Pergamon

Tetrahedron Letters 39 (1998) 9245–9248

TETRAHEDRON LETTERS

Generation of Near-enantiopure α-Alkyl α-Formyl α-Hydroxy Ketones/Esters and their Interception with Ethoxycarbonylmethylenetriphenylphosphorane

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Received 4 September 1998; accepted 22 September 1998

Abstract

Two protocols for the generation of the (*R*)-enantiomers of α-alkyl α-formyl α-hydroxy ketones/esters in states of high enantiomeric purity are developed; the formyl functions of such compounds undergo Wittig condensations with ethoxycarbonylmethylenetriphenylphosphorane in dimethyl sulfoxide to afford the corresponding alkenes with high (*E*)-stereoselectivities and with e.e.s of 91–99%.

Keywords: Carbohydrates; cleavage reactions; epoxides; Wittig reactions.

As summarised in Scheme 1, we recently reported [1] that vinylogous esters/carbonates of type **1** underwent stereoselective epoxidations with dimethyldioxirane to give mainly oxiranes of type **2**. When R^2 was an alkyl substituent, the diastereoselectivities were good (86:14–91:9) and it was possible to isolate essentially stereopure epoxides of type **2** in reasonable yields (52–74%) simply by fractional crystallisation. Removal of the sugar auxiliary from compounds **2a** and **2b** was achieved by the action of propane-1,3-dithiol and *p*-toluenesulfonic acid in hot toluene to give the corresponding dithianes **3a** (54% yield; 82% e.e.) and **3b** (83% yield; 98% e.e.). The partial racemisation accompanying the **2a**→**3a** transformation—attributed to the occurrence of some α-ketol rearrangment of the product **3a** under the reaction conditions—was minimized by the adoption of a methanolysis–transdithioacetalisation sequence conducted at room temperature; the route, which proceeded by way of the methoxy derivatives **4a** (as a mixture of epimers), afforded the dithiane **3a** with an e.e. of 98% in 55% overall yield. Similarly, the epoxide **2c** was converted by way of the methoxy derivatives **4c** into the dithiane **3c** (48% overall yield; 93% e.e.).

Representing a new class of trifunctional chirons, compounds of type **3** are of notable synthetic potential. However, if accessible, their parent aldehydes[1] would be expected to be of even wider synthetic utility. In this letter, we describe two protocols for the *in situ* generation of such compounds in states of high enantiomeric purity from epoxides of type **2** and, in particular, their interception with ethoxycarbonylmethylenetriphenylphosphorane.

[1]We are unaware of the characterisation of any enantiomerically pure/enriched α-alkyl α-formyl α-hydroxy ketone/ester although two ester representatives have been generated and intercepted *in situ* [2].

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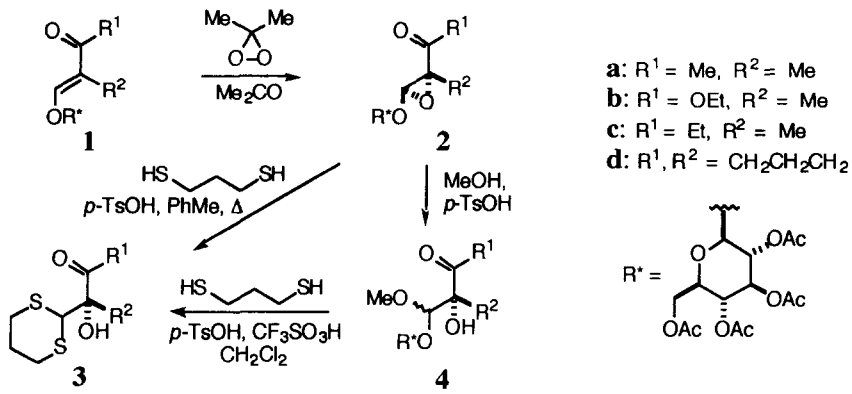
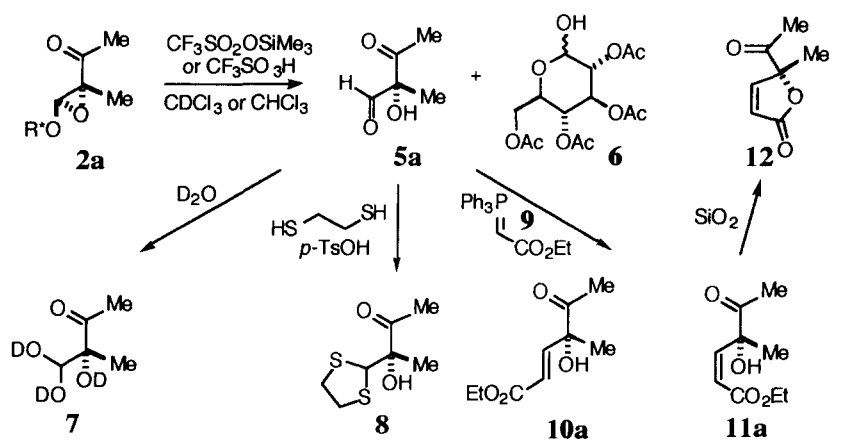
PII: S0040-4039(98)02011-5



