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Tetrahedron Letters 45 (2004) 257–259
Tetrahedron Letters

Studies towards the synthesis of FCRR toxin: an expeditious entry into 7–5–6 ring systems via [5+2] oxidopyrylium-alkene cycloaddition

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Received 21 September 2003; revised 17 October 2003; accepted 30 October 2003

Abstract—Synthetic studies towards the diterpene natural product FCRR toxin have been undertaken. An intermolecular [5+2] oxidopyrylium-alkene cycloaddition reaction was employed to construct the 7–5–6 tricyclic framework. The reaction proceeded with very high regio- and stereoselectivity and the bridging ether was reductively cleaved to unmask the carbocycle.

FCRR (Fusarium crown and root rot) toxin, a new phytotoxin from the culture filtrate of *Fusarium oxysporum* f. sp. *radicis-lycopersici* (FORL) was isolated in 1994 by Hirota et al. and its biological activities were studied.[1] It was found that the FCRR toxin induces leaf necrosis for 'Momotaro', a susceptible cultivar of tomato, and the threshold concentration was 0.25 μg/mL. The structure of FCRR toxin was established on the basis of spectroscopic evidence and was assigned as **1** (Fig. 1). In this letter we report the first synthetic study towards the diterpene natural product **1**.

Our preliminary studies focused on the construction of the fused 7–5–6 tricyclic skeleton with the correct stereochemistry. We envisioned synthesis of the synthon **2** via [5+2] oxidopyrylium-alkene cycloaddition.[2–4] The strategy outlined in Scheme 1 is based on the premise that the crucial oxidopyrylium-alkene cycloaddition will result in **2**, which would be formed by the *endo*-addition of indene **3** across the 3-oxidopyrylium ion and also that the regiochemical course of the reaction would follow the path shown as A in Figure 2.[5] Finally, the oxa-bridge should serve as a latent hydroxy substituent and unmasking of the oxa-bridge of **2** would provide the required carbocyclic framework.

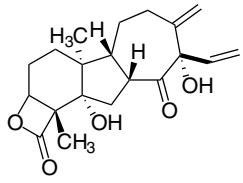
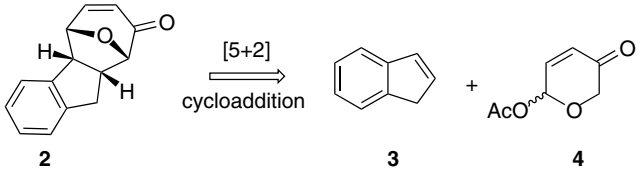


Figure 1. FCRR toxin (**1**, $C_{20}H_{26}O_5$).

The first step of our synthesis is the Achmatowicz reaction, which involves the oxidative rearrangement of furylcarbinols to hydroxypyranones.[6] This rearrangement has been used for the synthesis of a large number of polyoxygenated natural products.[7,8] Furfuryl alcohol **5** on treatment with NBS in THF–H_2O (4:1) gave the hydroxypyranone **6** (Scheme 2).[9] Acetylation of **6** at 0 °C afforded acetoxypyranone **4** in 59% yield in two steps. The acetoxypyranone **4** when treated with Et_3N in the presence of indene (**3**, 3 equiv), via the pyrylium ylide



2 **3** **4**

Scheme 1.

Keywords: FCRR toxin; Indene; [5+2] Cycloaddition; Reductive cleavage.
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doi:10.1016/j.tetlet.2003.10.185

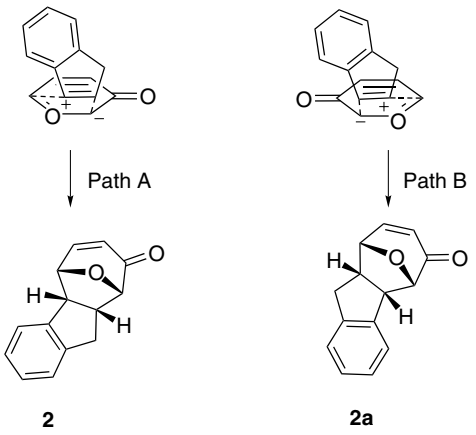


Figure 2.

