Pergamon

Tetrahedron Letters 41 (2000) 10135–10139

TETRAHEDRON LETTERS

Synthesis of chiral oxepinopyran and oxepinooxepane systems from 1,2-isopropylidene furanoside ring-fused cyclic ether derivatives through 4-*O*-allyl nitrone and nitrile oxide cycloadditions

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Received 2 August 2000; revised 2 October 2000; accepted 11 October 2000

Abstract

A novel strategy was developed by which chiral oxepinopyran and oxepinooxepane derivatives were synthesised from 1,2-isopropylidene furanoside fused pyran and oxepane derivatives by the cycloaddition of 4-*O*-allyl nitrone or nitrile oxide species generated from the furanoside ring

The application of intramolecular cycloaddition of nitrones and nitrile oxides prepared from *O*-alkenyl and *O*-alkynyl carbohydrate derivatives has led to an easy access to chiral cyclic ether skeletons of varying ring sizes.[1,2] A number of such cyclic ether derivatives are found to be fused to 1,2-isopropylidene furanoside moieties, which constitute the carbohydrate scaffold bearing the *O*-alkenyl and -alkynyl residues as well as the 1,3-dipolar moieties. One of the notable advantages of using this particular carbohydrate scaffold is its convertibility to other useful systems, such as a tetrahydrofuran ring through 2-*O*-allyl nitrone cycloaddition.[2,3] Herein we report a novel strategy for the construction of a dioxaheterobicyclic system **4** or **5** involving a facile transformation of the isopropylidene furanoside ring of a cyclic ether derivative **1** to another cyclic ether skeleton (Scheme 1).

The strategy essentially involves the transformation of the furanoside ring to a 4-*O*-alkenyl nitrone **2** or nitrile oxide **3**, cycloaddition of which leads to the formation of **4** or **5** incorporating the dioxaheterobicyclic skeleton. The importance of the strategy stems from the frequent occurrence of similarly fused cyclic ether skeletons in a number of marine toxins, e.g. brevetoxins and ciguatoxin. Recent synthetic exercises in this regard involved the construction of such

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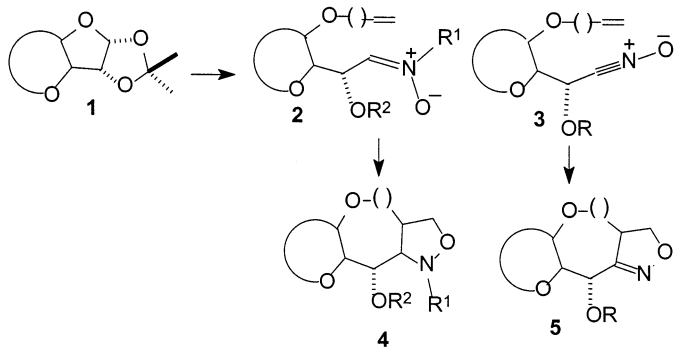
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01802-5



