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Stereoselective synthesis of sugar-fused *C*-aryl-carbasugar derivatives from sugar-derived terminally unsubstituted dienes and Baylis-Hillman product-derived trisubstituted olefins via Diels-Alder reaction

Kadigachalam Parasuraman[a,b], Sateesh Dubbu[a], Ande Chennaiah[a], A. K. Ibrahim Sheriff[b] and Yashwant D. Vankar*[a]

[a]Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur-208 016, Uttar Pradesh, India

E-mail: vankar@iitk.ac.in

[b]P.G. and Research Department of Chemistry, C. Abdul Hakeem College (Autonomous), Melvisharam-632 509, Tamil Nadu, India

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Sugar-fused *C*-aryl-carbasugar derivatives were synthesized in a stereoselective manner via Diels-Alder reaction between galactal- and glucal-derived terminally unsubstituted dienes and Baylis-Hillman product-derived trisubstituted olefins. This reaction is compatible with a variety of Baylis-Hillman product-derived trisubstituted olefins to give the corresponding sugar fused-*C*-aryl carbasugar derivatives with excellent regio- and stereoselectivity in good to excellent yields. Some of the products were converted into more functionalized scaffolds of wider utility and of possible biological importance.

Keywords: Carbohydrates, fused-sugars, *C*-aryl-carbasugar derivatives, Diels-Alder reaction, Baylis-Hillman product.

Introduction

Carbohydrates are the most important biomolecules whose role is not limited to energy storage alone since they are constituents of glycoconjugates and act as key elements in a variety of processes such as signaling, cell-cell communication, cell-cell adhesion, molecular and cellular targeting[1]. Carbohydrates are involved in many biological processes such as blood clotting[1k-1l], fertilization[1m-1n] and they are strongly related to diseases such as cancer, diabetes, or inflammatory processes[1]. Depending on the hetero atom present in the sugar ring, these carbohydrates are classified as iminosugars, carbasugars and thiasugars where oxygen atom is replaced by a nitrogen, a sulfur or a carbon atom[2]. Among them, carbasugars are polyhydroxylated cyclohexanes[3], and cyclohexenes[4] and their corresponding epoxides[5] have attracted a great deal of attention in the past few decades as they form a part of several natural products with a broad spectrum of reported biological activities such as glycosidase inhibition[6], anti-cancer, anti-diabetes and anti-bacterial. Carbasugars have also been used as synthetic intermediates in the total synthesis of several complex and bioactive molecules[7]. Carbasugar analogue of dapagliflozin[8] **1** (Fig. 1) shows sodium-glucose cotransporter-2 (SGLT-2) IC_{50} with 438 nM and sodium-glucose cotransporter-1 (SGLT-1) with IC_{50} 8740 nM. Similarly, cyclohexene analogue of dapagliflozin[8] **2** (Fig. 1) shows SGLT-2 with IC_{50} 24 nM and SGLT-1 with IC_{50} 9930 nM. Along with carbasugars, sugar-fused-carbasugars also show interesting bioactivities[9]. For example, bradyrhizose[9] **3** (Fig. 1) is a carbasugar fused with a sugar moiety and is known to play an important role in biological nitrogen fixation.

Baylis-Hillman reaction[10,11] is an efficient C-C bond forming reaction and produces products containing multifunctional groups. In our group, Baylis-Hillman products were converted into more useful products like di-, tri- and tetrasubstituted olefins and some bioactive compounds[12].

Sugar derived dienes are an important class of synthetic intermediates in carbohydrate chemistry, and from our group, several advances have been reported in recent years[13]. We

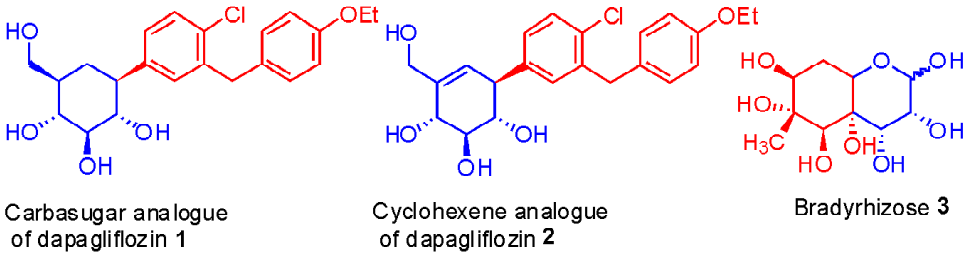


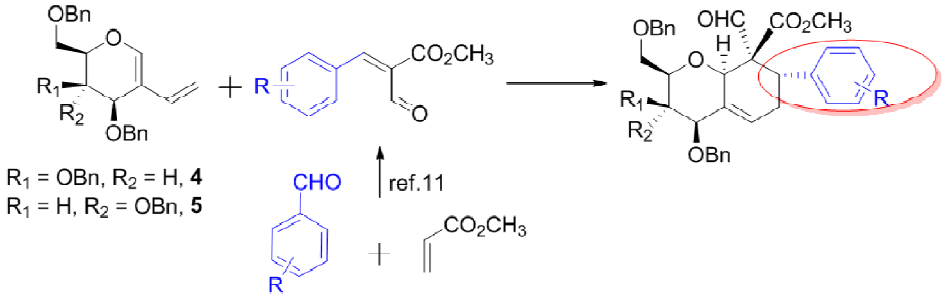
Fig. 1. Biologically active *C*-aryl-carbasugars and sugar-fused carbasugars.

reported the synthesis of sugar fused *C*-glycosyl α- and β-amino acids and sugar-carbamino hybrids by using terminally unsubstituted sugar-derived dienes and α-nitro acrylate and ethyl β-nitro acrylate via the Diels-Alder reaction[13a]. Based on this strategy, very recently, we reported the synthesis of 1,2-annulated *C*-aryl glycosides and temperature dependent sugar branched, fused, and naphthalenes from terminally unsubstituted sugar derived dienes and arynes[13b].

