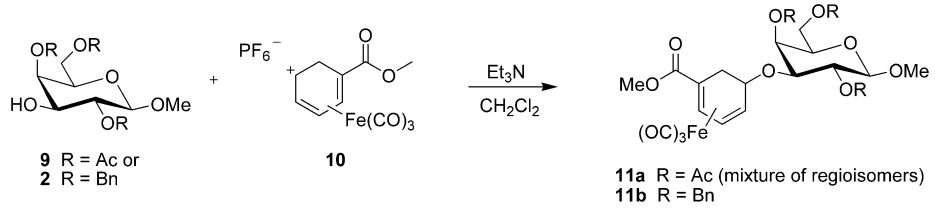
A solution to the problems caused by the protecting groups could be to employ the unprotected methyl galactopyranoside **12** (Scheme 4), and activate the C3-position via formation of the corresponding stannylene



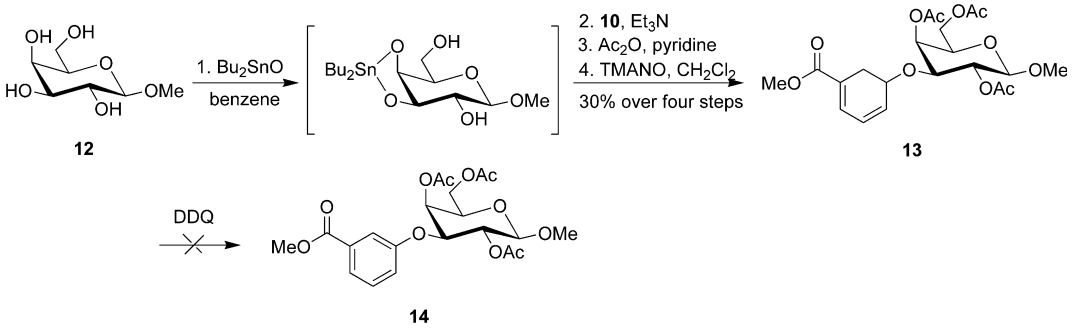
Scheme 1. Retrosynthetic strategies for the preparation of cyclohexadiene galactoside derivatives.



Scheme 2. Reaction of an aromatic nucleophile with a cationic iron carbonyl-complexed galactoside ester (sequence A).



Scheme 3. Direct reaction of protected galactoside **9** or **2** with cationic complex **10** (sequence B).



Scheme 4. Alternative strategy to sequence B, employing galactoside **12** activated as the corresponding stannylene acetal.

acetal, rather than protecting the other hydroxyl positions. Compound **12** was treated with di-*n*-butyltin in benzene, and the intermediate stannylene acetal was then exposed to cation **10** in the presence of triethylamine. Once the initial reaction was complete, the free hydroxyl groups were then acetylated to facilitate work-up. Decomplexation with TMANO in this case afforded diene **13**, without concomitant aromatization as in the earlier case, in a 30% yield calculated over four steps. To see if the aromatic compound **14** could also be produced using the same route, **13** was subjected to DDQ in order to oxidize the diene. These reaction conditions were found to be too harsh, causing elimination of the pendant galactoside, producing benzoic acid

methyl ester instead. Despite various attempts using other oxidative conditions, the aromatized product **14** could not be formed. However, the described method nevertheless provides a viable method for accessing the cyclohexadiene derivative **13**.

In summary, we have reported two different routes to methyl β-D-galactopyranosides derivatized in the C3-position. Preparation of a cyclohexadienoic acid ester of the galactoside and subsequent conversion to a cationic iron carbonyl complex enabled reaction with an aromatic nucleophile, affording, after oxidation, a galactoside derivatized with a substituted benzoic ester in the C3-position. Although we have only reported the proof of concept in this report, we envisage that this methodology can be expanded to other nucleophiles (carbon and heteroatom), allowing the formation of a wide variety of related derivatives with a *meta*-substituted aromatic ester in the C3-position. Alternatively, the galactoside can instead be activated as the corresponding stannylene acetal and used directly as the nucleophile in the reaction of a pre-prepared iron cation complex of a cyclohexadienoic ester. This method instead afforded carbohydrate with a substituted cyclohexadiene attached directly to the galactoside. To our knowledge, this is the first report of the use of cationic iron mediated reactions in the derivatization of galactosides in the C3-position, and we envision that this method can find use in the preparation of new carbohydrate derivatives of biological interest.