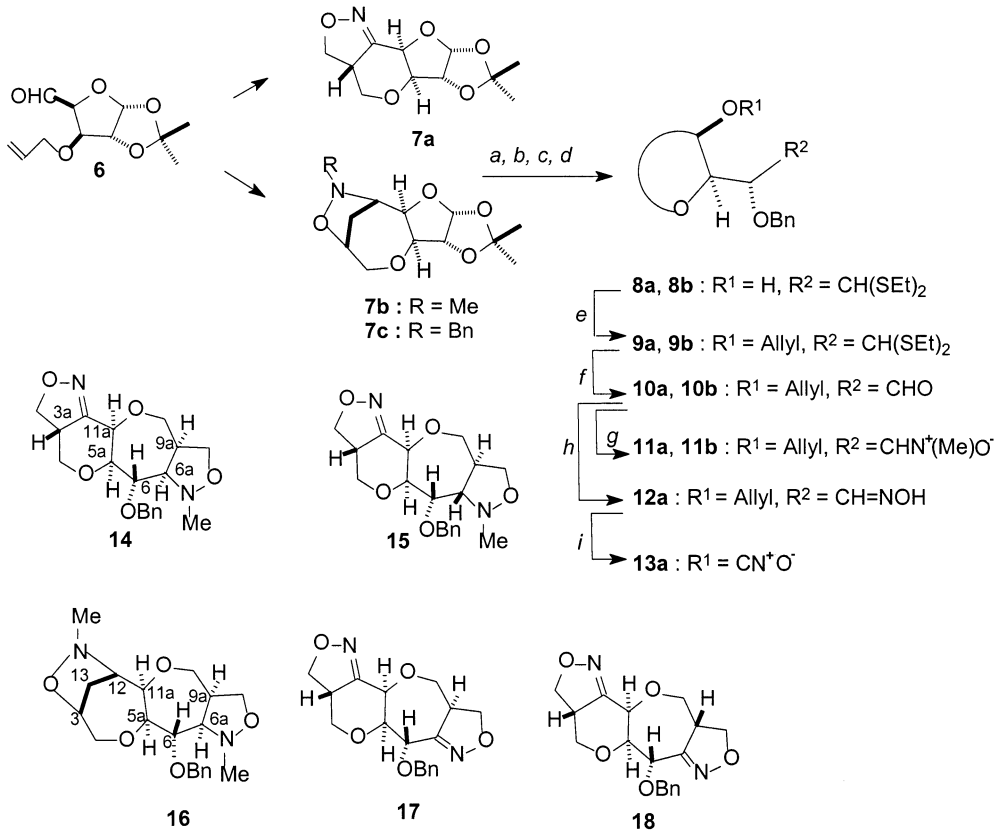
Scheme 1.

bicyclic systems through different methodologies.[4,5] We demonstrate our strategy by the synthesis of oxepinopyran and oxepinooxepane ring systems by the cycloaddition of 4-*O*-allyl nitrone and nitrile oxide species generated from the 1,2-isopropylidene furanoside fused cyclic ether derivatives **7a** and **7b** (Scheme 2).

Following the procedures reported in the literature, the isoxazole **7a** and the isoxazolidine **7b** were prepared from the aldehyde **6** by the application of 3-*O*-allyl nitrile oxide and 3-*O*-allyl nitrone cycloaddition.[6,7]

Although the more versatile *N*-Bn derivative **7c** was available,[8] the *N*-CH_3 derivative was used in this study for easier characterisation. A sequence of known[2,3] reactions on **7a** and **7b** involving (a) removal of the isopropylidene group and simultaneous methylglycosylation by treatment with *p*-TsOH and methanol, (b) benzylation of –OH with benzyl bromide in the presence of tetrabutylammonium bromide in CH_2Cl_2–50% aqueous NaOH, (c) deglycosylation with 50% aqueous trifluoroacetic acid and (d) dithioacetalisation with ethanethiol in conc. HCl gave the dithioacetal derivatives **8a** (91%) and **8b** (90%) (Scheme 2). Allylation of **8a** and **8b** with allyl bromide in the presence of tetrabutylammonium bromide in CH_2Cl_2–50% aqueous NaOH or NaH in THF afforded the *O*-allyl derivatives **9a** (89%) and **9b** (68%), dethioacetalisation of which furnished the aldehydes **10a** and **10b** (Scheme 2). All the intermediates involved in the above sequence of reactions were found to be liquids and could be characterised by ^1H and ^{13}C NMR spectroscopy and mass spectral analysis, but purification to a level suitable for microanalytical analysis was not possible because of the adherence of traces of unidentifiable contaminants. However, the aldehydes **10a** and **10b** were used immediately without any purification for the next step.

