Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2643–2646

TETRAHEDRON: *ASYMMETRY*

'Off template site' [3+3] annulation reaction on sugar derived enal: stereoselective synthesis of C–C-linked pseudo-saccharide precursors†

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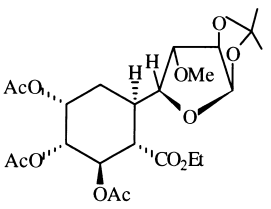
Received 19 January 2000; accepted 18 May 2000

Abstract

A [3+3] annulation protocol at an 'off template' site of a sugar-derived enal synthon is used effectively for the stereoselective synthesis of C–C-linked pseudo-saccharide precursors. The chirality is induced from the sugar synthon during the installation of carbocycle at the C-5 of sugar template.

The development of novel and efficient methods for the stereoselective construction of carbocycles[1] is an area of significant current activity. A variety of useful approaches for this purpose are found in the literature, such as intramolecular Diels–Alder reaction, double Michael cyclisation, 1,3–dipolar cycloadditions and radical induced reactions.[2] As part of our ongoing efforts on the transformation of sugars into C-glycosides,[3,4] C–C linked disaccharides,[5] C-linked spiro saccharides[6] etc. herein, we describe the synthesis of C–C linked pseudo-saccharide precursors[7] **1**, **2** and **3**, adopting a Michael–Wittig reaction on a sugar-derived enal.



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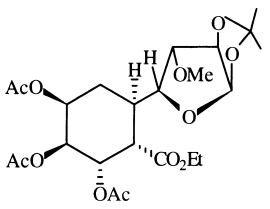

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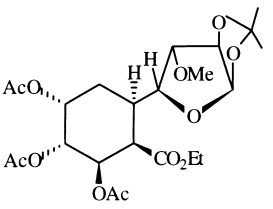

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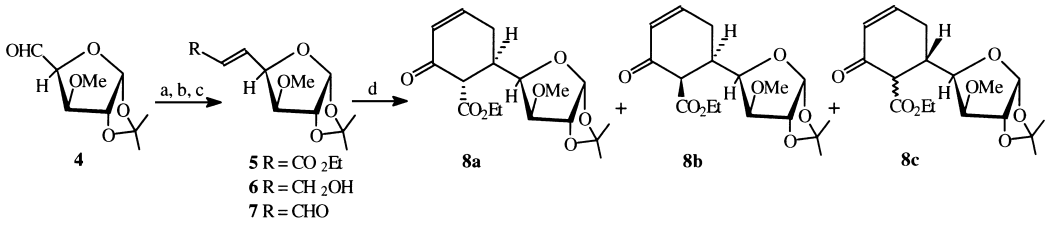
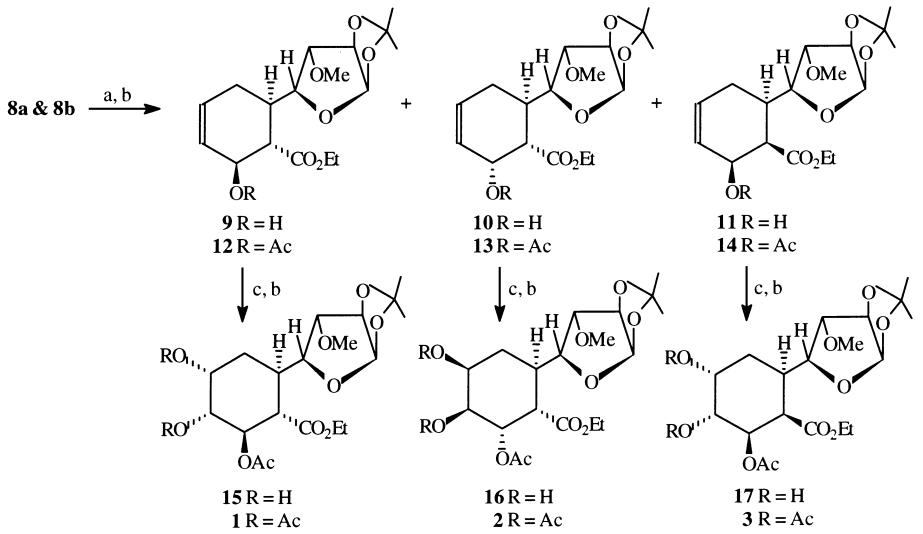
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00222-6