Fused-sugars and *C*-aryl-carbasugars are privileged core motifs that exist in a variety of natural products and biologically active molecules[3–5,8–9]. Thus, the development of efficient approaches to the direct construction of *C*-aryl-carbasugar derivatives from readily available starting materials under mild conditions is of interest in organic synthesis. In continuation of our interest in the synthesis of annulated/fused sugars[13a,14] and *C*-aryl-glycosides[13b,15], herein, we report (Scheme 1) a highly efficient route for the rapid synthesis of 1,2-annulated sugar-fused *C*-aryl-carbasugar derivatives starting from terminally unsubstituted sugar-derived dienes and Baylis-Hillman product-derived trisubstituted olefins via Diels-Alder reaction under mild conditions.

Results and discussion

To investigate the feasibility of the reaction, the starting materials, dienophiles **6a-6j** (Fig. 2) were prepared by known



Scheme 1. A synthetic strategy for the synthesis of sugar-fused *C*-aryl-carbasugars.

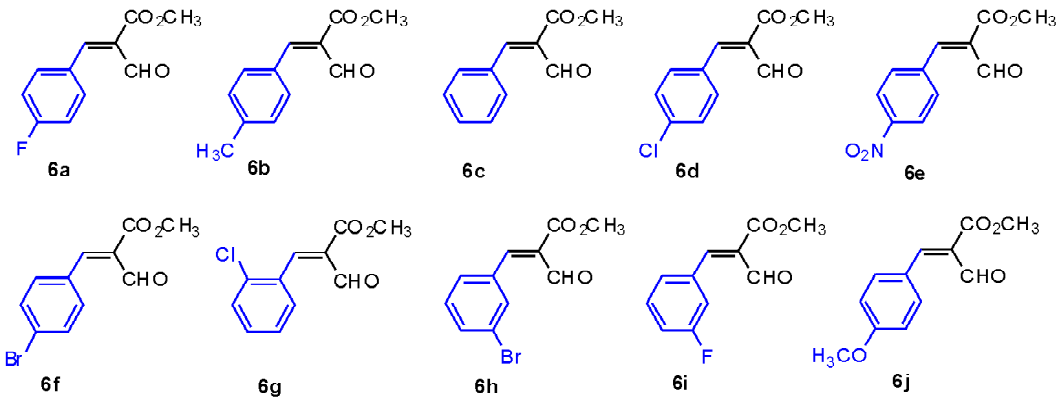
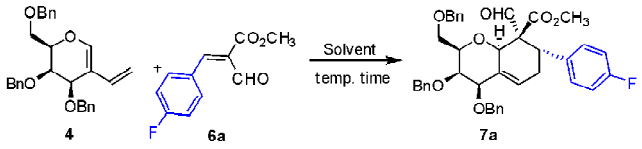


Fig. 2. A variety of dienophiles **6a-6j** were used in the reaction.

synthetic literature procedure[11]. As a model reaction, we initially attempted the cycloaddition of galactal derived terminally unsubstituted diene **4** (Table 1) with dienophile **6a** in ethanol from room temperature to reflux, however, no cyclization was observed under these conditions (Table 1, entry 1). A similar result was also observed with other solvents like CH_2Cl_2, 1,2-dichloroethane, and THF (Table 1, entries 2, 3 and 4).

Table 1. Optimization of the reaction condition



Entry	Solvent	Temp.	Time (h)	**7a** Yield (%)[b]
1	CH_3CH_2OH	r.t-80°C	24	nr
2	CH_2Cl_2	r.t	24	2
3	DCE	r.t-60°C	24	7
4	THF	r.t-60°C	24	7
5	**Toluene**	**r.t-110**°C	**8**	**82**[a]

[a]Conditions: diene **4** (1.0 equiv.), dienophile **6a** (1.1 equiv.), toluene at 110°C. [b]Yield refers to pure after column chromatography. nr = no reaction. DCE = 1,2-dichloroethane.

To our delight, after screening various solvents, toluene was found to be the best one (Table 1, entry 5) at room temperature to 110°C, we observed the formation of sugar-fused *C*-aryl-carbasugar derivative **7a** in 82% yield.

With the optimal condition in hand, we next set out to investigate the scope of this reaction with various dienophiles **6a-6j** (Table 2). In most cases, the products were obtained in good yields and high selectivity. This method is compatible with a wide range of functional groups such as halides, nitro, methyl and methoxy (Table 2). The reaction of galactal-derived terminally unsubstituted diene **4** with dienophiles **6a**, **6c**, **6d**, **6e**, **6f** and **6g** under stabilized condition (Table 1, entry 5) gave sugar-fused *C*-aryl-carbasugar derivatives **7a**, **7c**, **7d**, **7e**, **7f** and **7g** respectively in good to excellent yields. On the other hand, the reaction of diene **4** with dienophile **6b** gave sugar fused-*C*-aryl-carbasugar derivative **7b** in 65% yield. Likewise, glucal-derived terminally unsubstituted diene **5** also underwent reaction with different dienophiles **6c**, **6h**, **6i** and **6d** to give the corresponding products **7h**, **7i**, **7j** and **7l** in good yields. Furthermore, this reaction is also quite successful with acid sensitive dienophile **6j** which gave product **7k** in 65% yield. Surprisingly, we did not observe the formation of any other diastereomer during the Diels-Alder reaction which, if at all formed, may have been lost during the column chromatographic purification.

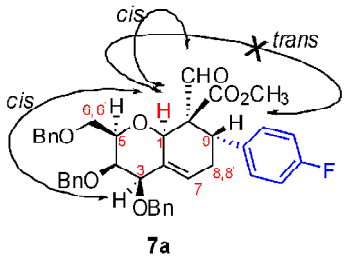
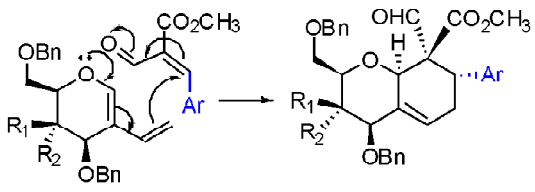


Fig. 3. NOE of fused compound **7a**.