1. Experimental

1.1. General methods

All solvents and reagents were obtained commercially and used as received. Methyl galactopyranoside (**12**) and 1-chloro-*N*,*N*,2-trimethylpropenylamine were purchased from SigmaAldrich. Reactions were performed under a nitrogen or argon atmosphere using oven-dried glass equipment. Infra-red spectra were obtained using a Perkin–Elmer 1600 FTIR. NMR spectra were recorded on a Varian 400 MHz UNITY-VXR 5000. Chemical shifts are reported using deuterated chloroform as reference. Column chromatography was carried out using Matrix Si 60 Å 35–70 μm. Thin layer chromatography (TLC) was performed using precoated alumina-backed plates (Merck 25 DC Alufolien Kieselgel 60 F254). Visualization was effected either by UV fluorescence ($v = 254$ nm) or by heating the plates after treatment with 10% H_2SO_4.

1.2. Preparation of precursors 1, 2, 9 and 10

Cyclohexa-1,3-diene carboxylic acid was prepared according to a procedure described by us earlier.[32] Methyl 2,4,6-tri-*O*-benzyl-galactopyranoside (**2**)[33] and methyl 2,4,6-tri-*O*-acetyl-galactopyranoside (**9**)[34,35] were prepared according to published procedures. Tricarbonyl(1-carbomethoxycyclohexa-1,3-dienyl)iron hexafluorophosphate (**10**)[36] was prepared using a method reported for the corresponding ethyl ester.[37]

1.3. Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(cyclohexa-1,3-dienecarbonyl) β-D-galactopyranoside (4)

1.3.1. Cyclohexa-1,3-dienecarboxylic acid chloride (3). 1-Chloro-*N*,*N*,2-trimethylpropenylamine (Ghosez' reagent) (134 mg, 4.83 mmol) was added to a solution of 1,3-cyclohexadienoic acid[32] (200 mg, 1.61 mmol) in dry CH_2Cl_2 (5 mL) and stirred under an atmosphere of nitrogen for 5 h. The reaction mixture was then concentrated in vacuo and the compound was used directly in the next reaction without further purification or isolation due to its instability. Crude product: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, $J = 5.6$ Hz, 1H, CH=CC(O)Cl), 6.37–6.32 (m, 1H) and 6.18–6.11 (m, 1H, CH=CH), 2.53–2.45 (m, 2H, CH_2) and 2.36–2.26 (m, 2H,CH_2).

1.3.2. Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(cyclohexa-1,3-dienecarbonyl) β-D-galactopyranoside (4). Cyclohexa-1,3-dienecarboxylic acid chloride (**3**) (458 mg, 3.23 mmol) and 4-dimethylaminopyridine (145 mg, 1.18 mmol) was added to a solution of **2** (500 mg, 1.07 mmol) in dry CH_2Cl_2 (5 mL) and stirred under an atmosphere of nitrogen. Trimethylamine (300 μL, 2.15 mmol) was added dropwise and the reaction mixture was stirred for 6 h. Thereafter, the reaction mixture was concentrated in vacuo and EtOAc (5 mL) was added. The organic phase was washed with brine (3 × 5 mL) and water (3 × 5 mL), the organic layer dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether–EtOAc 5:1) to give **4** as a yellow oil (422 mg, 68%): IR (neat) ν 2928, 2864, 1701, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.18 (m, 15H, Ph), 6.87 (d, $J = 5.3$ Hz, 1H, CH=CC(O)), 6.13 (m, 1H) and 6.03–5.99 (m, 1H, CH=CH), 5.03 (dd, $J = 7.2$, 3.9 Hz, 1H), 4.83 (d, $J = 11.6$ Hz, 1H), 4.63 (dd, $J = 4.8$, 11.6 Hz, 2H), 4.51–4.36 (m, 4H, 2Bn CH_2), 3.99 (d, $J = 2.8$ Hz, 1H), 3.81 (dd, $J = 7.7$, 2.5 Hz, 1H), 3.73 (dd, $J = 4.3$, 6.8 Hz, 1H), 3.61–3.58 (m, 2H, Bn CH_2), 3.56 (s, 3H, OMe), 2.39 (m, 2H, CH_2), 2.25 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 138.4, 138.3, 138.1, 137.8, 134.1, 133.9, 129.8, 128.4, 128.1, 127.9, 127.9, 127.7, 127.7, 127.7, 127.5, 127.4, 123.9, 104.8, 76.8, 74.9, 74.8, 74.5, 74.4, 73.4, 73.1, 68.4, 57.1, 22.8, 20.6 (one carbon overlaps with the signal from $CHCl_3$). FABMS *m*/*z* calcd for $C_{35}H_{38}O_7Na$ $[M+Na]^+$: 593.2516. Found: 593.2519.