Accordingly, known aldehyde **4**,[8] prepared from diacetone glucose, on Wittig olefination (Scheme 1), was converted into α,β-unsaturated ester **5** (82%), which, on DIBAL-H reduction, followed by oxidation of alcohol **6** with PDC, resulted in enal **7** (95%). ^{1}H NMR spectrum of **7** has the H-5 at δ 6.74 (dd, $J_{4,5}=5.8$, $J_{5,6}=14.7$ Hz), and H-6 at δ 6.32 (dd, $J_{5,6}=14.7$, $J_{6,7}=8.8$ Hz) indicating *trans* disposition of the olefinic double bond. The crucial [3+3] annulation reaction on the olefin **7** with ethyl 3-oxo-4-(triphenylphosphorylidene)butanoate **A**,[9] in the presence of NaH and a drop of water[10] in THF at 50°C for 10 min, resulted in the formation of **8a**, **8b** and **8c** as a mixture of diastereoisomers (6:1.5:2.5, HPLC-ODS preparative column, MeOH:H_2O, 7:3, UV 225 nm) in a combined yield of 75%. The stereochemical outcome of annulation products **8a** and **8b** was unambiguously determined by ^{1}H NMR spectrum. The formation of **8a** as a major product is in accordance with the literature,[11] evidence for the Michael addition of the sodium enolate of **A** on the γ-alkoxy enal system **7.**



Scheme 1. (a) $Ph_3P{=}CHCO_2Et$, C_6H_6, reflux, 82%; (b) DIBAL-H, CH_2Cl_2, –20°C, 86%; (c) PDC, CH_2Cl_2, reflux, 95%; (d) $Ph_3P{=}CHCOCH_2CO_2Et$ (**A**), NaH, two drops water, THF, 50°C, 75%

The mixture of major compounds **8a** and **8b**, separated from **8c** by column chromatography (Si-gel, 200 mesh, EtOAc:Pet. ether, 1:4) was subjected to $NaBH_4$ (Scheme 2) reduction under Luche's[12] reaction conditions to afford alcohols **9** (major), **10** (minor) and **11** (one isomer) in the ratio of 4:1:2 respectively in a combined yield of 88% from **8a+8b**. Acetylation of alcohols **9**, **10**



Scheme 2. (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 0°C, 88%; (b) Ac_2O–Py; (c) OsO_4–NMO, CH_3COCH_3:H_2O (3:1)

and **11** with Ac_2O-pyridine gave the acetates **12**, **13** and **14**, respectively, whose structures were assigned from the spectral data. *anti*-Facial stereoselective *cis*-dihydroxylation[13] of the olefins **12**, **13** and **14** was effected using OsO_4–NMO in acetone:water (3:1) system to afford the diols **15**, **16** and **17**, respectively, which, on subsequent acetylation, gave the corresponding acetates **1**, **2** and **3**, respectively. All the C–C-linked pseudo-saccharide precursors are thoroughly characterized from the ^1H NMR (vicinal couplings (J) as well as the data from the NOESY experiments) and other spectral data.[14]

Compound **1** has shown characteristic NOE cross-peaks H6–H8, H6–H10ax, H8–H10ax and H5–H7 and $J_{5,6}$, $J_{6,7}$, $J_{7,8}$ and $J_{5,10ax}$ values of about 10.0 Hz consistent with a chair conformation (Fig. 1; $^8C_5$), most of the substituents in equatorial position. The structure of **2** is supported by strong NOE cross-peaks between H5–H9 and H6–H10ax as well as a large value of about 10.0 Hz for $J_{5,6}$, $J_{5,10ax}$ and $J_{9,10eq}$, while large NOE cross-peaks between H5–H7 as well as $J_{5,10ax} = 13.0$ Hz and $J_{7,8} = 10.8$ Hz confirm the structure of **3**. Thus, in all the three pseudo-saccharide precursors **1**, **2** and **3** the carbocycle ring has $^8C_5$ chair conformation. Small values of $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ point to a twist conformation for the sugar ring. The presence of NOE cross-peaks between H1-Me(A) and H2-Me(A) implies an envelope conformation for the five-membered ring containing the isopropylidine group. The relative orientation of the carbocycle and sugar ring is confirmed by the strong NOE cross-peaks between H3–H10eq, H4–H10ax and weak NOE cross-peaks between H3–H10ax, H4–H10eq and H10eq–OMe. The NMR data compare well with the energy minimized structures obtained from PCMODEL.[15]

We have demonstrated the installation of the carbocycle ring system at C-5 of the sugar synthon, by adopting an 'off template site' stereoselective [3+3] annulation approach, where the chirality of the carbocycle is induced from the sugar template. Due to the ready availability of reagents and simple reaction conditions, the present protocol should find application for the synthesis of several pseudo-saccharide precursors.