The structure of the cycloadduct **7a** was confirmed by spectral studies and the stereochemistry of the newly generated stereocenters was established based on COSY followed by NOE studies[16]. Thus, in the NOE correlation studies of compound **7a** (Fig. 3), irradiation of the H-1 proton at δ 4.98 resulted in an enhancement of the signals for H-5 proton at δ 4.08–4.05, H-3 proton at δ 4.16 and aldehyde proton (-C*H*O) signal at δ 9.83 indicating that H-1 and H-3, H-5 and -CHO are in a *cis* relationship.

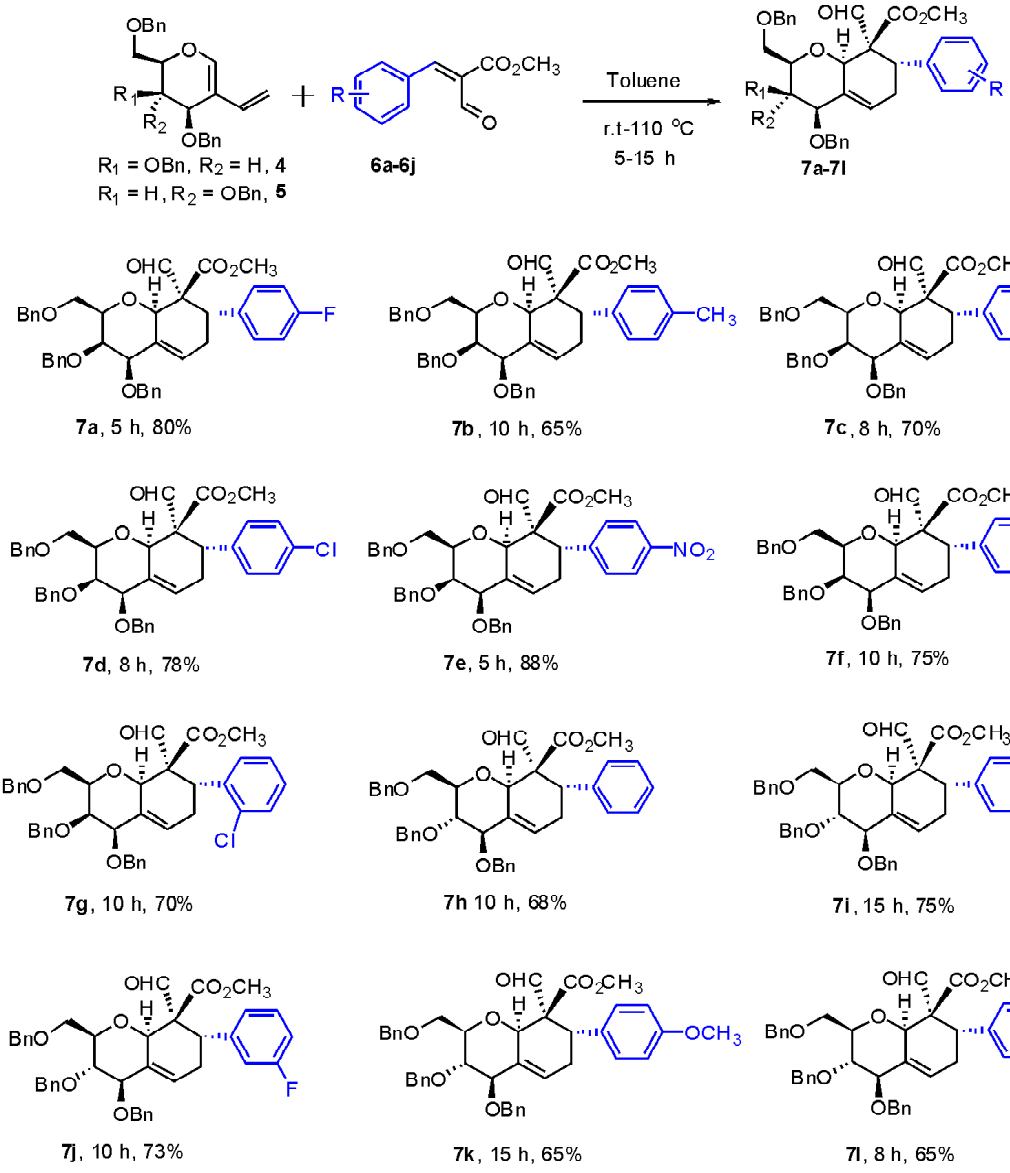
The observed regiochemistry of the Diels-Alder adducts is cleary understood by the orientation of the electron-rich diene and the electron deficient dienophiles so as to permit the allowed HOMO-LUMO interactions (Scheme 2). Likewise, inspection of the molecular models suggest that the secondary orbital interactions (Fig. 4) between the olefin and the α-oriented aldehyde group, will substantiate the stereoselectivity observed.



Scheme 2

Similarly, in the NOE studies[16] of compound **7h** (Fig. 5), irradiation of the H-1 proton at δ 5.14 resulted in an enhancement of the H-5 proton signal at δ 3.91–3.87, H-3 proton

Table 2. Stereoselective synthesis of sugar fused-*C*-aryl-carbasugar derivatives



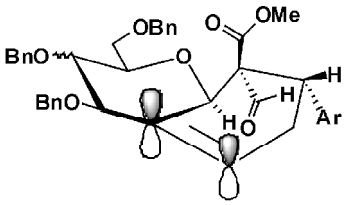
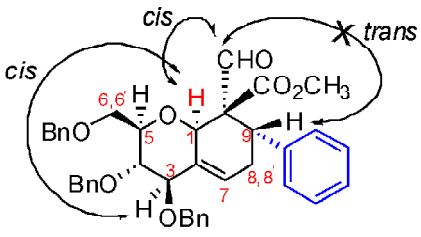


