Diels–Alder Reaction of 2-Nitro Glycals: A New Route to the Synthesis of Benzopyrans

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Dedicated to the late Professor Ray Lemieux.

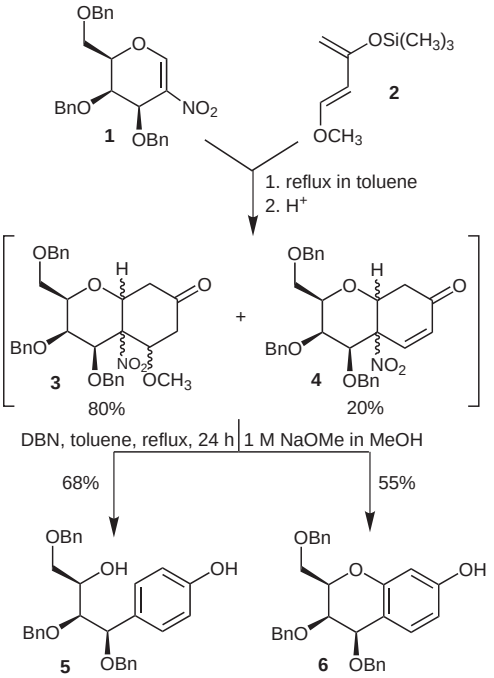
Abstract: Synthesis of different benzopyrans was achieved by Diels–Alder reaction of 2-nitro glycals with Danishefky's diene, hydrolysis of the enol ether moiety, and subsequent elimination of the nitro and methoxy group.

Key words: 2-nitro glycals, Diels–Alder reaction, chromans, benzopyrans, benzannulated dihydropyrans, C-glycosides

The benzannulated pyran skeleton is found in many naturally occurring biologically active compounds. Among them the well known rotinoids,[1] flavonoids,[2] chromones,[3] and griseorhodin antibiotics are included.[4] Furthermore, the contained glycal moieties are important as both synthetic and biological intermediates.[5] To the best of our knowledge, till now, only two types of approaches have been reported in the literature using glycal derivatives for the synthesis of benzopyrans: i) Diels–Alder reaction of C-2-vinyl glycals with dienophiles.[6] ii) Reaction of sugar derived Fischer carbene complexes with acetylenes.[7] As part of our ongoing interest in the exploitation of 2-nitro glycals[8,9] to the synthesis of a variety of 2-amino glycosides, we have recently reported the synthesis of O-,[8a–d] C-glycosides[8e] and N-nucleosides[8f] via Michael type addition of different hetero and carbon nucleophiles to 2-nitroglycals followed by reduction of the nitro group to the amino group. We, now, wish to report the synthesis of benzannulated C-glycosides via Diels–Alder reaction of 2-nitro glycals with Danishefky's diene, which, as reported, reacts with nitroalkenes.[10]

A convenient route to benzannulated dihydropyrans appeared to involve a Diels–Alder reaction of 2-nitroglycals with Danishefky's diene (**2**) and subsequent aromatisation of the cycloadduct. Indeed, cycloaddition of nitro galactal **1** with **2** in refluxing toluene worked well and produced almost quantitative yields of the cycloadduct which was hydrolysed using dilute H_2SO_4 to produce a mixture of **3** and **4** in the ratio of approximately 4:1 (Scheme 1).

The hydrolysed product was just filtered by column chromatography and used for the next step without separation. The hydrolysed product was refluxed in toluene in the presence of DBN[11] for 24 h in order to eliminate the nitro and methoxy group to get the desired product. To our surprise, compound **5** was produced in 68% yield instead of the expected product **6**, thus after β-elimination under opening of the tetrahydropyran ring a nitro group transfer to a nucleophile, presumably toluene, seems to take place. The structure of compound **5** was assigned on the basis of its NMR spectral data. For example, aliphatic and aromatic hydroxy groups appear as broad singlets at δ 2.86 ppm and 5.37 ppm, respectively.[12] Our basic aim was to get via HNO_2-elimination and enolization, the benzannulated dihydropyran **6** and hence several bases such as NaH, $NaOCH_3$ and *t*-BuOK were employed in THF to get the desired product. Among them NaH did yield the corresponding benzopyran **6** in 30% yield whereas $NaOCH_3$ and *t*-BuOK yielded a mixture of compounds **5** and **6** in the ratio of 2:1. However, elimination using 1 M $NaOCH_3$ in methanol produced the desired benzopyran **6** in 55% yield. Separation of **3** and **4** and then base treatment led to the same result because **3** was first transformed into **4**. The structure of compound **6** was confirmed on the basis of its spectral data. In its proton NMR, the phenolic hydroxy group appeared at δ 5.14 ppm as a broad singlet and it was also confirmed by methylation of the phenolic hydroxy group (Scheme 3). Further, extension of this reaction to



