Stereoselective Synthesis of Naturally Occurring α-Methylenebis-γ-butyrolactones: An Application of Novel Oxiranyl "Remote" Anions

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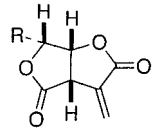
Stereospecific deprotonation of the epoxy proton at the β-position of the α,β-epoxy esters **5** and **6** yielded oxiranyl "remote" anions **7** and **8**, which could then be used for alkylation. The anions **7** and **8** underwent a consecutive aldol lactonization to give, respectively, epoxy lactones **11** and **13** with high stereoselectivity. Generation of the remote anions as well as their stereoselective reactions served as a new synthetic route to the naturally occurring α-methylenebis-γ-butyrolactones, **1**.

Introduction

Naturally occurring α-methylenebis-γ-butyrolactones xylobovide **1a**,[1] canadensolide **1b**,[2] and sporothriolide **1c**[3] are metabolites of *Xylaria obovata*, *Penicillium canadense*, and *Sporothrix* sp., respectively. The interest in these compounds lies not only in their significant biological activities (being antibacterial, antifungal, and phytotoxic) but also in their unique stereochemical features. Because of an all cis stereochemistry of the three adjacent methine protons, the alkyl substituent is interestingly situated in the sterically less accessible concave face of the molecule.



1 a) R = C_2H_5 ; Xylobovide
b) R = *n*-C_4H_9 ; Canadensolide
c) R = *n*-C_6H_{13} ; Sporothriolide

We recently reported a general synthetic route to the α-methylenebis-γ-butyrolactone nucleus by the use of the dimethyl itaconate−anthracene adduct **2** in a consecutive aldol−lactonization reaction followed by flash vacuum pyrolysis of the resulting bislactone adduct.[4] Although extremely efficient for the preparation of the bislactone skeleton, the method has a drawback in its application to the said natural products, **1a**−**c**. Because of the transition state requirements, the consecutive aldol−lactonization reaction between the anion derived from **2** and O-protected α-hydroxyaldehyde followed by hydrogenolysis gives the major product, **3**, with the opposite stereochemistry at the chiral carbon bearing the alkyl substituent.

Significantly, in an unrelated finding, we observed that the β-proton in a ketoepoxide is the preferred site of deprotonation, even in the case of an enolizable ketone. Thus, after treatment of chalcone epoxide with LTMP, the β-anion was preferentially formed and could be trapped with an aldehyde or, in the absence of an external electrophile, condensed with unreacted starting material.[5]

Here, we report significant findings, which involve a new alkylation strategy, based on stereospecific β-deprotonation of the epoxy ester, leading to short and convenient stereoselective syntheses of xylobovide **1a**, canadensolide **1b**, and sporothriolide **1c**.

(i) The epoxides **5** and **6**, prepared from **2**, are amenable to β-deprotonation by LTMP.[5] The deprotonation is stereospecific, affording the corresponding anions **7** and **8**, which are stable in THF solution at −78 °C apparently due to the ester oxygen−lithium stabilization in the form of a five-membered cyclic intermediate.[6] Significantly, none of the six-membered chelated anion, stabilized by the second ester group, i.e., **9**, is observed (Scheme 1). Remarkably, it should be mentioned that, as far as we are aware, *the remote carbonyl stabilized oxiranyl anion reported here is the first example of a Li−H exchange of the β-proton of the oxirane.*[7]

(ii) Anions **7** and **8** react stereospecifically with various electrophiles. For example, with aldehydes, anions **7** and **8** smoothly undergo a consecutive aldol−lactonization