1.4. Tricarbonyl[methyl 2,4,6-tri-*O*-benzyl-3-*O*-(cyclohexa-1,3-dienecarbonyl) β-D-galactopyranoside]iron complex (5, two diasteromers)

A solution of **4** (518 mg, 0.91 mmol) in degassed toluene (10 mL) was added to a slurry of diiron nonacarbonyl[†] (5.00 g, 13.8 mmol) in degassed toluene (20 mL). The mixture was stirred at 55 °C under an atmosphere of argon for 18 h. After cooling to room temperature, the mixture was then concentrated in vacuo and the residue purified by flash chromatography (petroleum ether–EtOAc, 8:2), to give **5** as a yellow oil (430 mg, 64%): IR (neat) 2862, 2052, 1983, 1702, 1496, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two diastereomers):[‡] δ 7.43–7.19 (m, 15H, Ph), 6.03 (m, 1H), 5.90 (m, 1H), 5.41–5.31 (m, 2H), 5.1–3.3 (m, 12H), 3.06 (s, 3H), 2.2–2.0 (m, 2H) and 1.9–1.8 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, two diastereomers): δ 172.2, 172.0, 138.6, 138.6, 138.2, 138.1, 137.9, 137.8, 133.1, 129.8, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.5, 127.4, 127.4, 104.9, 104.9, 89.4, 89.3, 85.3, 85.0, 77.2, 76.9, 75.9, 75.6, 75.5, 75.0, 74.9, 74.9, 74.8, 74.6, 74.6, 74.5, 74.4, 74.3, 73.5, 73.4, 73.4, 73.2, 73.1, 73.0, 68.6, 68.4, 68.4, 64.3, 64.3, 63.3, 62.9, 57.1, 57.1, 25.1, 24.9, 22.9, 22.8. FABMS *m/z* calcd for $C_{38}H_{38}FeNaO_{10}$ $[M+Na]^+$: 733.1712. Found: 733.1716.

1.5. Tricarbonyl[methyl 2,4,6-tri-*O*-benzyl-3-*O*-(cyclohexa-1,3-dienecarbonyl) β-D-galactopyranoside]iron hexafluorophosphate (6)

Ph_3CPF_6 (347 mg, 0.89 mmol) was added in two portions to a solution of complex **5** (540 mg, 0.74 mmol) in the minimum amount possible of dry CH_2Cl_2 and stirred under an atmosphere of argon for 3 h. Thereafter, diethyl ether was added to induce crystallization and the residue was filtered to give **6** as a red solid (490 mg, 75%). Anal. Calcd for $C_{38}H_{37}F_6FeO_{10}P$: C, 53.41; H, 4.36. Found C, 53.48; H, 4.33.