Fig. 4

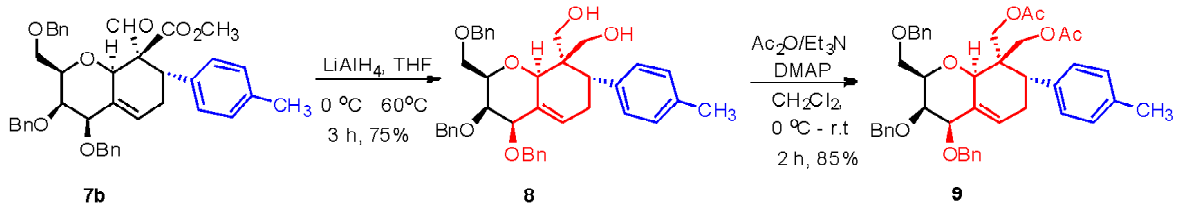


7h

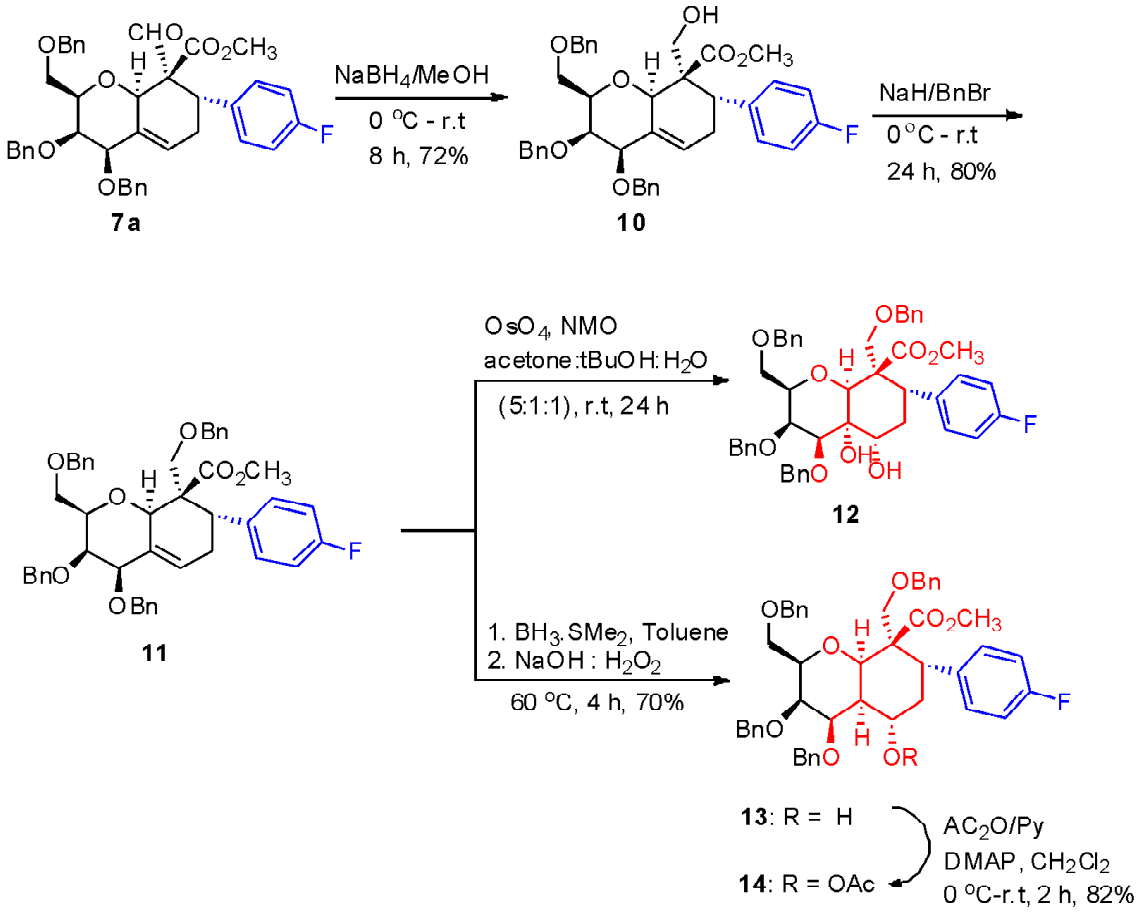
Fig. 5. NOE of fused compound **7h**.

signal at δ 4.02 and aldehyde proton (-C*H*O) signal at δ 10.01, but did not result in the enhancement of the signal of H-9 proton. It indicates that H-1 is in a *cis* relationship with H-5, H-3 and aldehyde (-CHO) protons and is *trans* to H-9.

With easy access to the sugar fused-*C*-aryl-carbasugar derivatives, we turned our attention to generate *C*-aryl-carbasugar derivatives having hydroxyl groups. The *C*-aryl-carbasugar derivatives have been the subject of numerous synthetic studies[8] due to their potential biological properties. Thus, the sugar-fused *C*-aryl-carbasugar derivative **7b** was reduced with $LiAlH_4$ to afford the corresponding diol **8** in 75% yield (Scheme 3). Further, the primary hydroxyl groups were protected as acetates to give compound **9**. Next, the aldehyde group in compound **7a** was selectively reduced with $NaBH_4$ to afford alcohol **10** and then protected as benzyl ether **11** using BnBr/NaH condition (Scheme 4). Stereoselective dihydroxylation[13b] of compound **11** with OsO_4 and NMO (*N*-methylmorpholine *N*-oxide) led to sugar-fused *C*-aryl-carbasugar derivative **12** in good yield. Similarly, the hydroboration-oxidation of compound **11** led to the formation of alcohol **13** and the free hydroxyl group was protected as acetate **14** in good yield (Scheme 4).



Scheme 3. Reduction of compound **7b** with $LiAlH_4$.



Scheme 4. Derivatization of product **7a**.

The stereochemistry of the newly generated stereocentres in the products obtained upon dihydroxylation, and hydroboration-oxidation was established based on COSY and NOE studies. Thus, in compound **12** irradiation of the proton H-9 at δ 3.12–3.09 resulted in an enhancement of the H-7 proton at δ 3.91–3.86 (Fig. 6) and did not show the enhancement of the H-1 proton indicating that H-9 is in *cis*-orientation with H-7 and *trans*-orientation with H-1 proton. The conformation of the same is shown in the Fig. 6.