Treatment of **10a** with MeNHOH·HCl in 80% aqueous MeOH in the presence of $NaHCO_3$ under reflux led to the formation of the nitrone **11a**, cycloaddition of which did not occur under the aforementioned conditions, as was evident from the ^1H NMR spectrum of the crude product. Heating the crude nitrone in toluene led to cycloaddition resulting in the formation of the oxepinopyran derivatives **14** and **15** in yields of 18 and 31% respectively (Scheme 2). The structures of **14** and **15** (and the products described later) were established by high-resolution mass spectral data and DEPT, HMQC/C,H-COSY, DQFCOSY/H,H-COSY and ROESY/NOESY experiments.[9] The *cis* relationship between 6a-H and 9a-H in **14** was indicated by $J_{6a,9a} = 8.2$ Hz, while the observation of cross peaks between 9a-H and 11a-H in the ROESY spectrum established the assigned stereochemistry of 6a-C and 9a-C in **14** (Scheme 2). On the other hand, the observation of $J_{6a,9a} = 9.3$ Hz was consistent with the *trans* relationship between 6a-H and 9a-H in **15**, and the occurrence of cross peaks between 9a-H and 11a-H in the ROESY spectrum indicated the assigned stereochemistry in **15** (Scheme 2).



Scheme 2. Reagents: (a) For **7a**: MeOH, TsOH (catalyst), reflux, 5 h; for **7b**: MeOH, HCl gas, 25°C, 15 h. (b) BnCl, Bu_4NBr, 50% aq. NaOH–CH_2Cl_2, 25°C, 15 h. (c) 50% aq. TFA, 25°C, 24 h. (d) EtSH, conc. HCl, 0°C, 18 h, 91% (**8a**), 90% (**8b**). (e) For **8a**: allyl bromide, Bu_4NBr, 50% aq. NaOH–CH_2Cl_2, 25°C, 15 h, 89%; for **8b**: allyl bromide, NaH, THF, 25°C, 20 h, 68%. (f) $HgCl_2$, $CaCO_3$, CH_3CN–H_2O (4:1), 25°C. (g) i. MeNHOH·HCl, $NaHCO_3$, 80% aq. EtOH, reflux, 20 h; ii. toluene, reflux, 8 h, 18% (**14**), 31% (**15**), 23% (**16**). (h) NH_2OH·HCl, MeOH, py, reflux, 8 h, 91%. (i) 4% aq. NaOCl, Et_3N, CH_2Cl_2, 25°C, 25 h, 23% (**17**), 14% (**18**)

The nitrone **11b**, obtained from the aldehyde **10b**, underwent cycloaddition under the conditions mentioned for **11a** leading to the formation of the oxepinooxepane derivative **16** as the exclusive product in 23% yield. The high diastereoselectivity of the cycloaddition of **11b** compared to that of **11a** is worth mentioning, although the reason for this is not known at present. The *cis* relationship between 6a-H and 9a-H in **16** was assigned on the basis of $J_{6a,9a} = 7.9$ Hz, and the observation of cross peaks between 9a-H and 11a-H as well as 5a-H and 6a-H in the ROESY spectrum established the stereochemistry at 6a-C and 9a-C.

In a separate route **10a** was converted to the oxime **12a** (91%) by treatment with NH_2OH·HCl in methanol–pyridine (Scheme 2), and oxidation of **12a** with NaOCl in CH_2Cl_2 led to the formation of **17** (23%) and **18** (14%) via the nitrile oxide **13a**. The ^1H and ^{13}C NMR spectra of the compounds clearly indicated that they were 9a-C epimers by their spectral similarity. The occurrence of cross peaks between 9a-H and 5a-H in **17** established the stereochemistry at 9a-C in **17**, and consequently the corresponding stereochemistry in **18** was also known.

A striking feature of the above work is that the conversion of the aldehyde **6** to the bicyclic compounds above made use of the difference in regioselectivity of 3-*O*-allyl carbohydrate nitrile oxide and nitrone cycloaddition (in the synthesis of **7a** and **7b**) as well as the regioselectivity of 4-*O*-allyl nitrone and nitrile oxide cycloaddition (in the formation of the oxepane skeleton from the furanoside ring). Another notable aspect is that all the five carbon atoms and three chiral centres of the carbohydrate backbone of **6** are retained in the dioxaheterobicyclic skeletons in **14**–**18**.