Scheme 1

In principle, under mild hydrolytic conditions, the epoxide **2a** should be convertible into the aldehyde **5a** and the sugar unit **6**. Numerous attempts to effect such a reaction led to the isolation of only the tetra-acetate **6** [3] (as a mixture of α- and β-anomers), suggesting that the aldehyde **5a** was a labile species. However, as Scheme 2 shows, when a deuteriochloroform solution of the epoxide **2a** was treated with a deuteriochloroform solution of either trimethylsilyl triflate or triflic acid (*ca.* 0.5 mol%), a reaction ensued to give the aldehyde **5a** [δ (300 MHz) 1.51 (3 H, s, 2-Me), 2.28 (3 H, s, 4-H_3) and 9.56 (1 H, s, 1-H)] and glycone products, which included the tetra-acetate **6** (as a mixture of anomers). Various work-ups led to the recovery of only the glycone products. When the reaction mixture was shaken with deuterium oxide, the aldehyde **5a** was transferred into the aqueous phase as its deuteriohydrate **7** [δ (300 MHz) 1.33 (3 H, s, 2-Me), 2.30 (3 H, s, 4-H_3) and 5.13 (1 H, s, 1-H)]. Although stable in deuterium oxide over a 15 h period, compound **7** was lost on removal of the solvent (by rotary evaporation or freeze drying).



Scheme 2

Treatment of the epoxide **2a** with triflic acid (2 mol%) in chloroform (EtOH-free) for 30 min followed by *p*-toluenesulfonic acid (100 mol%) and ethane-1,2-dithiol (100 mol%) for 16 h

gave, after work-up and chromatography, the dithiolane **8** [1] with an e.e. of 97%[2] in 51% yield. Clearly, the aldehyde **5a** had been generated in a state of high enantiomeric purity and little racemisation had accompanied the dithioacetalisation reaction.

The aldehyde **5a** could also be intercepted by the phosphorane **9**. Thus, addition of triflic acid (2 mol%) to a chloroform solution of the epoxide **2a** followed, after 50 min, by the phosphorane **9** (200 mol%) afforded, after 16 h, a 74:26 mixture of the (*E*)-alkene **10a** and the (*Z*)-alkene **11a**;[3] following chromatography, an 86:14 mixture of the (*E*)-alkene **10a** and the γ-lactone **12**[4] was recovered (*ca.* 38% yield).