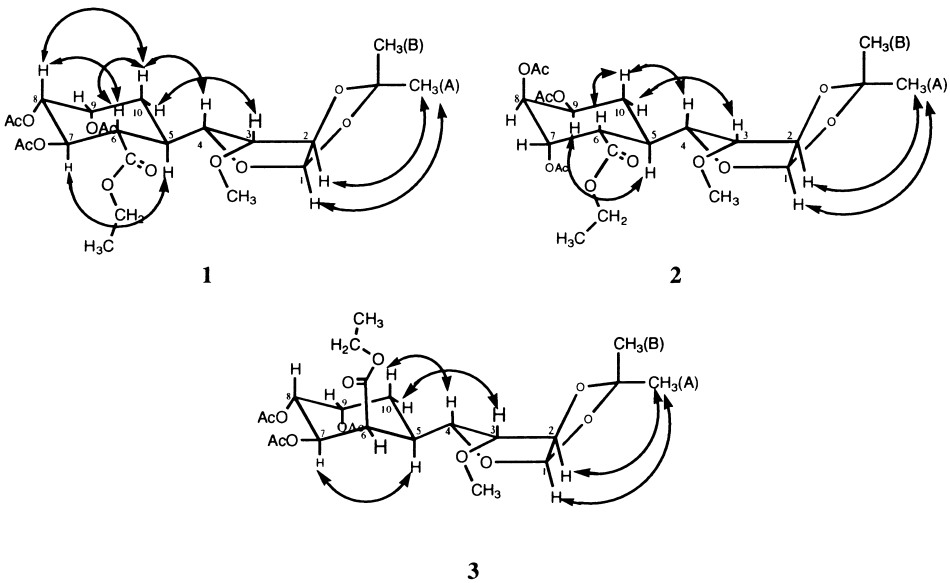


Figure 1.

Acknowledgements

One of the authors, A. Subhash Chander, is thankful to UGC, New Delhi, for financial support. This work was supported by a Grant-in-Aid project (CSIR Young Scientist Award to Dr. G. V. M. Sharma).