1.6. Methyl 2,4,6-tri-*O*-benzyl-3-[*O*-(trimethoxyphenyl)-benzoic acid] β-D-galactopyranosyl ester (8)

1,3,5-Trimethoxybenzene (43 mg, 0.25 mmol) was added to a solution of the cationic complex **6** (200 mg, 0.23 mmol) and PS-DIEA (25 mg, 0.25 mmol) in dry CH_2Cl_2 (15 mL) and the reaction mixture was stirred under an atmosphere of nitrogen for 8 h. The polymer was removed by filtration and the reaction mixture was then filtrated through a plug of silica and concentrated in vacuo. Thereafter, the residue was dissolved in dry CH_2Cl_2 (10 mL) and TMANO (92 mg, 1.2 mmol) was added. The reaction mixture was then stirred under an atmosphere of nitrogen for further 6 h. Thereafter, the solution was filtered through a plug of silica gel and concentrated in vacuo. The residue was dissolved in dry toluene (5 mL) and DDQ (150 mg, 0.66 mmol) was added. The solution was stirred under an atmosphere of nitrogen for 5 h, and then filtered through a plug of alumina, and concentrated in vacuo to give **8** as a colourless oil (20 mg, 12% over three steps): IR (neat) 3002, 2943, 2292, 2252, 1635, 1442, 1375, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H, Ar), 7.90 (d, $J = 7.2$ Hz, 1H, Ar), 7.55 (d, $J = 7.6$ Hz, 1H, Ar), 7.43 (t, $J = 7.2$ Hz, 1H, Ar), 7.32–7.11 (m, 15H, Ph), 6.21 (s, 2H, anisyl Ar), 5.22 (dd, $J = 10.4$, 3.2 Hz, 1H), 4.80 (d, $J = 11.2$ Hz, 1H), 4.69 (t, $J = 11.2$ Hz, 2H), 4.50–4.39 (m, 4H, $2CH_2$), 4.04 (d, $J = 2.8$ Hz, 1H), 3.91–3.87 (m, 4H, anisyl OMe and 1H), 3.75 (t, $J = 6.4$ Hz, 1H), 3.62–3.60 (m, 7H, 2 anisyl OMe and 1H), 3.57 (s, 3H, OMe), 3.58–3.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 160.8, 158.2, 138.1, 137.8, 136.3, 134.5, 132.9, 129.1, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7, 127.7, 127.5, 127.4, 111.2, 104.9, 100.4, 90.7, 77.5, 77.2, 77.1, 76.5, 75.4, 74.8, 74.5, 74.2, 73.4, 73.2, 68.5, 57.1, 55.8, 55.7, 55.4, 29.7, 29.7. FABMS *m/z* calcd for $C_{44}H_{46}NaO_{10}$ $[M+Na]^+$: 757.2989. Found: 757.2997.

1.7. Methyl-3-(5-cyclohexa-1,3-dienoic acid methyl ester)2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (13)

To a round-bottom flask, equipped with a Dean–Stark trap, di-*n*-butyltin oxide (165 mg, 0.66 mmol) was added to a solution of methyl β-D-galactopyranoside (117 mg, 0.60 mmol) in benzene (25 mL) and the reaction mixture was heated at reflux overnight. Thereafter, the clear solution was cooled to room temperature and **10** (275 mg, 0.65 mmol) was added. The reaction mixture was stirred at room temperature for 2 h whereupon triethylamine (50 μL, 0.36 mmol) was added. The mixture was stirred for further 2 h and then concentrated in vacuo. The crude residue was dissolved in a solution of pyridine and acetic anhydride (1:3, 25 mL) and stirred for 1 h. The crude product was co-evaporated with toluene, re-dissolved in CH_2Cl_2 whereupon TMANO (74 mg, 2.7 mmol) was added. The reaction mixture was stirred at room temperature for 5 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 5:1) affording **13** as a yellow syrup (86 mg, 30%, over four steps). ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, $J = 6.1$ Hz, 1H, C*H*=CCO$_2$Me), 6.26–6.22 (m, 1H) and 6.15–6.08 (m, 1H, CH=CH), 5.41 (br app d, $J = 3.4$ Hz, 1H, H-4), 5.17 (app t,

[†] The diiron nonacarbonyl was treated with 1 M HCl to remove any traces of pyrophoric free metallic iron and subsequently washed several times with ethanol and toluene before use.

[‡] Severe line broadening due to the presence of paramagnetic Fe-species. Chemical shifts are approximate.

$J = 9.1$ Hz, 1H, CH=CH–C*H*O), 4.99 (dd, $J = 9.2$, 3.2 Hz, 1H, H-2), 4.36 (d, $J = 7.8$ Hz, 1H, H-1), 4.18–4.01 (m, 1H, H-6), 3.78 (m, 4H, CO_2Me and H-6), 3.65–3.62 (m, 1H, H-5), 3.51 (s, 3H, OMe), 3.41 (app t, $J = 9.1$ Hz, 1H, H-3), 2.89–2.79 (m, 1H) and 2.60–2.50 (m, 1H, C=CCH_2), 2.15 (s, 3H, Ac), 2.05 (s, 3H, Ac), 1.97 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 69.6, 167.3, 130.5, 130.5, 130.4, 127.4, 127.3, 126.0, 102.2, 72.3, 71.2, 69.2, 67.6, 65.3, 57.1, 51.9, 27.9, 20.9, 20.8, 20.7; IR (neat) 2957, 2924, 2852, 1750, 1724, 1222, 1073 cm^{-1}. FABMS *m/z* calcd for $C_{21}H_{28}NaO_{11}$ $[M+Na]^+$: 479.1529. Found: 479.1537.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.04.020.

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