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Scheme 1

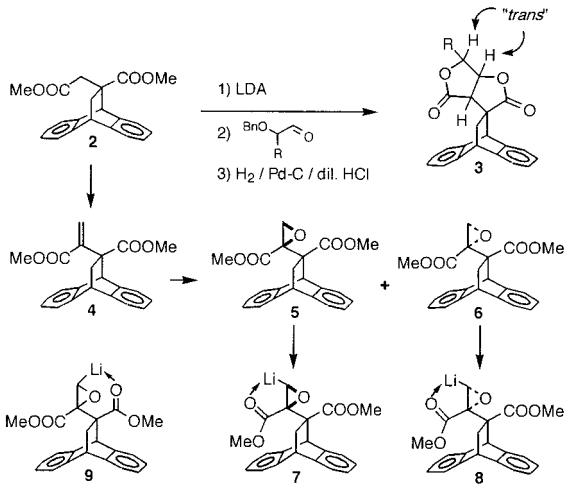
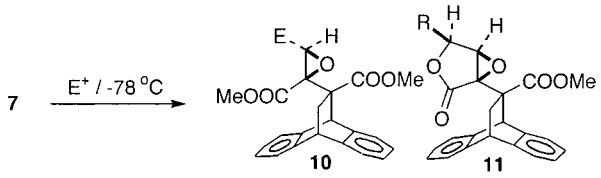


Table 1. Percent Yields from Reactions between the Anion 7, Generated from 5, and Electrophiles



electrophile	**10** (%)	**11** (%)
(a) CD_3OD	58	
(b) CH_3I	76	
(c) PhCHO		53
(d) C_2H_5CHO		68
(e) *n*-C_4H_9CHO		63
(f) *n*-$C_6H_{13}CHO$		57

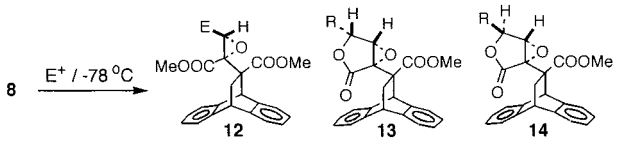
reaction to give respectively epoxy lactones **11** and **13** with high stereoselectivity.

(iii) Samarium iodide catalyzed ring opening of the epoxide moieties in **11** and **13** followed by treatment with DBU is effective in affecting the cis fused ring closure to the respective bislactones **16** and **18**, which then yield the natural product, **1**, after flash vacuum pyrolysis.

Thus, epoxidation of the anthracene adduct **4**, prepared directly from **2**,[8] provided two separable epoxides, **5** and **6**, in almost equal amounts. Deprotonation of epoxide **5** by LTMP in THF at −78 °C followed by the addition of electrophiles gave **10** and, in the case of an aldehyde, the cis epoxy lactone, **11**, with yields as shown in Table 1. Likewise, epoxide **6** provided **12** and **13**. However, in this latter case, a small amount of the undesired trans isomer **14** was also isolated (Table 2). The structures and stereochemistry of all products described are fully supported by NMR and, in certain cases, X-ray data.[9]

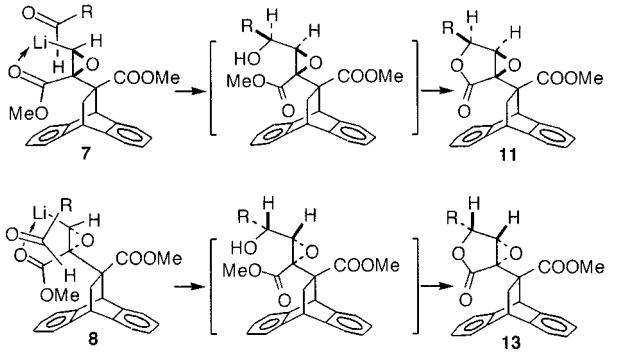
The key to obtain the "correct" cis relative stereochemistry between the epoxy and the alkyl groups in **11** and **13** lies in the high stereoselectivity of the reaction between the anions **7** and **8** with aldehydes. This can be explained in terms of the sterically more favorable

Table 2. Percent Yields from Reactions between the Anion 8, Generated from 6, and Electrophiles



electrophile	**12** (%)	**13** (%)	**14** (%)
(a) CD_3OD	64		
(b) CH_3I	77		
(c) PhCHO		83	
(d) C_2H_5CHO		80	4
(e) *n*-C_4H_9CHO		79	6
(f) *n*-$C_6H_{13}CHO$		66	16

Scheme 2. Transition States of the Reaction between Anions 7 and 8 with an Aldehyde



approach of the aldehyde to the anions via the transition states proposed in Scheme 2.