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14. Selected spectral data: compound **1**: m.p. 95–97°C; $[\alpha]_D = -53.4$ (*c* 1.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, 3H, $J = 7.1$ Hz, $-OCH_2CH_3$), 1.28 (s, 3H, Me(A)), 1.45 (s, 3 H), 1.52 (ddd, 1H, $J_{5,10a} = 12.4$, $J_{10a,10e} = 13.6$, $J_{9,10a} = 2.3$ Hz, H-10a), 1.98 (s, 3H, –OAc), 1.99 (s, 3H, –OAc), 2.02 (dt, 1H, H-10e), 2.13 (s, 3H, –OAc), 2.56 (dd, 1H, $J_{5,6} = 11.3$, $J_{6,7} = 10.5$ Hz, H-6), 2.65 (m, 1H, $J_{5,10e} = 3.5$ Hz, H-5), 3.35 (s, 3H, OMe), 3.60 (d, 1H, $J_{3,4} = 2.9$ Hz, H-3), 3.93 (dd, 1H, $J_{3,4} = 2.9$, $J_{4,5} = 8.8$ Hz, H-4), 4.13 (q, 2H, $J = 7.1$ Hz, $-OCH_2CH_3$), 4.51 (d, 1H, $J_{1,2} = 3.9$ Hz, H-2), 4.88 (dd, 1H, $J_{7,8}$-9.9, $J_{8,9} = 3.1$ Hz, H-8), 5.33 (m, 1H, $J_{9,10a} = 2.3$, $J_{9,10e} = 4.2$ Hz, H-9), 5.60 (t, 1H, H-7), 5.80 (d, 1H, $J_{1,2} = 3.9$ Hz, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.31, 20.64, 20.98, 26.17, 26.83, 28.02, 29.53, 33.16, 47.08, 57.20, 60.38, 68.62, 70.37, 72.32, 80.85, 81.06, 85.32, 104.56, 111.38, 168.11, 170.18, 170.24, 170.88; MS (FAB) *m*/*z* (%): 503 (36), 487 (11), 457 (100), 443 (27); HR-MS (FAB): calcd for (M–OEt) $C_{21}H_{29}O_{11}$: 457.170987; found: 457.169200; compound **2**: $[\alpha]_D = +3.2$ (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, 3H, $J = 7.1$ Hz, $-OCH_2CH_3$), 1.31 (s, 3H, CH_3(A)), 1.49 (s, 3H, CH_3(B)), 1.64 (dt, 1H, $J_{5,10a} = 9.8$, $J_{9,10a} = 9.9$, $J_{10a,10e} = 13.2$ Hz, H-10a), 1.99 (dt, 1H, $J_{10a,10e} = 13.2$, $J_{9,10e} = 4.2$, $J_{5,10e} = 4.8$ Hz, H-10e), 2.03, 2.08, 2.10 (3s, 9H, –OAc), 2.67 (dq, 1H, $J_{5,10e} = 4.8$ Hz, H-5), 2.92 (dd, 1H, $J_{5,6} = 9.1$, $J_{6,7} = 3.5$ Hz, H-6), 3.40 (s, 3H, –OMe), 3.57 (d, 1H, $J_{3,4} = 3.0$ Hz, H-3), 4.10 (qd, 2H, $J = 7.1$ Hz, $-OCH_2CH_3$), 4.11 (dd, 1H, $J_{3,4} = 3.0$, $J_{4,5} = 9.1$ Hz, H-4), 4.55 (d, 1H, $J_{1,2} = 3.8$ Hz, H-2), 5.30 (ddd, 1H, $J_{8,9} = 3.2$, $J_{9,10a} = 9.9$, $J_{9,10e} = 4.2$ Hz, H-9), 5.34 (dd, 1H, $J_{7,8} = 6.0$, $J_{8,9} = 3.2$ Hz, H-8), 5.42 (dd, 1H, $J_{6,7} = 3.5$, $J_{7,8} = 6.0$ Hz, H-7), 5.83 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.85, 20.77, 20.83, 26.21, 26.27, 26.74, 28.62, 32.85, 44.71, 57.32, 60.81, 67.70, 68.21, 68.59, 80.66, 81.30, 83.73, 104.50, 111.54, 160.33 (2C), 160.80, 171.18; MS (FAB) *m*/*z* (%): 503 (100), 457 (52), 443 (22); HR-MS (FAB): calculated for (M+1) $C_{23}H_{35}O_{12}$: 503.212852; found: 503.210874; compound **3**: m.p. 95–97°C; $[\alpha]_D = -54.5$ (*c* 2.3, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, 3H, $J = 7.1$ Hz, $-OCH_2CH_3$), 1.31 (s, 3H, CH_3(A)), 1.41 (s, 3H, CH_3(B)), 1.64 (dt, 1H, $J_{9,10e} = 5.8$, $J_{5,10e} = 3.3$, $J_{10a,10e} = 14.2$ Hz, H-10e), 2.00, 2.01, 2.09 (3s, 9H, –OAc), 2.23 (m, 1H, $J_{9,10e} = 2.5$, $J_{5,10a} = 13.0$ Hz, H-10a), 2.58 (m, 1H, $J_{4,5} = 10.5$, $J_{5,6} = 4.2$, $J_{5,10e} = 3.3$ Hz, H-5), 3.36 (s, 3H, –OMe), 3.53 (t, 1H, H-6) 3.54 (d, 1H, $J_{3,4} = 3.0$ Hz, H-3), 3.83 (dd, 1H, $J_{3,4} = 2.9$, $J_{4,5} = 10.5$ Hz, H-4), 4.11–4.25 (m, 2H, $-OCH_2CH_3$), 4.54 (d, 1H, $J_{1,2} = 3.8$ Hz, H-2), 5.36 (dd, 1H, $J_{7,8} = 10.8$ Hz, H-7), 5.44 (m, 1H, $J_{8,9} = 3.3$ Hz, H-9), 5.6 (dd, 1H, $J_{8,9} = 3.3$, $J_{7,8} = 10.8$ Hz, H-8), 5.85 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.31, 20.69, 20.76, 26.25, 26.40, 26.61, 29.64, 31.30, 45.15, 57.66, 60.60, 69.16, 69.57, 69.68, 79.93, 80.97, 83.23, 104.60, 111.48, 169.75, 169.97, 170.19, 171.30; MS (FAB) *m*/*z* (%): 503 (36), 457 (52), 279 (100); HR-MS (FAB): calculated for (M+1) $C_{23}H_{35}O_{12}$: 503.212852; found: 503.214328.
15. PCMODEL, Gilbert, K. E.; Gajewski, J. J. Senna Software, Box 3076, Bloomington IN47402, USA.