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TETRAHEDRON: *ASYMMETRY*

Facile synthesis of a key intermediate for the synthesis of prostanes and isoprostanes

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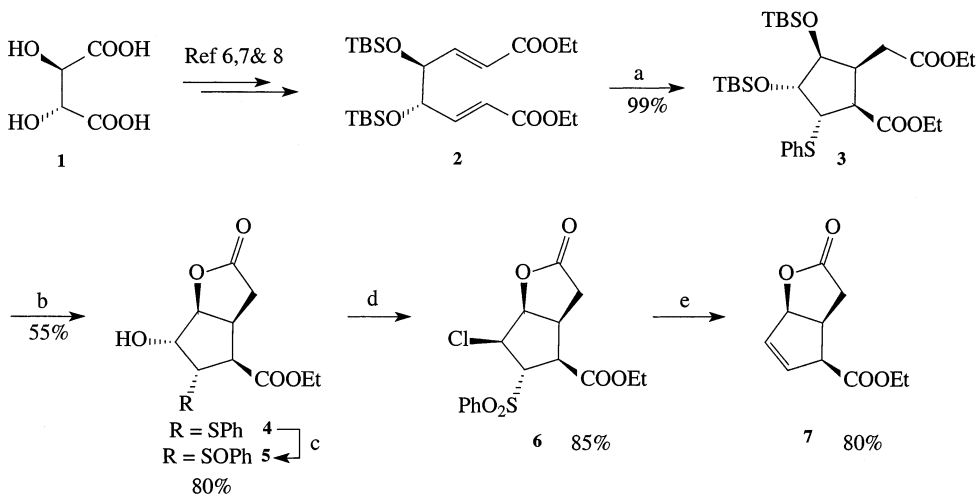
Abstract—An unconventional ring opening of β-sultines followed by an elimination step was achieved, leading to the formation of an important synthon for various prostanes and isoprostanes.

1. Introduction

Prostaglandins (PG's) have been synthesized by a variety of elegant methods which have been well documented in excellent reviews.[1] Recently, a new class of epimeric PGs, the isoprostanes,[2] which are characterized by *cis*-dialkyl stereochemistry at the five-membered ring junction, were found to exert more potent biological activity than the equivalent prostanes.[3] Corey's lactone[4] is the most widely used intermediate for the synthesis of naturally occurring PGs and, due to its potential to furnish isoprostanes, the synthesis of all *cis* Corey's lactone has recently gained greater significance.

2. Results and discussion

During the course of our studies towards the synthesis of *cis* Corey's lactone[5] starting from L-tartaric acid, an unusual ring opening of β-sultines in the bicyclic lactone intermediate was observed. The key strategy planned for the synthesis of Corey's lactone involved synthesis of the cyclopentane derivative **3** via a tandem Michael reaction as reported by Saito et al.[6] (Scheme 1). The high diastereoselectivity (>99% d.e.) of the cyclopentane ring formation using this methodology prompted us to apply the same strategy for the build-up of the bicyclic lactone **7**, a useful common intermediate



Scheme 1. (a) PhSH/*n*-BuLi, −78 to −40°C, 3 h; (b) (i) TBAF, THF (1.0 M solution in THF), 45 min, (ii) *p*-TSA, benzene, rt, 1 h; (c) H_2O_2, AcOH, 2 h; (d) SO_2Cl_2, DCM, rt, 30 min; (e) *n*-Bu_3SnH, AIBN, benzene, reflux, 2 h.

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in the synthesis of both prostanes and isoprostanes. Accordingly, intermediate **2** was prepared by the reported method[7,8] and subjected to the double Michael reaction with lithium benzene thiolate to give the corresponding adduct **3** {$[\alpha]_D = -35.2$ (*c* 1.09, $CHCl_3$)} in 99% yield and with 99% d.e.[6] Since the stereochemistry of the phenylthio group has been previously established,[9] we were interested in elaborating this intermediate to the bicyclic lactone **4**. The two TBSO groups can be differentiated and were deprotected using TBAF solution in THF.[8] The dihydroxy compound obtained was then directly subjected to cyclization without isolation using *p*-TSA to yield hydroxy lactone **4** {$[\alpha]_D = +69.6$ (*c* 1.04, $CHCl_3$)}.

Initial attempts were directed towards conversion of the hydroxy group of **4** to a halide for subsequent E2 elimination. However, all attempts by conventional methodologies failed to form the desired objective, probably as a result of steric hindrance caused by the rigid bicyclic ring and the adjacent thiophenoxy group. For example, a simultaneous single-pot elimination of thiophenyl and hydroxy group, akin to Julia's elimination,[10] was pursued with less than encouraging results. Attempts to react the analogous hydroxy sulphoxide and hydroxy sulphone compounds, formed by oxidation of the thiophenoxy group, also proved unfruitful.

