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Domino Knoevenagel hetero-Diels–Alder reactions: a stereoselective synthesis of sugar fused furo[3,2-*b*]pyrano[4,3-*d*]pyran derivatives

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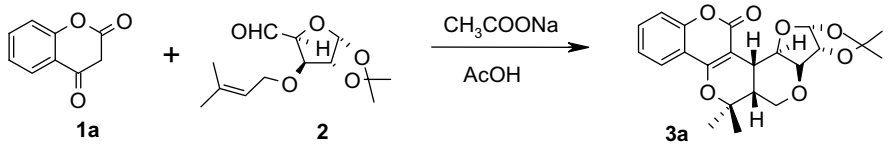
Abstract—The *O*-prenyl derivative of a sugar aldehyde derived from D-glucose undergoes smooth intramolecular domino Knoevenagel hetero-Diels–Alder reactions with 1,3-diones to afford a novel class of carbohydrate analogues, *cis*-fused furopyranopyrans in good yields with a high degree of chemoselectivity. The stereochemistry of the products was assigned by NMR.

Coumarin derivatives are widely distributed in Nature and are reported to have a wide range of biological activities such as anti-coagulant, insecticidal, anthelmintic, hypnotic and anti-fungal activity. Others are phytoalexins and are inhibitors of HIV protease.[1,2] Many naturally occurring compounds such as isoethuliacoumarin A, isoethuliacoumarin B, isoethuliacoumarin C, ethuliacoumarin A, ethuliacoumarin B and pterophyllin possess the pyrano[3,2-*c*]coumarin skeleton and have been isolated from various sources.[3,4] The domino Knoevenagel intramolecular hetero-Diels–Alder reaction is one of the most powerful synthetic routes for the synthesis of various heterocycles and natural products.[5,6] However, there are no examples of domino Knoevenagel hetero-Diels–Alder reactions using an *O*-prenylated sugar aldehyde derived from D-glucose.

In this article, we describe a novel protocol for the synthesis of sugar fused furo[3,2-*b*]pyrano[4,3-*d*]pyrans via domino Knoevenagel hetero-Diels–Alder reactions between an *O*-prenylated sugar aldehyde and 1,3-diones. Thus, treatment of 4-hydroxycoumarin with an *O*-prenyl derivative of a sugar aldehyde in the presence of sodium acetate in acetic acid at 80 °C resulted in the formation of *cis*-fused pyrano[3,2-*c*] coumarin **3a** in 82% yield (Scheme 1).

The reaction proceeds via a tandem Knoevenagel and hetero-Diels–Alder pathway. This reaction is a highly stereoselective affording exclusively *cis*-fused pyrano[3,2-*c*]coumarin derivatives. The *cis*-stereochemistry of the products was assigned by detailed NMR studies. (^{1}H NMR studies of product **3a** were carried out in $CDCl_3$ solution at 500 MHz). The couplings of $^3J_{H6a-H7pro\text{-}R)}$ =



Scheme 1.

Keywords: Domino Knoevenagel hetero-Diels–Alder reaction; 1,3-Diones; Sugar aldehyde; *cis*-Annelated polycyclic heterocycles.
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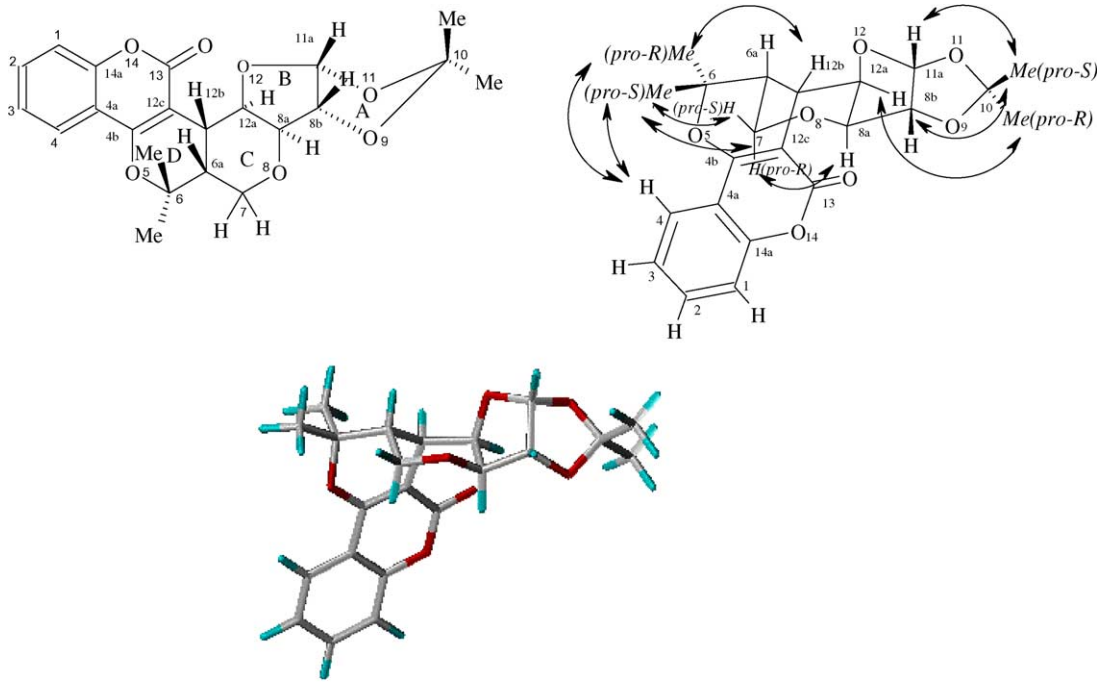