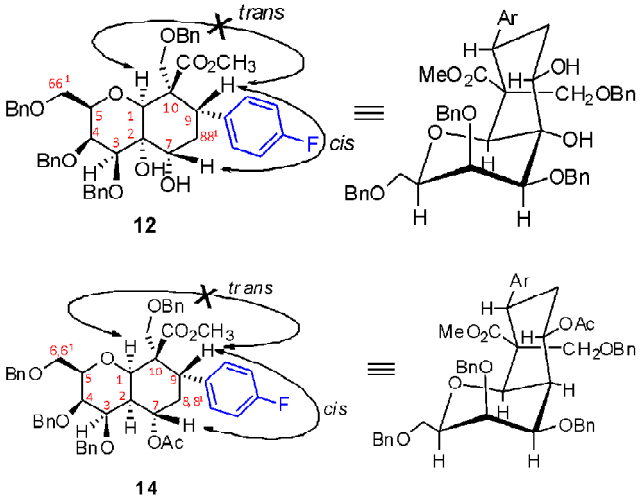


Fig. 6. NOE of compounds **12** and **14**.

Likewise, irradiation of the H-9 proton at δ 3.21–3.19 in compound **14** (Fig. 6) resulted in an enhancement of the H-7 proton signal at δ 5.17–5.12 and did not show the enhancement of the H-1 proton indicating that H-9 is in a *cis*-orientation with H-7 and *trans*-orientation with H-1 proton.

Conclusion

In summary, we have synthesized sugar-fused *C*-aryl-carbasugar derivatives via Diels-Alder reaction between galactal and glucal derived terminally unsubstituted dienes and Baylis-Hillman product derived trisubstituted olefins. This reaction is compatible with a variety of Baylis-Hillman product derived trisubstituted olefins to give the corresponding sugar-fused *C*-aryl-carbasugar derivatives with excellent stereochemistry in good to excellent yields. The synthetic utility of the obtained scaffolds was further explored by functionalizing the isolated *exo*-double bond and reduction of carbonyl groups through stereoselective dihydroxylation, hydroboration-oxidation.

Experimental

General procedure: To a stirred solution of terminally unsubstituted sugar derived diene **4**/**5** (100 mg, 1.0 equiv.) in dry toluene (5 mL) was added a Baylis-Hillman product-derived trisubstituted olefin (**6a**-**6j**) (1.1 equiv.) at room temperature. The temperature of this reaction mixture was slowly increased to 110°C and continued to stir at this temperature for 5–15 h, as indicated in Table 2. Upon completion of the reaction (TLC monitoring), the solvent was evaporated and the crude product was directly purified by column chromatography to afford sugar fused-*C*-aryl-carbasugar derivative (**7a**-**7l**).

*(2R,3R,4R,7S,8S,8aR)-Methyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-(4-fluoro-phenyl)-8-formyl-3,4,6,7,8,8a-hexahydro-2H-chromene-8-carboxylate (**7a**):*

Following the general procedure, compound **7a** was isolated as a colorless oil in 80% yield (114 mg); R_f = 0.5 (hexane:ethyl acetate, 8:2); $[\alpha]_D^{25}$ = +43.46 (*c* 0.68, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 2922, 2854, 1721, 1509, 1453, 1232, 1100, 837, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.36–7.24 (m, 15H), 6.99–6.96 (m, 2H), 6.78–6.73 (m, 2H), 5.92 (s, 1H), 4.99 (s, 1H), 4.68 (dd, *J* 11.68, 6.64 Hz, 2H), 4.59–4.54 (m, 4H), 4.41–4.37 (m, 1H), 4.17 (d, *J* 1.84 Hz, 1H), 4.07 (dd, *J* 11.2, 8.5 Hz, 1H), 3.89 (dd, *J* 5.96, 2.76 Hz, 1H), 3.81 (dd, *J* 11.22, 3.42 Hz, 1H), 3.73–3.69 (m, 1H), 3.57 (s, 3H), 2.85–2.80 (m, 1H), 2.36–2.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.07, 168.54, 138.61, 138.31, 138.13, 137.18, 132.62, 129.57, 129.49, 128.57, 128.50, 128.39, 127.82, 127.75, 127.56, 127.52, 127.38, 126.99, 115.51, 115.29, 77.14, 76.09, 75.49, 73.38, 72.17, 70.76, 66.19, 65.90, 63.22, 52.46, 40.84, 29.92; HRMS Calcd. for $C_{40}H_{39}FNaO_7$ $[M+Na]^+$ = 673.2578, Found: 673.2579.

*(2R,3S,4R,7S,8S,8aR)-Methyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-8-formyl-7-(4-methoxyphenyl)-3,4,6,7,8,8a-hexahydro-2H-chromene-8-carboxylate (**7k**):*

Following the general procedure, compound **7k** was isolated as a colorless oil in 65% yield (97 mg); R_f = 0.5 (hexane:ethyl acetate, 8:2); $[\alpha]_D^{25}$ = +58.7 (*c* 0.54, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 2921, 2866, 1720, 1611, 1512, 1454, 1251, 1179, 1094, 832, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.33–7.24 (m, 15H), 6.99–6.97 (m, 2H), 6.71–6.69 (m, 2H), 5.95 (s, 1H), 5.09 (s, 1H), 4.69–4.50 (m, 5H), 4.41 (d, *J* 11.75 Hz, 1H), 4.15–4.11 (m, 1H), 3.99 (d, *J* 2.7 Hz, 1H), 3.88 (dd, *J* 10.6, 7.15 Hz, 1H), 3.78–3.67 (m, 6H),

3.60 (s, 3H), 2.90–2.84 (m, 1H), 2.41–2.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.92, 168.83, 158.71, 138.52, 138.06, 138.00, 133.33, 130.88, 129.88, 128.97, 128.59, 128.51, 128.39, 127.81, 127.74, 127.63, 127.57, 127.49, 113.89, 78.57, 76.22, 74.97, 73.23, 71.33, 70.05, 68.04, 66.63, 64.36, 55.25, 52.46, 40.96, 30.11; HRMS Calcd. for $C_{41}H_{46}NO_8$ $[M+NH_4]^+$ = 680.3223, Found: 680.3220.

