Pergamon

Tetrahedron Letters 43 (2002) 5471–5473

TETRAHEDRON LETTERS

Enantiospecific synthesis of [7*R*,6*S*,5*S*,4*R*]-triacetoxy-(−)-goniotriol

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Received 11 April 2002; revised 24 May 2002; accepted 31 May 2002

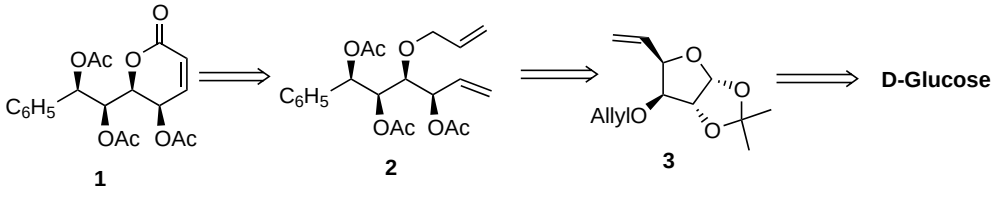
Abstract—A short and efficient synthesis of [7*R*,6*S*,5*S*,4*R*]-triacetoxy-(−)-goniotriol starting form D-glucose is described. A sequence of ring closing metathesis (RCM) followed by a PCC oxidation was used to construct the core six-membered α,β-unsaturated lactone moiety.

Styryllactones, isolated from the stem bark of *Goniothalamus giganteus* (Annanoceae) have interesting heterocyclic skeletons.[1] They show significant murine toxicity to lymphocytic leukemia systems. The isolation of further styryllactones, their structure elucidation and cytotoxic studies are active areas of interest.[2,3] Goniotriol, an important member of this family, which showed significant cytotoxicity in the potato disc test and the brine shrimp test, is known to occur in both enantiomeric forms.[4] Syntheses of naturally occurring [7*R*,6*R*,5*R*,4*S*]-(+)-goniotriol[5–8] and its analogues have been reported and their bioactivities were studied. Furthermore, biomimetic syntheses of other styryllactones from goniotriol have been reported.[6] Owing to its biological importance, especially its cytoxicity to lymphocytic leukemia, and the fact that goniotriol could be further converted to other styryllactones, it appeared of interest to synthesize various diastereomers of goniotriol. The synthesis of [7*R*,6*S*,5*S*,4*R*]-triacetoxy-(−)-goniotriol **1**, a diastereomer of natural goniotriol and the enantiomer of 7-*epi*-goniotriol is reported here.

Results and discussion

The retrosynthetic analysis of our approach is shown in Scheme 1. It was envisioned that goniotriol **1** could be synthesized from a RCM product of the dialkenyl ether **2** followed by a PCC oxidation reaction. Furthermore, **2** could originate from the acetonide **3** by incorporating the required phenyl group in a stereocontrolled step. The acetonide **3** can be synthesized from D-glucose[9] by known steps.

The synthesis commenced with the dialkenyl acetonide **3**, which was subjected to hydrolysis using acetic acid in water at 90°C to furnish an inseparable mixture of anomeric diols **4** in 86% yield. The anomeric mixture of diols was subjected to a Grignard reaction with phenylmagnesium bromide resulting in an inseparable mixture of diastereomeric triols **5a** and **b** in a 3:1 ratio. The stereochemistry of the major isomer was deduced to be **5a** by literature analogy[9] and was later corroborated by the single crystal X-ray structure of **1**, which was derived from isomer **5a**. The diastereomeric triols **5a**



Scheme 1.

Keywords: styryllactones; goniotriol; ring closing metathesis; PCC oxidation.

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PII: S0040-4039(02)01048-1

and **b** on acetylation followed by column chromatography afforded essentially pure triacetate **2** in 49% yield (Scheme 2).

The triacetate **2** on subjection to a ring closing metathesis reaction[10] using Grubb's catalyst [benzylidine-bis(tricyclohexylphospine)-dichlororuthenium (5 mol%)] in dry DCM yielded the cyclic allyl ether **6** in a 90% yield. The allylic methylene moiety in ether **6** was oxidized using the conditions reported by Bonadies et al.[11] Treatment of the cyclic allyl ether with 3 equiv. of PCC and pyridine in dry DCM furnished the required styryllactone, [7*R*,6*S*,5*S*,4*R*]-triacetoxy-(−)-goniotriol in an overall 12% yield (Scheme 3). As mentioned earlier the configuration at C-7 derived through the Grignard reaction on the anomeric diol **4** was based on a literature analogy,[9] which could be ascertained unambiguously from the single crystal X-ray analysis[12] (see Fig. 1).

Syntheses of natural products containing six-membered α,β-unsaturated lactones as a core feature using RCM reactions have been reported[13,14] earlier. These were achieved through intramolecular RCM reactions of appropriately substituted acrylyl alkenylic esters. In the present synthesis we have utilized an allyl ether as a masked acrylic ester moiety to minimize the protection and deprotection steps. Since allyl ethers are known to withstand harsher reaction conditions (both acidic and basic), the present methodology offers an attractive alternative to acrylyl ester derived syntheses of cyclic lactones of various ring sizes.

The present synthesis of [7*R*,6*S*,5*S*,4*R*]-triacetoxy-(−)-goniotriol from D-glucose has demonstrated the utility of allyl ethers in constructing six-membered α,β-unsaturated lactone moieties through sequential RCM and PCC oxidation reactions. Further adoption of this strategy in syntheses of other diastereomers of the title compound is in progress.