The structure of **3a**, characteristic NOE's and the energy minimised structure.

11.7 Hz, $^{3}J_{H6a–H7(pro\text{-}S)} = 4.3$ Hz, $^{3}J_{H8a–H12a} = 2.3$ Hz, $^{3}J_{H6a–H12b} = 5.5$ Hz, and $^{3}J_{H12a–H12b} = 2.3$ Hz, and a NOE between $H_{7(pro\text{-}R)}$-H_{8a} amply support a $^{6a}C_{8a}$ conformation for the pyran ring (C). The observation of a long range ω-coupling $^{3}J_{H7(pro\text{-}S)–H12b} = 1.3$ Hz further supports this chair conformation. The small $^{3}J_{H6a–H12b} = 5.5$ Hz value shows the *cis* fusion of pyran ring (C) with pyran ring (D) at C_{6a}–C_{12b}. These conclusions were further supported by the medium intensity NOE between $H_{7(pro\text{-}S)}$–$Me_{6(pro\text{-}S)}$, $H_{7(pro\text{-}R)}$–$Me_{6(pro\text{-}S)}$, and H_{12b}–$Me_{6(pro\text{-}R)}$ and the weak NOE intensity between H_4–$Me_{6(pro\text{-}R)}$ and H_4–$Me_{6(pro\text{-}S)}$, which also suggest that the six-membered pyran ring (D) adopts a twisted form. The structure was further confirmed by molecular mechanics calculations.[7]

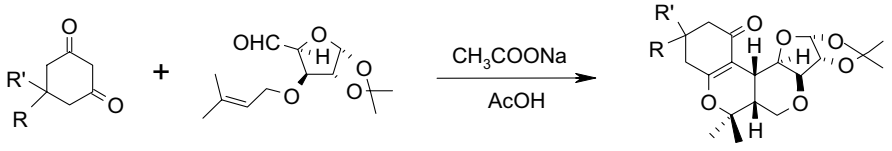
Analogous to 4-hydroxycoumarin, 4-hydroxy-1,2-dihydro-2-quinoline gave sugar fused pyrano[3,2-*c*]quinoline **3b** in 73% yield. Furthermore, cyclic 1,3-diketones such as 1,3-cyclohexadione and dimedone (Scheme 2) and 1,3-dimethylbarbituric acid also afforded cycloadducts in fairly good yields (Scheme 2, Table 1, entries c, d, and e).

For example, in cycloadduct **3c**, the pyran ring (C) exists in a chair conformation. This $^{6a}C_{8a}$ chair conformation is supported by NOE's between the diaxially disposed protons $H_{7(Pro\text{-}R)}$ and H_{8a} and coupling constants $^{3}J_{H6a–H7pro\text{-}R)} = 11.7$ Hz, $^{3}J_{H6a–H7(Pro\text{-}S)} = 4.5$ Hz which suggest that $H_{7(Pro\text{-}R)}$ and $H_{7(Pro\text{-}S)}$ occupy axial and equatorial positions, and long range 'ω' coupling between $H_{7(Pro\text{-}S)}$–$H_{12b} = 1.1$ Hz.

Similarly, acetyl acetone and methyl acetoacetate also reacted smoothly with the sugar aldehyde to give the corresponding perhydrofuro[3,2-*b*]pyrano[4,3-*d*]pyrans (Scheme 3, Table 1, entries f and g).