Seeking a more-efficient means of effecting the **2a**→**10a** transformation, it was decided to investigate the hydrolysis of the bromides **13a** and (or) **14a** as a route to the intermediary aldehyde **5a**. Hydrobrominolysis[5] of the epoxide **2a** gave an 89:11 mixture of the bromides **13a** and **14a**[6] in essentially quantitative yield, from which the major bromide **13a**,[7,8] mp 127 °C, $[\alpha]_D$ −102 (*c* 0.66, CH_2Cl_2), was isolated in 80% yield after fractional crystallisation. On standing in perdeuteriodimethyl sulfoxide, the bromides **13a** and **14a** were converted cleanly (by NMR spectroscopy) into a 50:50 mixture of the aldehyde **5a** [δ (300 MHz) 1.28 (3 H, s, 2-Me), 2.18 (3 H, s, 4-H_3) and 9.53 (1 H, s, 1-H)] and the tetra-acetate **6** (largely as the α-anomer) over a 2 h period. When the phosphorane **9** was added, depletion of the aldehyde **5a** occurred concurrent with the production of a 92:8 mixture of the alkenes **10a** and **11a**. The aforecited results are summarised in Scheme 3. In a preparative experiment,[9] the bromides **13a** and **14a** were transformed into the (*E*)-alkene **10a**[7,10] (50% yield after chromatography), $[\alpha]_D$ −15.6 (*c* 0.5, CH_2Cl_2) with an e.e. of 97%.[2]

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[2]The enantiomers were separated by HPLC using a Chiralpak AD column [eluent: hexanes–propan-2-ol (90:10) for **8** and hexanes–ethanol (95:5) for **10a-d**; flow rate: 1 cm^3 min^{-1}].

[3]The composition was determined by 300 MHz ^1H NMR spectroscopy ($CDCl_3$) from the integrals of the doublets at δ 6.23 and 7.02 (*J* 15.5 Hz) (attributed to the 2- and 3-H of **10a**) and those at δ 5.92 and 6.57 (*J* 12.5 Hz) (ascribed to the 2- and 3-H of **11a**).

[4]The composition was determined by 300 MHz ^1H NMR spectroscopy ($CDCl_3$) from the integrals of the doublets at δ 6.22 and 7.01 (*J* 15.5 Hz) (attributed to the 2- and 3-H of **10a**) and those at δ 6.17 and 7.39 (*J* 5.5 Hz) (ascribed to the 2- and 3-H of **12**).

[5]A saturated solution of hydrogen bromide in dry dichloromethane (15 cm^3) was added to a stirred solution of the epoxide **2a** (0.800 g, 1.8 mmol) in dry dichloromethane (15 cm^3) at −78 °C; evaporation after 1.5 h left an 89:11 mixture of the bromides **13a** and **14a** [δ (300 MHz) 5.99 and 6.08 (0.11 and 0.89 H, each s, CHBr)]. Crystallisation of the mixture (from CH_2Cl_2–Et_2O–hexanes) gave the bromide **13a** (0.756 g, 80%).

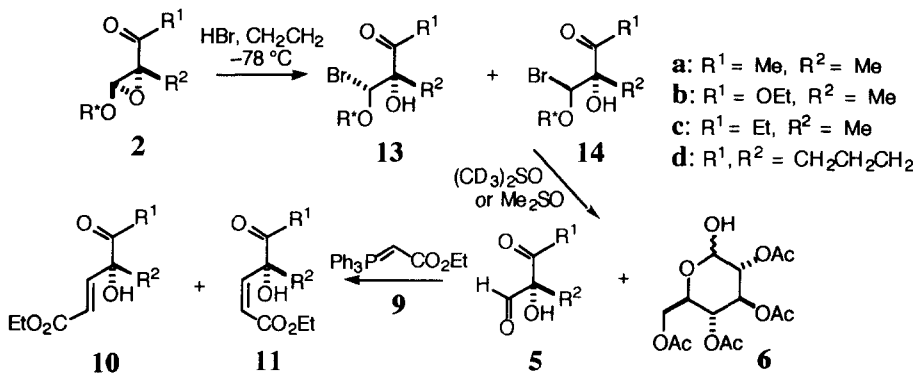
[6]The evidence for the stereostructures of these compounds will be presented elsewhere.

[7]This compound gave a satisfactory elemental analysis and showed spectral properties in accord with its assigned structure.