Scheme 1

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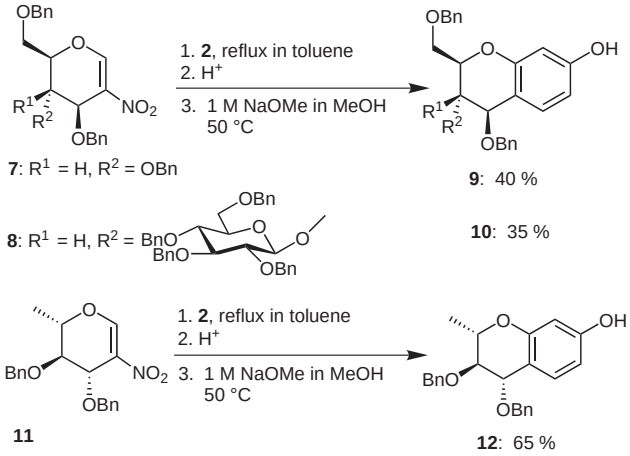
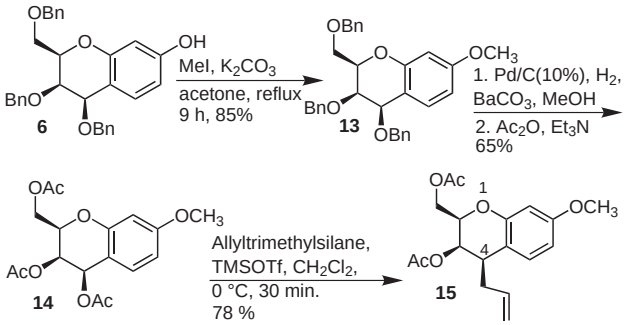
other glycals such as **7**, **8** and **11** produced the desired adducts **9**, **10**, **12** in 40%, 35% and 65% yields, respectively (Scheme 2). Although, the yields were moderate in the elimination step but yields of the cycloaddition reactions and hydrolysis steps were quantitative in all the cases studied.



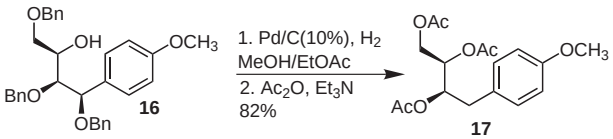
Scheme 2

Since, some naturally occurring compounds[1a,e] have C-C bonds at the benzylic position of the phenolic group, we intended to generate a C-C bond at the benzylic position of the phenolic group of compound **6**. For this purpose, compound **6** was *O*-methylated (→ **13**) and then debenzylated using Pd-C/H_2 and 1 equivalent of $BaCO_3$ in methanol, in order to avoid acid supported hydrogenolysis of the α-benzyloxy group;[13] following acetylation of the free hydroxy groups using Et_3N and Ac_2O in dichloromethane gave the corresponding triacetate **14** in 65% yield (two steps). Triacetate **14** was reacted with allyltrimethylsilane in dichloromethane in the presence of TMSOTf at 0 °C to produce the desired 4-*C*-allyl product **15** in 78% yield (Scheme 3).



Scheme 3

The stereochemistry of the newly formed C-C bond was established on the basis of NOE experiments. In its NOE experiment, strong NOE enhancement was observed between 3-H and 4-H and also between 4-H and 2-H thus confirming the structure **15**. Surprisingly, the stereochemistry of the C-C bond was β and it shows that there was no neighbouring group participation of the adjacent acetyl group during the reaction.



Scheme 4

Also compounds **5** and **17** (Schemes 1 and 4) are useful chiral intermediates for the synthesis of some alkaloids.[14,15] For instance, compound **5** can easily be transformed to the alkaloid condonopsinine[14] whereas compound **17** can be converted to an analog of diolmycin.[15] For this purpose, the aryl hydroxy group of compound **5** was methylated using MeI and K_2CO_3 in refluxing acetone for 9 h, thus producing in 90% yield compound **16** which was debenzylated; acetylation of the free hydroxy groups furnishing desired triacetate **17** (Scheme 4).