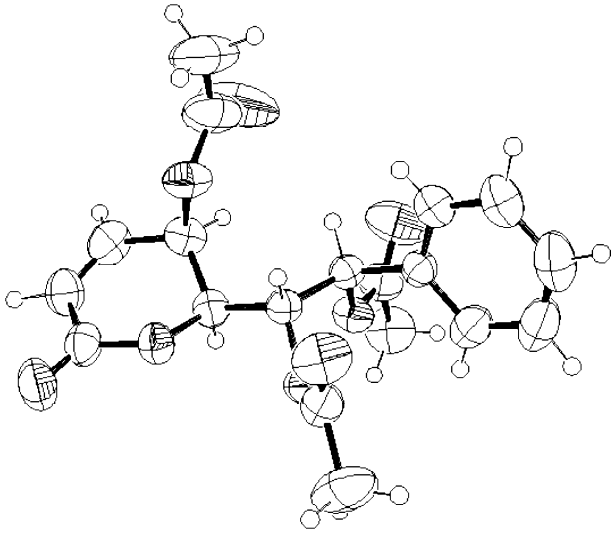
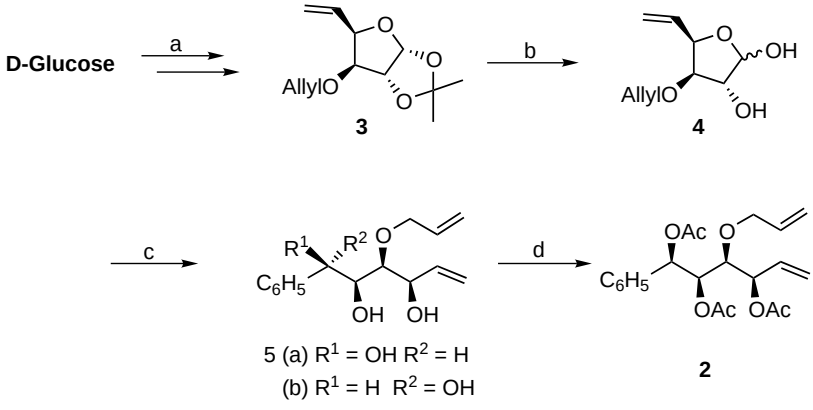
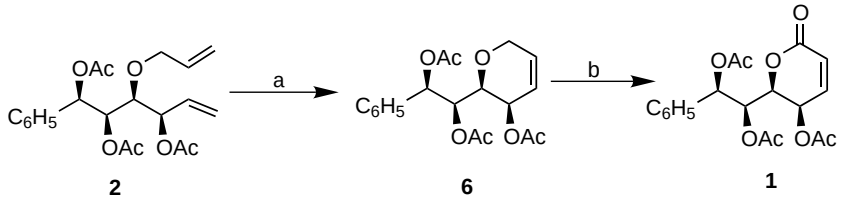


Figure 1. X-Ray crystal structure of **1**.



Scheme 2. *Reaction conditions*: (a) four steps (Ref. 9); (b) CH_3CO_2H:H_2O (4:1), reflux, 12 h (86% yield); (c) PhMgBr, THF, 0°C–rt, 30 h (74% yield **a**:**b** = 3:1); (d) Ac_2O, C_5H_5N, DMAP, 24 h (49% yield).



Scheme 3. *Reaction conditions*: (a) Grubb's catalyst (5 mol%), DCM, rt, 24 h (90% yield); (b) PCC, C_5H_5N, DCM, reflux, 8 h (68% yield).

Acknowledgements

G.S.C.S. would like to thank IIT Bombay and U.M.K. to DST for a fellowship. We wish to thank Professor P. Mathur and the National Single Crystal X-Ray Diffraction Facility at IIT Bombay. Also Dr. Shilpa Korde and Dr. Dinesh Rele are highly acknowledged for their helpful discussions.

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10. Compound **6**: $[\alpha]_D^{25}$ −152.1 (*c* 0.2, MeOH): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.34 (m, 5H), 6.01 (m, 3H), 5.52 (t, $J=5.4$ Hz, 1H), 4.97 (m, 1H), 4.30 (part of an AB system, $J=19.8$ Hz, 1H), 4.08 (part of an AB system, $J=19.8$ Hz, 1H), 3.55 (dd, $J=2.5$, 5.12 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz): δ_C 170.3, 169.6, 136.5, 131.8, 128.6, 126.9, 122.2, 74.2, 73.5, 73.1, 66.1, 65.49, 20.96, 20.92, 20.86.
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12. Compound **1**: $[\alpha]_D^{25}$ −135.0 (*c* 0.2, MeOH): ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.34 (m, 5H), 6.93 (dd, $J=5.4$, 9.5 Hz, 1H), 6.16 (d, $J=9.5$ Hz, 1H), 6.05 (d, $J=6.2$ Hz, 1H), 5.62 (dd, $J=5.1$, 6.2 Hz, 1H), 5.24 (dd, $J=3.2$, 5.1 Hz, 1H), 4.43 (dd, $J=3.2$, 5.1 Hz, 1H), 2.1 (s, 6H), 2.08 (s, 3H). Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK for compound **1** CCDC No. 183172). Crystal data for **1**: empirical formula, $C_{19}H_{20}O_8$; formula weight, 376.35; crystal color, habit colorless, prism; crystal dimensions, 0.4×0.35×0.4 mm; crystal system, orthorhombic; lattice parameters, $a=90070(7)$, $b=9.4630(6)$, $c=23.027(2)$ Å, $\alpha=90.00(6)$, $\beta=90.000(7)$, $\gamma=90.00(5)°$; Vol. 1962.7(3) Å^3; $Z=4$; calculated density = 1.274 mg/m^3.
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