We assume that the cycloaddition proceeds in a concerted manner via an *endo-E-syn* transition state. Mechanistically, a 1-oxa-1,3-butadiene may be formed from 4-hydroxycoumarin and *O*-prenylated sugar aldehyde, which can undergo an intramolecular hetero-Diels–Alder reaction leading to the *cis*-fused pyrano[3,2-*c*]coumarin derivative (Scheme 4).

In the case of unsymmetrical 1,3-dicarbonyl compounds, chemoselective synthesis of pyrano[3,2-*c*]coumarin derivatives was achieved using this procedure (Table 1, entries a, b, and g). Due to the mild basic conditions and low reactivity of the ester or amide car-

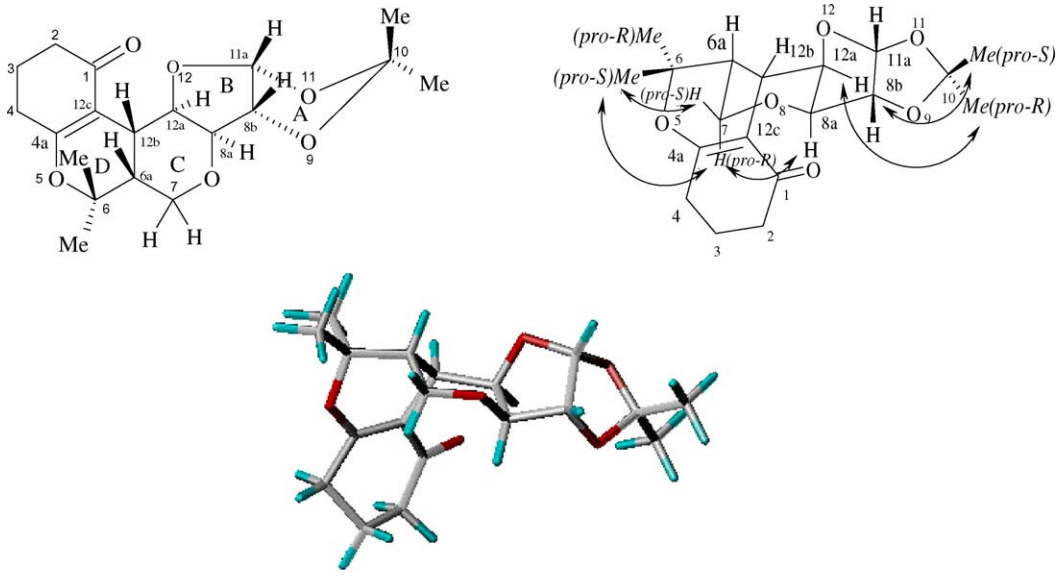


1c: R=R¹=H
1d: R=R¹=Me

2

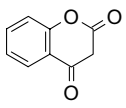
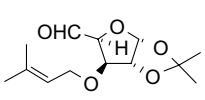
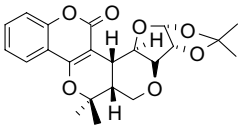
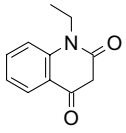
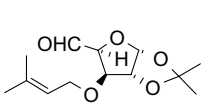
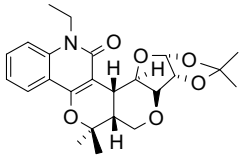
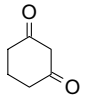
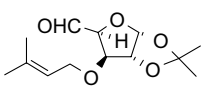
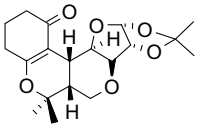
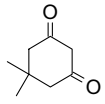
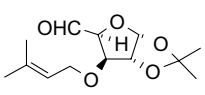
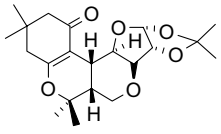
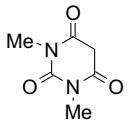
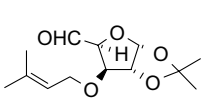
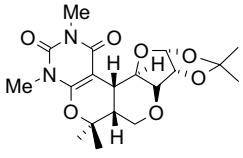
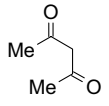
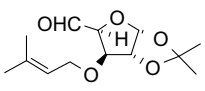
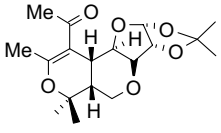
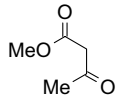
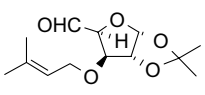
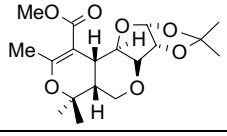
3c: R=R¹=H
3d: R=R¹=Me

Scheme 2.