In conclusion, we have described the synthesis of benzannulated dihydropyrans via Diels–Alder reaction of 2-nitro glycals with Danishefky's diene, hydrolysis of the enol ether of the cycloadduct followed by elimination of the nitro and methoxy group. In addition to this, a useful chiral intermediate **5** has been obtained. Furthermore, a new C-C bond was generated at the benzylic position of the phenolic moiety of compound **14**. Transformation of the benzannulated pyranosides and the chiral intermediate **5** to natural product synthesis are in progress in our laboratory.

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(12) General experimental procedure for **6**, **9**, **10** and **12**: A solution of 2-nitro glycal (1 mmol) and Danishefky's diene (1.1 mmol) in dry toluene (2 mL) was refluxed under argon for 36 h. The reaction mixture was allowed to cool and the toluene was removed under reduced pressure. Then a mixture of THF–10% H_2SO_4 in H_2O (2:1) was added and stirred at room temperature for 30 min. The product was isolated by extractive workup followed by filtration by column chromatography. The hydrolyzed product was dissolved in 1 M $NaOCH_3$ in methanol (2 mL) and heated at 50 °C for 1.5 h. Methanol was evaporated followed by neutralization with saturated aq NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded the benzannulated pyrans.
For compound **5**: A mixture of hydrolyzed products **3** and **4** and DBN (3 equiv) in toluene (2 mL) was refluxed for 24 h. The reaction mixture was neutralized with aq NH_4Cl after removal of the toluene followed by extraction with ethyl acetate. The organic layer was washed with dilute HCl, water, brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification by column chromatography yielded the product **5** in 68% yield.
Some selected data:
5: $[\alpha]_D^{20}$ = –39.1 (c 1, $CHCl_3$); ^{1}H NMR (250 MHz): δ 2.86 (br s, 1 H), 3.45–3.55 (m, 2 H), 3.59 (dd, *J* = 1.99, 7.82 Hz, 1 H), 3.93 (d, *J* = 10.8 Hz, 1 H), 4.09 (d, *J* = 10.8 Hz, 1 H), 4.19 (br s, 1 H), 4.25 (d, *J* = 11.46 Hz, 1 H), 4.44 (d, *J* = 11.46 Hz, 1 H), 4.43–4.54 (m, 3 H), 5.37 (br s, 1 H), 6.81–6.85 (m, 2 H), 6.93–6.97 (m, 2 H), 7.18–7.35 (m, 15 H). ^{13}C NMR (62.9 MHz): δ 69.7, 70.4, 71.2, 73.3, 73.9, 80.3, 81.1, 115.4, 127.6, 127.7, 127.9, 128.2, 128.3, 129.1, 130.5, 137.5, 137.8, 156.1. MALDI: *m/z* 507 (M + Na^+). Calcd: C, 76.80; H, 6.66. Found: C, 76.55; H, 6.39.
6: $[\alpha]_D^{20}$ = +6.3 (c 1, $CHCl_3$); ^{1}H NMR (250 MHz): δ 3.71–3.83 (m, 2 H), 4.14 (dd, *J* = 2.2 Hz, 3.2 Hz, 1 H), 4.34 (td, *J* = 1.4 Hz, 5.9 Hz, 1 H), 4.44 (d, *J*= 11.9 Hz, 1 H), 4.53 (d, *J* = 11.9 Hz, 1 H), 4.57–4.86 (m, 5 H), 5.14 (br s, 1 H), 6.29 (d, *J* = 2.4 Hz, 1 H), 6.39 (dd, *J* = 2.5 Hz, 8.3 Hz, 1 H), 7.20–7.40 (m, 16 H). ^{13}C NMR (62.9 MHz): δ 69.1, 70.1, 71.8, 73.1, 73.5, 74.0, 75.8, 103.1, 108.6, 114.0, 127.7, 127.8, 128.1, 128.3, 128.4, 129.3, 137.7, 138.1, 153.9, 156.7. MALDI: *m/z* 505 (M + Na^+). Calcd: C, 77.16; H, 6.27. Found: C, 76.82; H, 6.57.