In conclusion, the above work demonstrates a useful and novel transformation of the 1,2-isopropylidene furanoside ring according to Scheme 1, and the inherent potential of the strategy for the construction of polyether frameworks of marine toxins becomes visible through a variation in the structure and stereochemistry of the *O*-alkene residue. The tetracyclic compounds **14**, **15**, **17** and **18** incorporate *cis*-fused oxepinopyran skeletons and **16** incorporates a *cis*-fused oxepinooxepane skeleton *unlike* the naturally occurring marine toxins. The stereochemistry of this ring fusion is determined by that of 3-C and 4-C of the starting aldehyde **6**. So, the application of this strategy to toxin synthesis requires the use of stereochemically different starting materials as well as different alkene moieties in order to allow for the correct substitution pattern present in toxins. Work in this field is currently in progress.

Acknowledgements

A.B. is grateful to DST, India, for financial assistance, and thankfully acknowledges a joint grant from Ranbaxy Research Laboratories and DST, India. A.P. thanks DST, India, for a Senior Research Fellowship. The experimental assistance of Mr Sandip Chowdhury is gratefully acknowledged. Thanks are due to IICT, India, for the mass spectroscopy including HRMS analysis and the Bose Institute, Calcutta, for the 500 MHz NMR analysis.

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8. Datta, S.; Chattopadhyay, P.; Mukhopadhyay, R.; Bhattacharjya, A. *Tetrahedron Lett.* **1993**, *34*, 3585.
9. **Spectroscopic and other physical data**: **14**: sticky material; $[\alpha]_D$ −13.2 ($CHCl_3$, *c* 0.15); HRMS: calcd for $C_{19}H_{24}N_2O_5$, 360.16852; found, 360.16958; ^1H NMR (500 MHz, $CDCl_3$): δ 2.70 (s, 3H), 2.96 (br d, $J=8.2$ Hz, 1H), 3.33 (d, $J=2.6$ Hz, 1H), 3.34 (t, $J=10.6$ Hz, 1H), 3.57 (m, 1H), 3.60–3.64 (m, 2H), 3.76–3.80 (m, 2H), 3.82 (dt, $J=7.5$, 9.1 Hz, 1H), 3.99 (t, $J=7.5$ Hz, 1H), 4.02 (dd, $J=7.5$, 10.5 Hz, 1H), 4.32 (dd, $J=6.8$, 10.5 Hz, 1H), 4.43 (dd, $J=7.6$, 10.1 Hz, 1H), 4.64 (d, $J=11.8$ Hz, 1H), 4.66 (s, 1H), 4.86 (d, $J=11.6$ Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (75 MHz): δ 41.6 (CH), 44.0 (CH_3), 45.0 (CH), 68.5 (CH_2), 68.7 (CH), 69.2 (CH_2), 70.0 (CH_2), 72.1 (CH), 72.6 (CH_2), 73.5 (CH_2), 75.1 (CH), 81.9 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 138.0 (q), 156.4 (q). **15**: sticky material; $[\alpha]_D$ +97.8 ($CHCl_3$, *c* 0.22); HRMS: calcd for $C_{19}H_{24}N_2O_5$, 360.16852; found, 360.16900; ^1H NMR (500 MHz, $CDCl_3$): δ 2.75 (s, 3H), 3.27 (dd, $J=10.7$, 10.9 Hz, 1H), 3.35–3.44 (m, 1H), 3.40 (d, $J=5.9$ Hz, 1H), 3.47 (d, $J=9.3$ Hz, 1H), 3.57 (t, $J=7.7$ Hz, 1H), 3.72 (m, 1H), 3.85 (t, $J=8.5$ Hz, 1H), 4.03 (dd, $J=6.6$, 12.1 Hz, 1H),