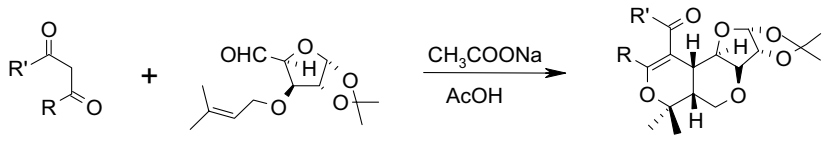


The structure of **3c**, characteristic NOE's and the energy minimised structure.

Table 1. Domino-Knoevenagel hetero-Diels–Alder reaction

Entry	1,3-Dione	Aldehyde	Product[a]	Reaction time (h)	Yield (%)[b]
a			 **3a**	6.5	82
b			 **3b**	7.5	73
c			 **3c**	5.0	80
d			 **3d**	6.0	82
e			 **3e**	8.5	72
f			 **3f**	5.0	79
g			 **3g**	6.0	70

[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b] Isolated and unoptimized yields.

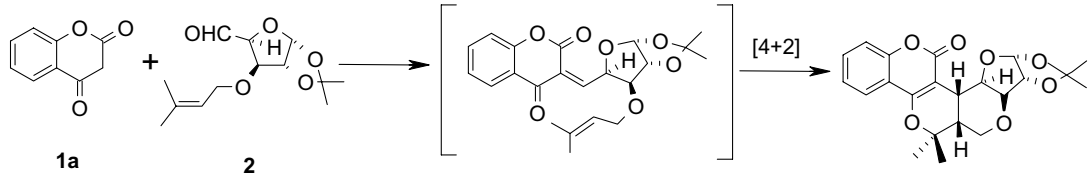


1f: R=R¹=Me
1g: R=Me, R¹=OMe

2

3f: R=R¹=Me
3g: R=Me, R¹=OMe

Scheme 3.



1a **2** **3a**

Scheme 4.

bonyl group compared to a simple carbonyl functionality, no other regioisomer was observed. Simple cyclic ketones such as cyclohexanone, cyclopentanone, and tetralone failed to give the desired products under the reaction conditions. Similarly, an *O*-allylated sugar aldehyde also did not undergo the hetero-Diels–Alder reaction with 1,3-diones. This reaction was successful only with the *O*-prenylated sugar aldehyde and 1,3-dicarbonyl compounds.

In conclusion, we disclose a simple and novel protocol for the synthesis of chiral polyoxygenated heterocycles via a domino Knoevenagel-hetero-Diels–Alder reaction between an *O*-prenylated sugar aldehyde derived from D-glucose and 1,3-diones. The reaction is highly stereoselective leading to *cis*-annelated heterocycles in a single-step operation.[8] It is an entirely new synthetic route to construct optically active *cis*-annelated tricyclic-, tetracyclic-, and pentacyclic heterocycles.