*((2R,3R,4R,7S,8aS)-3,4-bis(Benzyloxy)-2-(benzyloxymethyl)-7-p-tolyl-3,4,6,7,8,8a-hexa-hydro-2H-chromene-8,8-diyl)dimethanol (**8**):*

To a stirred solution of compound **7b** (80 mg, 0.12 mmol, 1.0 equiv.) in dry THF (2 mL) was added a suspension of $LiAlH_4$ (47 mg, 1.2 mmol, 10.0 equiv.), dissolved in dry THF (2 mL), at 0°C. The reaction mixture was slowly brought to room temperature and continued to stir at 60°C for 3 h. Upon reaction completion (TLC monitoring), the reaction mixture was cooled to 0°C and quenched by drop-wise addition of EtOAc followed by water. The resulting solution was filtered through celite® pad and the aqueous filtrate was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine (1×3 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents *in vacuo* gave a crude compound which was further purified by column chromatography to afford the diol **8** as a colorless liquid (53 mg, 75% yield); R_f = 0.5 (hexane:ethyl acetate, 7.5:2.5); $[\alpha]_D^{25}$ = +21.13 (*c* 0.53, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 3437, 2922, 2855, 1453, 1088, 1027, 816, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–6.97 (m, 19H), 5.85 (d, *J* 3.64 Hz, 1H), 4.73–4.32 (m, 5H), 4.22 (d, *J* 3.24 Hz, 1H), 4.07–3.93 (m, 3H), 3.77–3.49 (m, 5H), 3.19 (t, *J* 11.28 Hz, 1H), 2.94 (bs, 1H), 2.87–2.7 (m, 2H), 2.52–2.48 (m, 1H), 2.3–2.29 (m, 4H), 2.16–2.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.07, 138.03, 137.54, 136.92, 136.58, 132.63, 129.35, 128.94, 128.90, 128.53, 128.49, 128.30, 128.19, 128.05, 127.90, 127.68, 127.57, 124.27, 119.40, 81.09, 78.09, 74.11, 73.46, 71.37, 70.73, 70.55, 69.92, 69.37, 65.93, 65.28, 65.01, 61.38, 43.1, 41.63, 28.82, 21.05; HRMS Calcd. for $C_{44}H_{45}O_6$ $[M+H]^+$ = 621.3216, Found: 621.3212.

*((2R,3R,4R,7S,8aS)-3,4-bis(Benzyloxy)-2-(benzyloxymethyl)-7-p-tolyl-3,4,6,7,8,8a-hexahydro-2H-chromene-8,8-diyl)bis(methylene)diacetate (**9**):*

To a stirred solution of compound **8** (51 mg, 0.08 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) under N_2 atmosphere was added Et_3N (23 μL, 0.16 mmol, 2.0 equiv.), acetic anhydride (16 μL, 0.16 mmol, 2.0 equiv.) followed by addition of a catalytic amount of DMAP (1 mg, 0.008 mmol, 0.1 equiv.) at 0°C. The reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction (TLC monitoring), it was quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine (1×3 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure and the crude product was purified by silica gel column chromatography to afford a colorless viscous oil **9** (49 mg, 85% yield); R_f = 0.6 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ = +39.13 (*c* 0.23, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 2923, 2854, 1740, 1453, 1242, 1045, 736, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–6.93 (m, 19H), 5.91 (s, 1H), 4.63–3.81 (m, 10H), 4.15–3.80 (m, 5H), 3.21 (bs, 1H), 2.40–2.28 (m, 5H), 1.82 (s, 6H), 1.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92, 170.74, 138.62, 138.41,138.36, 136.42, 133.16, 129.10, 128.46, 128.39, 127.72, 127.52, 127.37, 126.91, 77.93, 77.58, 77.27, 76.94, 76.82, 76.60, 75.62, 73.06, 71.57, 70.43, 66.35, 65.86, 65.65, 65.06, 42.31, 41.25, 29.29, 21.01, 20.87, 20.83; HRMS Calcd. for $C_{44}H_{52}NO_8$ $[M+NH_4]^+$ = 722.3693, Found: 722.3694.

*(2R,3R,4R,7S,8R,8aR)-Methyl 3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-(4-fluoro-phenyl)-8-(hydroxymethyl)-3,4,6,7,8,8a-hexahydro-2H-chromene-8-carboxylate (**10**):*

To a stirred solution of compound **7a** (280 mg, 0.43 mmol, 1.0 equiv.) in dry methanol (5 mL) at 0°C was added $NaBH_4$ (50 mg, 1.29 mmol, 3 equiv.) in portions. Once addition was over, the reaction mixture was brought to room temperature and continued to stir for 8 h. Upon completion of reaction (TLC monitoring), the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (1 mL) at 0°C. The solvent methanol was evaporated *in vacuo* and the aqueous portion was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by silica gel column chromatography afforded the colorless viscous oil **10** (202 mg, 72% yield); R_f = 0.5 (hexane:ethyl acetate, 7.5:2.5); $[\alpha]_D^{25}$ = +18.25 (*c* 0.48, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 3472, 2923, 2853, 1722, 1510, 1224, 1090, 736, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.25 (m, 15H), 7.02–6.99 (m, 2H), 6.93–6.89 (m, 2H), 5.89 (dd, *J* 5.5, 2 Hz, 1H), 4.78 (d, *J* 12.05 Hz, 1H), 4.71 (s, 1H), 4.63–4.41 (m, 7H), 4.24 (d, *J* 3.4 Hz, 1H), 3.93 (dd, *J* 11.75, 3.75 Hz, 1H), 3.79–3.72 (m, 3H), 3.66 (s, 3H),

3.59 (t, *J* 11.15 Hz, 1H), 3.04 (dd, *J* 10.5, 4.5 Hz, 1H), 2.47 (dd, *J* 17.5, 11 Hz, 1H), 2.21 (dt, *J* 17.5, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.03, 163.03, 161.08, 138.41, 138.22, 138.06, 135.94, 135.92, 133.65, 130.16, 130.09, 128.44,128.37, 128.07, 127.98, 127.84, 127.76, 127.66, 127.57, 127.53, 127.01, 114.85, 114.69, 74.93, 73.34, 71.03, 69.86, 66.08, 65.25, 63.61, 54.87, 51.4, 41.81, 29.79; HRMS Calcd. for $C_{40}H_{45}FNO_7$ $[M+NH_4]^+$ = 670.3180, Found: 670.3181.