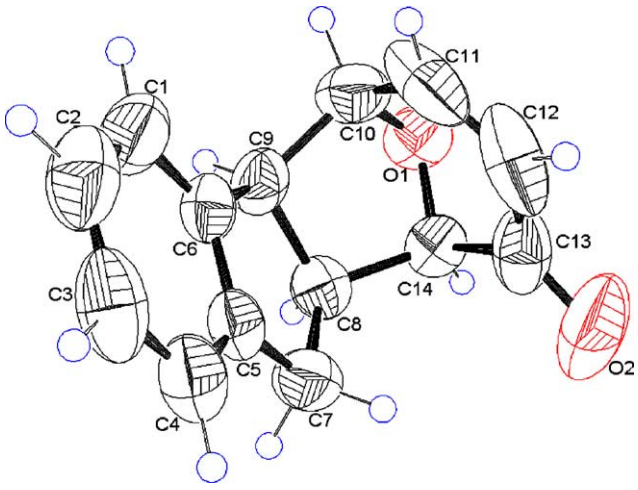
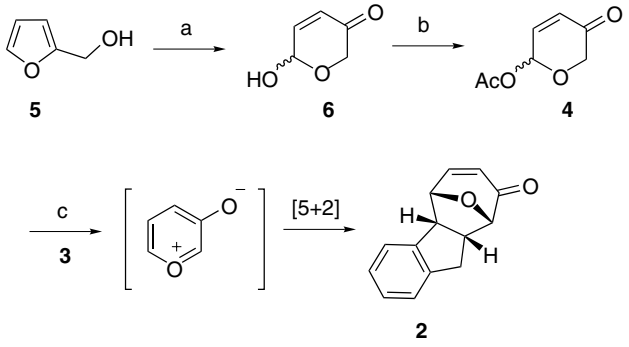


Figure 3. ORTEP drawing of the X-ray structure of **2**.



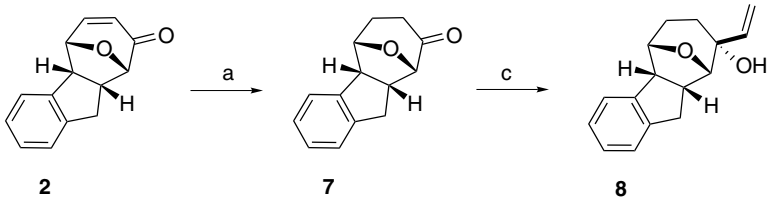
Scheme 2. Reagents and conditions: (a) NBS, THF–H_2O (4:1), 0 °C, 0.5 h; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 59% (two steps); (c) Et_3N, CH_2Cl_2, 0 °C–rt.

generated in situ, smoothly underwent cycloaddition with indene to furnish the [5+2] cycloadduct **2** in 59–63% isolated yield as the only observed product.[10] The product was characterized by its ^1H NMR data, which exhibited signals for the enone system with δ 6.76 (dd, $J = 9.8$, 4.8 Hz, 1H), 5.77 (dd, $J = 9.8$, 1.2 Hz, 1H) and the oxa-bridge protons at δ 5.09 (dd, $J = 7.3$, 4.8 Hz, 1H) and 4.73 (dd, $J = 8.8$, 1.2 Hz, 1H). The *endo* mode of cycloaddition was inferred from the high coupling values observed for the oxa-bridge protons. The structure of **2** was unambiguously established by single crystal X-ray analysis (Fig. 3).[11] We were pleased to find that the relative regiochemistry of the cycloadduct **2** correlates well with the targeted molecule **1**.

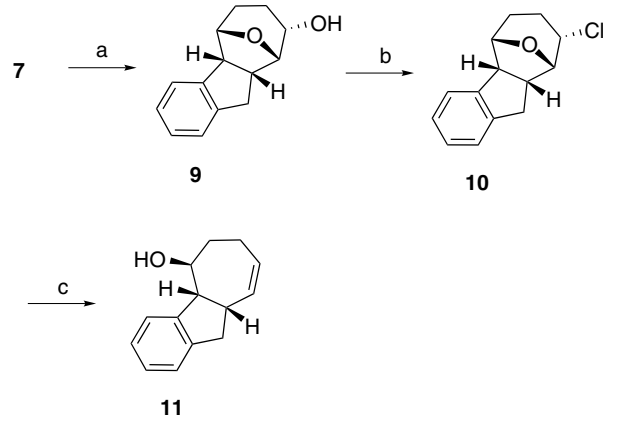
Having obtained sufficient quantities of **2**, in a highly stereocontrolled fashion, we turned our attention to functionalize the seven-membered portion of the cycloadduct. Hydrogenation of **2** over activated Pd/C (10%) gave the dihydro-product **7** (98% yield, Scheme 3). Grignard reaction of **7** with vinylmagnesium bromide at −20 °C resulted in the formation of **8** in 86% yield.[10] The stereochemistry of **8** was assigned on the basis of literature analogy, which can be rationalized by the approach of the Grignard reagent from the least hindered side of the ketone (*exo*-face) as well as chelation control by the bridging ether.[12]