9: $[\alpha]_D^{20}$ = +26.7 (c 1, $CHCl_3$); ^{1}H NMR (250 MHz): δ 3.7–3.89 (m, 2 H), 4.04 (t, *J* = 6.1 Hz, 1 H), 4.29–4.35 (m, 1 H), 4.58–4.80 (m, 7 H), 5.4 (br s, 1 H), 6.34 (d, *J* = 2.43 Hz, 1 H), 6.4 (dd, *J* = 2.44 Hz, 8.34 Hz, 1 H), 7.1 (d, *J* = 8.38 Hz, 1 H), 7.23–7.37 (m, 15 H). ^{13}C NMR (62.9 MHz): δ 69.0, 71.2, 73.1, 73.5, 73.6, 76.1, 77.01, 103.3, 109, 113.9, 127.7, 127.9, 128.0, 128.5, 130.2, 137.8, 138.2, 154.6, 156.7. MALDI: *m/z* 505(M + Na^+).
10: $[\alpha]_D^{20}$ = +30.1 (c 1, $CHCl_3$); ^{1}H NMR (250 MHz): δ 3.53–3.92 (m, 6 H), 4.35–4.92(m, 17 H), 5.18 (br s, 1 H), 5.34 (d, *J* = 3.6 Hz, 1 H), 6.37 (d, *J* = 2.18 Hz, 1 H), 6.42 (dd, *J* = 2.32 Hz, 8.24 Hz, 1 H), 7.12 (dd, *J* = 3.26 Hz, 7.06 Hz, 1 H), 7.24–7.30 (m, 30 H). ^{13}C NMR (62.9 MHz): δ 68.4, 69.0, 69.4, 70.9, 72.9, 73.3, 73.4, 74.5, 75.0, 75.5, 76.9, 80.0, 81.7, 96.1, 103.7, 109.1, 112.7, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 131.1, 137.9, 138.0, 138.1, 138.3, 138.8, 154.9, 156.9. MALDI: *m/z* 937 (M + Na^+).
12: $[\alpha]_D^{20}$ = –27.1 (c 1, $CHCl_3$); ^{1}H NMR (250 MHz): δ 1.46 (d, *J* = 6.48 Hz, 3 H), 3.69 (dd, *J* = 6.83 Hz, 8.08 Hz, 1 H), 4.11–4.19 (m, 1 H), 4.65–4.88 (m, 6 H), 6.27 (d, *J* = 2.48 Hz, 1 H), 6.40 (dd, *J* = 2.51 Hz, 8.39 Hz, 1 H), 7.15 (dd, *J* = 0.64 Hz, 8.41 Hz, 1 H), 7.23–7.36 (m, 10 H). ^{13}C NMR (62.9 MHz): δ 17.9, 71.5, 73.7, 74.4, 77.3, 79.1, 102.9, 109.0, 114.7, 127.7, 127.87, 127.89, 127.9, 128.5, 129.8, 137.8, 138.2, 155.0, 156.5. Cald: C, 76.57; H, 6.43. Found: C, 76.25; H, 6.32.
15: $[\alpha]_D^{20}$ = +53.6 (c 0.5, $CHCl_3$); ^{1}H NMR (600 MHz): δ 2.02, 2.12 (2 s, 6 H), 2.25–2.33 (m, 1 H), 2.4–2.5 (m, 1 H), 2.9 (t, *J* = 6.7 Hz, 1 H), 3.77 (s, 3 H), 4.2–4.35 (m, 3 H), 5.08–5.17 (m, 3 H), 5.8–5.9 (m, 1 H), 6.46 (d, *J* = 1 Hz, 1 H), 6.53 (dd, *J* = 2.5 Hz, 8.4 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H). ^{13}C NMR (150.8 MHz): δ 20.8, 21.0, 38.4, 41.5, 55.3, 63.3, 68.0, 69.9, 101.2, 108.5, 118.0, 130.5, 134.8, 153.5, 159.4, 170.4, 170.7. Calcd: C, 64.66; H, 6.63. Found: C, 64.95; H, 7.0.
17: $[\alpha]_D^{20}$ = +29.6 (c 1, $CHCl_3$); ^{1}H NMR (250 MHz): δ 1.98, 2.0, 2.1 (3 s, 9H), 2.77 (d, *J* = 6.9 Hz, 2 H), 3.75 (s, 3 H), 4.07 (dd, *J* = 6.8 Hz, 11.8 Hz, 1 H), 4.23 (dd, *J* = 4.6 Hz, 11.8 Hz, 1 H), 5.13–5.26 (m, 2 H), 6.92–7.2 (m, 4 H). ^{13}C NMR (62.9 MHz): δ 20.6, 20.7, 21.0, 36.2, 62.2, 70.6, 72.0, 121.6, 130.2, 133.6, 149.6, 169.3, 170.0, 170.4.
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