[8]For compound **13a**: δ (300 MHz; $CDCl_3$) 1.46 (3 H, s, 3-Me), 2.02, 2.04, 2.08 and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.32 (3 H, s, 1-H_3), 3.60 (1 H, s, 3-OH), 3.75–3.82 (1 H, m, 5'-H), 4.14 and 4.27 [each 1 H, dd (*J* 12.5 and 2.5 Hz) and dd (*J* 12.5 and 4.5 Hz), 6'-H_2], 4.81 (1 H, d, *J* 8 Hz, 1'-H), 5.03–5.13 (2 H, m, 2'- and 4'-H), 5.28 (1 H, t, *J* 9 Hz, 3'-H) and 6.08 (1 H, s, 4-H).

[9]An 89:11 mixture of the bromides **13a** and **14a** [obtained from the reaction of the epoxide **2a** (0.520 g, 1.16 mmol)] was dissolved in dimethyl sulfoxide (9 cm^3) and, after 16 h, the phosphorane **9** (0.850 g, 2.45 mmol) was added. After a further 24 h, the mixture was diluted with dichloromethane and washed twice with aqueous sodium hydroxide (5% w/v) and then with water. Evaporation of the dried ($MgSO_4$) organic phase and subjection of the product to silica gel column chromatography (hexanes–EtOAc; gradient elution) gave the (*E*)-alkene **10a** (0.108 g, 50%) as a chromatographically homogeneous syrup.

[10]For compound **10a**: δ_H (300 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.50 (3 H, s, 4-Me), 2.29 (3 H, s, 6-H_3), 4.12 (1 H, s, 4-OH), 4.20 (2 H, q, *J* 7 Hz, OCH_2Me), 6.22 (1 H, d, *J* 15.5 Hz, 2-H) and 7.01 (1 H, d, *J* 15.5 Hz, 3-H); δ_C (75 MHz; $CDCl_3$) 14.00 (CH_3CH_2), 23.92 and 24.81 (4-CCH_3 and 6-CH_3), 60.54 (OCH_2), 79.10 (4-C), 122.3 (3-CH), 146.5 (2-CH), 165.9 (1-CO) and 207.1 (5-CO).



Scheme 3

The generality of the technology was demonstrated by its application to three further examples. Thus, the epoxide **2b** reacted with hydrogen bromide to give an 85:15 mixture of the bromides **13b** and **14b**,[6] which was transformed[11] into the (*E*)-alkene **10b**[7] (59% yield after chromatography), $[\alpha]_D$ –0.4 (*c* 1, CH_2Cl_2), with an e.e. of 97%.[2] An 84:16 mixture of the bromides **13c** and **14c**,[6] arising from the reaction of the epoxide **2c** with hydrogen bromide, gave rise to the (*E*)-alkene **10c**[7] (59% yield after chromatography), $[\alpha]_D$ –14.3 (*c* 0.5, CH_2Cl_2), with an e.e. of 91%.[2] Finally, the spiro epoxide **2d** was converted by way of an 87:13 mixture of the bromides **13d** and **14d**[6] into the (*E*)-alkene **10d**[7] (46% yield after chromatography), mp 48–49 °C, $[\alpha]_D$ –5.2 (*c* 0.5, CH_2Cl_2), with an e.e. of 99%.[2]

The aforecited results are of interest in a number of respects. They illustrate new facets of the reactivity of epoxides of type **2**. They demonstrate that species of type **5**, featuring a high functional density, can be generated and intercepted under mild reaction conditions. They exemplify technology for the assembly of compounds of type **10** in a near-enantiopure state; such chirons are expected to have useful applications in synthesis. Finally, they highlight that dimethyl sulfoxide is capable of notably enhancing the (*E*)-stereoselectivity of Wittig condensations of the stabilised phosphorane **9** with α-oxyaldehydes compared with chloroform. It is well established that alcoholic solvents increase the (*Z*)-stereoselectivity of such reactions [5].

[11]The *O*-benzyl ether of the intermediary alcohol **5b** has been synthesised [4]; it is reported to be a relatively unstable compound.

Acknowledgements

We thank the EPSRC for a research grant (GR/J/65464), the Isle of Man Government for a research studentship (to R. F. L.) and Dr. C. M. Raynor for the HPLC analyses.

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