Reduction of **7** with sodium borohydride at 0 °C afforded the alcohol **9**. Treatment of **9** with thionyl chloride and DMF (catalytic) in CH_2Cl_2 afforded the chloride **10** in good yield. Reductive ring opening of **10** using finely dispersed sodium in ether, yielded the hydroxy cycloheptanoid **11** in 58% overall yield from **9** (Scheme 4).[10,13]

In conclusion, the [5+2] cycloaddition of a 3-oxidopyrylium with indene provided a facile entry into a 7–5–6 tricyclic framework. The noteworthy point is that the cycloaddition proceeded with exceptional regio- and stereoselectivity. Functionalities can be introduced to the seven-membered portion in stereoselective fashion, by virtue of its conformational rigidity. Our efforts towards functionalization of the aromatic ring and further studies with substituted indene derivatives are currently in progress.



Scheme 3. Reagents and conditions: (a) H_2, Pd/C (10%), EtOH, 98%; (b) vinylmagnesium bromide (1 M in THF), −20 °C, 86%.



Scheme 4. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1 h, 89%; (b) $SOCl_2$, DMF (cat.), CH_2Cl_2, 0 °C–rt, 24 h, 95%; (d) Na, Et_2O, 70%.

Acknowledgements

We thank the Department of Science and Technology, New Delhi (India) for the financial support of this project and the National Single Crystal X-ray Diffraction facility at IIT Bombay for the X-ray crystal structure of **2**.

References and Notes

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10. All compounds were characterized by spectroscopic data. Selected data of compound **2**: mp 138–139 °C. IR ν_{max} 1690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (m, 4H), 6.76 (dd, $J = 9.8$, 4.8 Hz, 1H), 5.77 (dd, $J = 9.8$, 1.2 Hz, 1H), 5.09 (dd, $J = 7.3$, 4.8 Hz, 1H), 4.73 (dd, $J = 8.8$, 1.2 Hz, 1H), 4.41 (m, 1H), 3.65 (m, 1H), 3.1 (dd, $J = 18$, 10.9 Hz, 1H), 2.63 (dd, $J = 18$, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 153.2, 144.4, 140.0, 127.7, 127.0, 126.8, 125.5, 124.4, 85.3, 75.7, 55.9, 42.5, 31.5. GC–MS: m/z 212 (M^+, 59%), 97 (100%).
8: mp 97–99 °C. IR ν_{max} 3450, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.12 (m, 4H), 6.52 (dd, $J = 17.6$, 11 Hz, 1H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.12 (d, $J = 11$ Hz, 1H), 4.54 (dd, $J = 7.7$, 4 Hz, 1H), 4.17 (dd, $J = 12.8$, 8 Hz, 1H), 4.05 (d, $J = 4$ Hz, 1H), 3.58–3.46 (m, 1H), 3.02 (dd, $J = 17.6$, 11.2, 1H), 4.04 (dd, $J = 7.7$, 1.8 Hz, 1H), 1.87–1.18 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 145.1, 141.2, 127.1, 126.2, 125.1, 124.9, 112.0, 82.2, 76.7, 73.6, 55.7, 45.3, 29.9, 29.8, 26.0. GC–MS: m/z 242 (M^+, 21%), 128 (100%).
11: mp 79–80 °C. IR ν_{max} 3476 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 4H), 5.61 (m, 2H), 3.71 (m, 1H), 3.40–3.17 (m, 2H), 3.16 (dd, $J = 10.3$, 7.7 Hz, 1H), 3.08 (dd, $J = 15.4$, 7.7 Hz, 1H), 2.78 (dd, $J = 15.4$, 10.3 Hz, 1H), 2.40 (m, 1H), 2.20 (m, 2H), 1.68 (d, $J = 3$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 143.1, 131.1, 128.0, 127.3, 126.5, 125.9, 124.9, 71.4, 55.2, 42.6, 39.8, 34.7, 25.5. GC–MS: m/z 200 (M^+). HRMS calcd for $C_{14}H_{16}NaO$: 223.1099 (M^+Na^+), found 223.1087.
11. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-176798. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Selected bond lengths (Å) and bond angles (°): C(10)–O(1) = 1.435(3), C(14)–O(1) = 1.416(2), C(13)–O(2) = 1.222(3), O(2)–C(13)–C(14) = 120.7(3), O(2)–C(13)–C(12) = 124.1(3), C(14)–O(1)–C(10) = 102.61(15).
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