Acknowledgements

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7. Molecular mechanics calculations were carried out using the Sybyl 6.8 program on a Silicon Graphics O2 workstation.
8. General procedure: A mixture of *O*-prenylated sugar aldehyde **2** (1.5 mmol), 1,3-diketone **1** (1.5 mmol), and sodium acetate (4.5 mmol) in acetic acid (10 mL) was stirred at 80 °C for the appropriate time. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate followed by brine solution and dried over anhydrous Na_2SO_4. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford the pure *cis*-annelated polycyclic heterocycle. Data for selected compounds, **3a**: liquid, $[\alpha]_D^{25}$ −24.6 ($c = 1.0$, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (dd, $J_{H3-H4} = 8.0$, $J_{H2-H4} = 1.6$ Hz, 1H, H4), 7.51 (ddd, $J_{H2-H3} = 7.4$, $J_{H1-H2} = 8.3$, $J_{H2-H4} = 1.6$ Hz, 1H, H2), 7.29 (dd, $J_{H1-H2} = 8.3$, $J_{H1-H3} = 1.1$ Hz, 1H, H1), 7.23 (ddd, $J_{H3-H4} = 8.0$, $J_{H2-H3} = 7.4$, $J_{H1-H3} = 1.1$ Hz, 1H, H3), 5.84 (d, $J_{H8b-H11a} = 3.8$ Hz, 1H, H11a), 5.45 (t, $J_{H8a-H12a} = J_{H12a-H12b} = 2.3$ Hz, 1H, H12a), 4.40 (d, $J_{H8b-H11a} = 3.8$ Hz, 1H, H8b), 3.95 (ddd, $J_{H7(pro\text{-}S)-H7(pro\text{-}R)} = 11.7$, $J_{H6a-H7(pro\text{-}S)} = 4.3$, $J_{H7(pro\text{-}S)-H12b} = 1.3$ Hz, 1H, $H7_{(pro\text{-}S)}$), 3.68 (d, $J_{H8a-H12a} = 2.3$ Hz, 1H, H8a), 3.45 (ddd, $J_{H6a-H12b} = 5.5$, $J_{H12a-H12b} = 2.3$, $J_{H7(pro\text{-}S)-H12b} = 1.3$ Hz, 1H, H12b), 3.17 (t, $J_{H7(pro\text{-}S)-H7(pro\text{-}R)} = J_{H6a-H7pro\text{-}R)} = 11.7$ Hz, 1H, $H7_{(pro\text{-}R)}$), 2.33 (ddd, $J_{H6a-H7(pro\text{-}R)} = 11.7$, $J_{H6a-H7(pro\text{-}S)} = 4.3$, $J_{H6a-H12b} = 5.5$ Hz, 1H, H6a), 1.56 (s, 3H, $Me10_{(pro\text{-}R)}$), 1.54 (s, 3H, $Me6_{(pro\text{-}S)}$), 1.37 (s, 3H, $Me6_{(pro\text{-}R)}$), 1.31 (s, 3H, $Me10_{(pro\text{-}S)}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 160.4, 152.7, 132.0, 123.7, 122.8, 116.4, 115.5, 112.1, 104.3, 97.6, 84.0, 79.2, 76.1, 72.5, 62.9, 35.5, 29.8, 26.8, 26.5, 25.5, 24.8.

IR (KBr): ν_{max}: 2927, 1709, 1616, 1386, 1215, 1096, 1016, 763 cm^{-1}. FAB Mass: m/z: 401 (M+1), 300, 154, 137, 121, 109, 95, 83, 69, 57. **3c**: Liquid, $[\alpha]_D^{25}$ −65.5 ($c = 1.0$, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 5.86 (d, $J_{H8b–H11a} = 3.6$ Hz, 1H, H11a), 4.43 (d, $J_{H8b–H11a} = 3.6$ Hz, 1H, H8b), 5.12 (t, $J_{H8a–H12a} = J_{H12a–H12b} = 2.0$ Hz, 1H, H12a), 3.66 (d, $J_{H8a–H12a} = 2.0$ Hz, 1H, H8a), 3.20 (m, 1H, H12b), 3.89 (ddd, $J_{H6a–H7(Pro\text{-}R)} = 11.7$, $J_{H6a–H7(Pro\text{-}S)} = 4.5$, $J_{H6a–H12b} = 5.7$ Hz, 1H, H6a), 3.15 (t, $J_{H7(Pro\text{-}R)–H7(Pro\text{-}S)} = J_{H6a–H7(Pro\text{-}R)} = 11.7$ Hz, 1H, $H7_{(Pro\text{-}R)}$), 2.15 (ddd, $J_{H7(Pro\text{-}R)–H7(Pro\text{-}S)} = 11.7$, $J_{H7(pro\text{-}S)–H6a} = 4.5$, $J_{H7(pro\text{-}S)–H12b} = 1.1$ Hz, 1H, $H7_{(Pro\text{-}S)}$), 1.55 (s, 3H, $Me10_{(pro\text{-}R)}$), 1.33 (s, 3H, $Me6_{(pro\text{-}S)}$), 1.31 (s, 3H, $Me10_{(pro\text{-}S)}$), 1.19 (s, 3H, $Me6_{(pro\text{-}R)}$), 2.46 (m, 2H, H2), 2.27 (m, 2H, H4), and 1.93 (m, 2H, H3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 171.8, 111.8, 108.3, 104.3, 83.9, 77.4, 75.9, 73.7, 62.9, 37.4, 35.5, 29.5, 28.7, 26.8, 26.5, 25.5, 24.4, 19.8. IR (KBr): ν_{max}: 2932, 1735, 1647, 1601, 1380, 1295, 1218, 1145, 1094, 1015, 771 cm^{-1}. FAB Mass: m/z: 351 (M+1), 293, 250, 233, 207, 191, 179, 165, 154, 145, 137, 123, 109, 95, 81, 69, 55.