*(2R,3R,4R,7S,8R,8aR)-Methyl3,4-bis(benzyloxy)-2,8-bis(benzyloxymethyl)-7-(4-fluoro-phenyl)-3,4,6,7,8,8a-hexahydro-2H-chromene-8-carboxylate (**11**):*

To a stirred solution compound **10** (320 mg, 0.49 mmol, 1.0 equiv.) in DMF (8 ml) at 0°C was added NaH (98 mg, 2.45 mmol, 5.0 equiv., 60% dispersion in paraffin oil) followed by drop-wise addition of BnBr (117 μL, 0.98 mmol, 2.0 equiv.). The reaction mixture was continued to stir for 24 h at room temperature. Upon completion of reaction (TLC monitoring), the reaction mixture was quenched with cold ice-water and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was further purified by column chromatography to obtain a viscous oil **11** (291 mg, 80% yield); R_f = 0.6 (hexane:ethyl acetate, 7.5:2.5); $[\alpha]_D^{25}$ = +46 (*c* 0.36, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 3029, 2926, 1730, 1509, 1453, 1215, 1092, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.17 (m, 20H), 7.12–7.08 (m, 2H), 6.88 (t, *J* 8.48 Hz, 2H), 5.86 (s, 1H), 4.86 (s, 1H), 4.79 (d, *J* 11.92 Hz, 1H), 4.64 (d, *J* 11.92 Hz, 1H), 4.56–4.36 (m, 7H), 4.22–4.17 (m, 2H), 3.98 (dd, *J* 11.44, 2.78 Hz, 1H), 3.91 (d, *J* 9.16 Hz, 1H), 3.76 (q, *J* 2.78 Hz, 1H), 3.60 (s, 3H), 3.44 (d, *J* 8.72 Hz, 1H), 3.29 (q, *J* 4.57 Hz, 1H), 2.74 (dd, *J* 17.86, 9.16 Hz, 1H), 2.29 (dt, *J* 18.32, 5.50 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.96, 163.13, 160.69, 139.02, 138.94, 138.61, 138.42, 136.49, 134.72, 130.51, 130.43, 128.45, 128.39, 128.26, 128.18, 127.68, 127.55, 127.46, 127.29, 127.16, 127.05, 126.32, 114.81, 114.59, 77.74, 77.59, 77.46, 73.27, 73.16, 71.29, 71.01, 69.89, 67.04, 64.18, 54.29, 51.41, 41.02, 29.82; HRMS Calcd. for $C_{47}H_{51}FNO_7$ $[M+NH_4]^+$ = 760.3650, Found: 760.3653.

*(2R,3S,4S,4aS,5S,7S,8R,8aS)-Methyl 3,4-bis(benzyloxy)-2,8-bis(benzyloxymethyl)-7-(4-fluorophenyl)-4a,5-dihydroxyoctahydro-2H-chromene-8-carboxylate (**12**):*

To a stirred solution of compound **11** (90 mg, 0.12 mmol, 1.0 equiv.) dissolved in acetone:*t*-butanol:water (5:1:1) at room temperature was added NMO (17 mg, 0.144 mmol, 1.2 equiv.) followed by addition of a catalytic amount of OsO_4 (3 mg, 0.012 mmol, 10 mol%). The reaction mixture was continued to stir at the same temperature for 24 h. Upon completion of reaction (TLC monitoring), it was treated with $Na_2S_2O_5$ (23 mg, 0.12 mmol, 1.0 equiv.) and stirred for further 1 h. The contents of the reaction mixture were filtered through a celite pad and the aqueous filtrate was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by purification by column chromatography afforded exclusively the *cis* dihydroxylated compound **12** (71 mg, 70% yield); R_f = 0.5 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ = +27.34 (*c* 0.32, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 2924, 2854, 1749, 1509, 1454, 1222, 1095, 736, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.12 (m, 20H), 6.88 (t, *J* 8.88 Hz, 2H), 6.8 (dd, *J* 7.15, 2.97 Hz, 2H), 4.99 (d, *J* 11.45 Hz, 1H), 4.67–4.61 (m, 2H), 4.56 (d, *J* 11.45 Hz, 1H), 4.47 (s, 2H), 4.45–4.41 (m, 1H), 4.30 (s, 1H), 4.24–4.20 (m, 2H), 4.12–4.05 (m, 2H), 4.03 (dd, *J* 6.58, 3.05 Hz, 1H), 3.89 (td, *J* 11.18, 5.52 Hz, 1H), 3.78–3.75 (m, 2H), 3.63 (d, *J* 9.15 Hz, 1H), 3.53 (s, 3H), 3.13 (s, 1H), 3.12–3.10 (dd, *J* 13.48, 2.58 Hz, 1H), 2.65 (q, *J* 12.87 Hz, 1H), 2.12 (d, *J* 11.45 Hz, 1H), 1.91–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.06, 162.89, 160.44, 138.34, 138.19, 138.17, 137.72, 137.56, 137.54, 131.52, 131.45, 128.71, 128.65, 128.45, 128.05, 127.98, 127.81, 127.69, 127.52, 127.09, 126.84, 114.15, 113.94, 75.68, 75.22, 74.76, 73.18, 72.89, 72.75, 72.60, 71.99, 69.17, 65.13, 53.29, 51.24, 42.07, 34.47; HRMS Calcd. for $C_{47}H_{53}FNO_9$ $[M+NH_4]^+$ = 794.3704, Found: 794.3707.