Pursuing this course of eliminations for the β-hydroxy sulphoxides, it was known that $NCS/NBS/SO_2Cl_2$ are utilized to convert β-hydroxy sulphoxides to β-sultines,[11] which are generally found to have limited thermal stability and tend to eliminate SO_2 to give olefins. These reactions have not been previously exploited in a synthetic strategy and, hence, we wanted to explore the possibility of sultine formation for generation of the corresponding olefin. The hydroxy lactone **4** was accordingly converted to the corresponding sulphoxide **5** {$[\alpha]_D = -64.0$ (*c* 1, MeOH)} and was then subjected to sulphuryl chloride in DCM at rt to furnish intermediate **6** {$[\alpha]_D = +105.3$ (*c* 1.05, $CHCl_3$)}, which was found to be the chlorosulphone. Elemental analysis confirmed the presence of chlorine and IR spectroscopy showed the presence of the sulphone moiety. ^{1}H NMR of **6** indicated the presence of seven protons (as well as the ester and aromatic protons), indicating that the hydroxyl group had been displaced by chlorine during the reaction. Gratifyingly, **6** crystallized and X-ray crystallographic data unequivocally confirmed the presence of chlorine and sulphone and the *trans*-stereochemistry (Fig. 1). The *trans*-stereochemistry may be attributable to the formation of a four-membered cyclic intermediate during the reaction with sulphuryl chloride (as seen in β-sultines). Attack of chloride would then lead to opening of the unstable four-membered ring, and the observed *trans*-stereochemistry of **6** would result. This unusual ring opening is particularly useful in light of the earlier unsuccessful attempts at E2 elimination of the hydroxyl group.

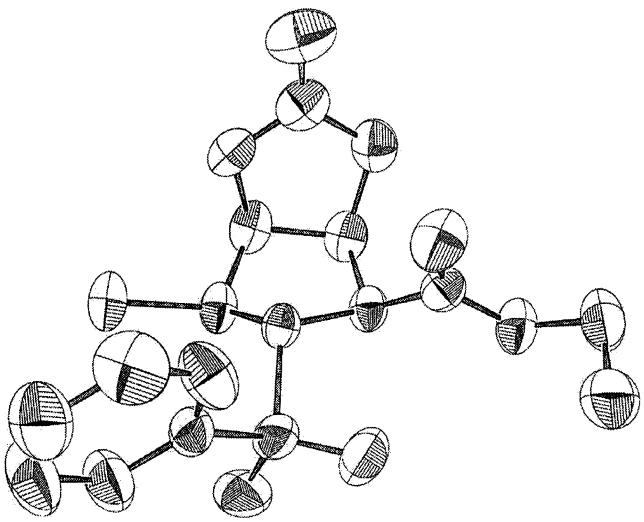

Figure 1. The X-ray structure of intermediate **6**.

The chlorosulphone **6** was then reduced under radical conditions using tri-*n*-butyl tin hydride to furnish the desired olefin **7**[14] in 80% yield {$[\alpha]_D = -18.6$ (*c* 0.66, $CHCl_3$)}. Thus, the ring opening and elimination protocol gave the α,β-unsaturated ester **7**,[13] which is an important synthon for a variety of prostanes[12] and isoprostanes such as 8-*epi* $PGF_{2\alpha}$[3] as well as Corey's lactone.

Another key feature of this strategy is that the α- and ω-sidechains for the prostaglandins can be synthesized in either the *cis*- or *trans*-stereochemical disposition, as both enantiomers of **7** can be easily accessed by choosing the appropriate tartaric acid starting material.

In conclusion, this approach of β-sultine ring opening can serve as a useful alternative for hindered E2 eliminations and applications to other hindered systems are currently being probed. Also, further elaboration of the key intermediate **7** to Corey's lactone and other prostanoids is under progress and will be reported in due course.

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14. Satisfactory analytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) data was obtained for compound **7**. IR (neat): 2982, 1775, 1740, 1610 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H), 2.32 (dd, $J=7.9$, 18.6 Hz, 1H), 2.68 (dd, $J=6.6$, 18.6 Hz, 1H), 3.53 (ddd, $J=6.6$, 7.9, 10.6 Hz, 1H), 3.79 (d, $J=10.6$ Hz, 1H), 4.23 (q, 2H), 5.53 (d, $J=6.6$ Hz, 1H), 6.02 (bd, $J=5.3$ Hz, 1H), 6.16 (d, $J=5.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (q), 31.5 (t), 38.7 (d), 52.5 (d), 61.2 (t), 87.7 (d), 131.2 (d), 133.8 (d), 171.1 (s), 176 (s); MS (m/z): 197 (M+1, 1), 179 (3), 151 (7), 124 (32), 106 (5), 95 (23), 80 (52), 79 (100), 78 (69), 67 (29).