4.07–4.13 (m, 3H), 4.28 (dd, $J=6.8$, 10.5 Hz, 1H), 4.44 (dd, $J=8.5$, 10.5 Hz, 1H), 4.64 (d, $J=11.5$ Hz, 1H), 4.77 (s, 1H), 5.01 (d, $J=11.5$ Hz, 1H), 7.26–7.47 (m, 5H); ^{13}C NMR (75 MHz): δ 45.1 (CH), 45.6 (CH_3), 46.9 (CH), 68.6 (CH), 68.7 (CH_2), 69.7 (CH_2), 69.9 (CH_2), 72.1 (CH_2), 73.0 (CH), 74.8 (CH_2), 80.5 (CH), 81.1 (CH), 127.7 (CH), 128.4 (CH), 138.5 (q), 156.1 (q). **16**: sticky material; $[\alpha]_D$ −16.4 ($CHCl_3$, *c* 0.80); HRMS: calcd for $C_{20}H_{28}N_2O_5$, 376.19982; found, 376.19900; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (m, 1H), 2.55 (d, $J=12.5$ Hz, 1H), 2.65 (s, 3H), 2.66 (s, 3H), 2.87 (d, $J=7.9$ Hz, 1H), 3.34 (dd, $J=5.3$, 6.7 Hz, 1H), 3.52 (m, 1H), 3.55–3.62 (m, 4H), 3.57 (d, $J=3.0$ Hz, 1H), 3.79 (d, $J=5.0$ Hz, 1H), 3.91–4.00 (m, 2H), 3.92 (d, $J=3.0$ Hz, 1H), 4.53 (dd, $J=2.5$, 8.5 Hz, 1H), 4.71 (d, $J=11.7$ Hz, 1H), 4.78 (d, $J=11.7$ Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (100 MHz): δ 27.1 (CH_2), 41.7 (CH), 43.9 (CH_2), 46.8 (CH_3), 67.5 (CH), 68.6 (CH_2), 68.8 (CH_2), 71.8 (CH), 72.6 (CH_2), 72.7 (CH_2), 73.5 (CH), 75.1 (CH), 75.4 (CH), 78.9 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 138.4 (q). **17**: mp 164–165°C; $[\alpha]_D$ +26.7 ($CHCl_3$, *c* 0.01); HRMS: calcd for $C_{18}H_{20}N_2O_5$, 344.13722; found, 344.137124; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31 (t, $J=10.7$ Hz, 1H), 3.55 (d, $J=0.9$, 4.7 Hz, 1H), 3.64–3.75 ((m, 2H), 3.85 (t, $J=8.6$ Hz, 1H), 3.99 (d, $J=13.0$ Hz, 1H), 4.06 (dd, $J=4.5$, 13.1 Hz, 1H), 4.09 (dd, $J=8.0$, 14.1 Hz, 1H), 4.34 (dd, $J=6.8$, 10.6 Hz, 1H), 4.42 (dd, $J=8.4$, 10.6 Hz, 1H), 4.52 (d, $J=11.8$ Hz, 1H), 4.63 (dd, $J=7.9$, 10.8 Hz, 1H), 4.64 (d, $J=11.8$ Hz, 1H), 4.72 (br s, 1H), 4.75 (d, $J=4.6$ Hz, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (75 MHz): δ 45.0 (CH), 51.1 (CH), 68.8 (CH_2), 70.0 (CH_2), 72.0 (CH_2), 72.3 (CH_2), 73.3 (CH_2), 74.3 (CH), 74.7 (CH), 79.7 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 136.6 (q), 155.8 (q), 157.2 (q). **18**: mp 113–114°C; $[\alpha]_D$ +264.9 ($CHCl_3$, *c* 0.01); HRMS: calcd for $C_{18}H_{20}N_2O_5$, 344.13722; found, 344.138039; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (t, $J=10.6$ Hz, 1H), 3.61 (dd, $J=1.1$, 5.5 Hz, 1H), 3.73–3.83 (m, 4H), 3.86 (dd, $J=7.9$, 9.1 Hz, 1H), 4.01 (m, 1H), 4.32 (dd, $J=6.7$, 10.7 Hz, 1H), 4.45 (dd, $J=8.0$, 10.6 Hz, 1H), 4.50 (m, 1H), 4.56 (d, $J=5.5$ Hz, 1H), 4.57 (d, $J=11.7$ Hz, 1H), 4.80 (br s, 1H), 4.81 (d, $J=11.7$ Hz, 1H), 7.33 (m, 5H); ^{13}C NMR (75 MHz): δ 44.8 (CH), 52.6 (CH), 68.2 (CH_2), 70.1 (CH_2), 70.9 (CH_2), 71.2 (CH_2), 72.1 (CH), 72.6 (CH_2), 73.2 (CH), 82.2 (CH), 128.1 (CH), 128.2 (CH), 137.0 (q), 155.9 (q), 157.9 (q).