*(2R,3R,4R,4aR,5S,7S,8R,8aR)-Methyl 3,4-bis(benzyloxy)-2,8-bis(benzyloxymethyl)-7-(4-fluorophenyl)-5-hydroxyoctahydro-2H-chromene-8-carboxylate (**13**):*

To a stirred solution of compound **11** (90 mg, 0.12 mmol, 1.0 equiv.), in dry toluene (2 mL) was added 10 *M* solution of BH_3-Me_2S (BMS) in THF (25 μL, 2 equiv.) at 0°C. The temperature of the reaction mixture was slowly increased to 60°C and continued to stir at this temperature for 4 h. Upon completion of reaction (TLC monitoring), THF:H_2O (1:1, 0.2 mL), 2 *N* NaOH (0.5 mL) and 30% H_2O_2 (0.3 mL) were added consecutively at 0°C. After stirring the reaction mixture for 2 h at room temperature, to it was poured cold-ice water and then extracted with EtOAc (3×5 mL). The combined organic

extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated *in vacuo* to give the crude product which was purified by silica gel column chromatography to get a colorless viscous oil **13** (64 mg, 70% yield). R_f = 0.5 (hexane:ethyl acetate,7:3); $[\alpha]_D^{25}$ = –24.06 (*c* 0.16, CH_2Cl_2); IR (neat) ν_{max}: 3425, 2924, 1724, 1509, 1453, 1217, 1091, 735, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.17 (m, 18H), 7.05–6.99 (m, 4H), 6.90 (t, *J* 8.6 Hz, 2H), 4.75–4.52 (m, 6H), 4.42–4.37 (m, 3H), 4.29–4.21 (m, 3H), 4.12 (dd, *J* 11.2, 8 Hz, 1H), 3.98 (dd, *J* 6.4, 2.8 Hz, 1H), 3.95–3.85 (m, 3H), 3.53 (s, 3H), 3.42 (d, *J* 8.4 Hz, 1H), 3.14–3.10 (m, 1H), 2.68 (dt, *J* 10.8, 2.8 Hz, 1H), 2.03–1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.48, 162.79, 160.84, 139.06, 138.89, 138.79, 138.41, 136.55, 130.52, 130.46, 128.44, 128.31, 128.27, 128.11, 127.64, 127.51, 127.36, 127.34, 127.07, 126.80, 114.50, 114.34, 73.01, 72.96, 72.82, 71.89, 71.78, 71.23, 71.13, 68.91, 66.72, 65.58, 55.63, 51.22, 45.50, 40.94, 38.77, 29.79; HRMS Calcd. for $C_{47}H_{53}FNO_8$ $[M+NH_4]^+$ = 778.3755, Found: 778.3754.

*(2R,3R,4R,4aR,7S,8R,8aR)-Methyl 5-acetoxy-3,4-bis(benzyloxy)-2,8-bis(benzyloxymethyl)-7-(4-fluorophenyl)octahydro-2H-chromene-8-carboxylate (**14**):*

To a stirred solution of compound **13** (64 mg, 0.08 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) under N_2 atmosphere were added pyridine (13 μL, 2.0 equiv.), acetic anhydride (15 μL, 2.0 equiv.) and followed by addition of a catalytic amount of DMAP (2 mg, 10 mol%) at 0°C. The reaction mixture was continued to stir for 2 h at room temperature. After completion of the reaction (TLC monitoring), it was quenched by drop-wise addition of saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated *in vacuo* and the crude was further purified by silica gel column chromatography to afford a colorless oil **14** (55 mg, 82% yield); R_f = 0.6 (hexane:ethyl acetate, 7.5:2.5); $[\alpha]_D^{25}$ = –11.76 (*c* 0.2, CH_2Cl_2); IR (neat) $\tilde{\nu}_{max}$: 3422, 2923, 2852, 1731, 1603, 1510, 1453, 1366, 1220, 1092, 1027, 735, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.17 (m, 18H), 7.05–7.04 (m, 2H), 6.99–6.97 (m, 2H), 6.89 (t, *J* 8.6 Hz, 2H), 5.16 (td, *J* 11.0, 5.5 Hz, 1H), 4.73 (d, *J* 12 Hz, 1H), 4.71 (d, *J* 2.3 Hz, 1H), 4.59 (d, *J* 12 Hz, 1H), 4.52–4.46 (m, 2H), 4.41 (dd, *J* 12.25, 5.83 Hz, 3H), 4.28 (d, *J* 12 Hz, 1H), 4.22 (d, *J* 12 Hz, 1H), 4.14 (dd, *J* 11.5, 6.5 Hz, 1H), 4.03 (dd, *J* 6.75, 3.17 Hz, 1H), 3.89–3.86 (m, 2H), 3.73 (t, *J* 2.75 Hz, 1H), 3.55 (s, 3H), 3.42 (d, *J* 8 Hz, 1H), 3.20 (dd, *J* 13, 3 Hz, 1H), 2.92 (dt, *J* 11.5, 2.5 Hz, 1H), 2.06–1.94 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.47, 170.67, 162.82, 160.87, 138.91, 138.77, 138.73, 138.45, 136.09, 130.41, 128.38, 128.28, 128.26, 128.10, 127.78, 127.62, 127.59, 127.44, 127.31, 127.82, 114.51, 114.34, 72.98, 72.90, 71.84, 71.65, 71.30, 70.49, 66.49, 64.99, 55.50, 51.21, 42.22, 40.58, 34.53, 21.09; HRMS Calcd. for $C_{49}H_{55}FNO_9$ $[M+NH_4]^+$ = 820.3861, Found: 820.3860.

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16. The Supporting Information (ESI) for spectral details is available with the Indian Chemical Society.