The samarium iodide induced epoxide ring opening of the epoxy lactone **11**, conducted according to the published method,[10] gave the corresponding alcohol, which lactonized after being boiled in benzene for 2 h in the presence of DBU, to allow complete isomerization of stereochemistry at the chiral carbon α to the lactone group and yielded the bislactone **16** (**16d** = 60%; **16e** = 60%; and **16f** = 58%). Similar treatment of **13** yielded **18** (**18d** = 61%; **18e** = 60%; and **18f** = 54%). Finally, flash vacuum pyrolysis[11] of **16** and **18** affected the retro Diels−Alder reaction to cleanly furnish the α-methylenebis-γ-butyrolactone, **1** (see Scheme 3).

The findings that β-oxiranyl anions can be formed and stereospecifically trapped with electrophiles have provided a novel synthetic methodology, whereby xylobovide **1a**, canadensolide **1b**, and sporothriolide **1c** can be conveniently synthesized.

Experimental Section

11-Carbomethoxy-11-(4′-ethyl-2′-oxo-3′,6′-dioxabicyclo-[3.1.0]hex-1′-yl)-9,10-dihydro-9,10-ethanoanthracene (11d). To a solution of the epoxide **5**[8] (0.5 g, 1.37 mmol) in THF (80 mL) was added a solution of LTMP (4.12 mmol) in THF (10

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(9) Structures of compounds **10b** (E = Me) and **13d** (R = Et) have been confirmed by X-ray crystallography whose data have been deposited with the Cambridge Crystallographic Data Center and allocated the deposition numbers CCDC 144329 and CCDC 144330, respectively. Copies of the data can be obtained free of charge on application to The Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; web site: http://www.ccdc.cam.ac.uk).

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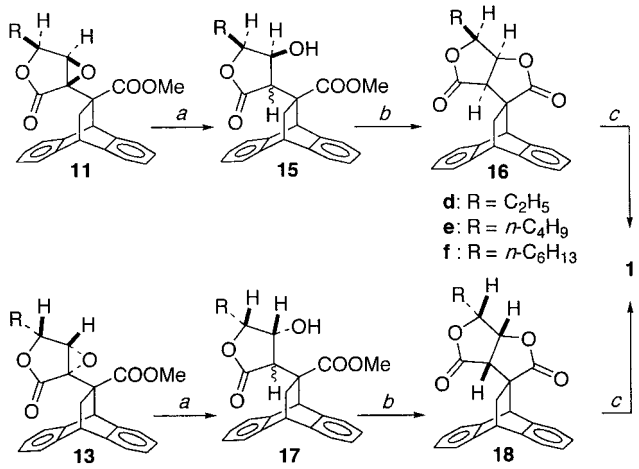
Scheme 3[a]



[a] Key: (a) SmI_2 (2.5 equiv), *N*,*N*-Dimethyl-2-hydroxyethylamine (5 equiv), THF, 0 °C to rt, 0.5 h. (b) DBU (cat), benzene, reflux, 2 h. (c) FVP.

mL) at −78 °C, and the reaction mixture was stirred for 1 h. Excess propanal (0.99 mL, 13.7 mmol) was added at −78 °C, and the mixture was stirred for an additional 4 h. After the reaction was quenched with saturated aqueous ammonium chloride solution, the crude product was extracted several times with dichloromethane. The combined dichloromethane extracts were washed with water and brine and dried over $MgSO_4$. The solution was filtered and evaporated to dryness. Silica gel PLC purification (hexane:ethyl acetate; 9:1 as eluent) followed by crystallization from dichloromethane−hexane provided the epoxy lactone **11d** (0.36 g, 68%); mp 216−218 °C (colorless crystals from dichloromethane−hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0 (t, 3H, J = 7.4 Hz), 1.62 (ddq, 1H, J = 7.4, 7.5, 14.5 Hz), 1.83 (ddq, 1H, J = 6.5, 7.4, 14.5 Hz), 1.64, 2.64, 4.41 (ABX, 3H, J = 2.7, 2.9, 12.4 Hz), 3.24 (d, 1H, J = 1.0 Hz), 3.65 (s, 3H), 4.13 (ddd, 1H, J = 1.0, 6.5, 7.5 Hz), 5.34 (s, 1H), 7.10−7.45 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.9, 23.2, 34.9, 44.1, 48.0, 51.0, 53.2, 58.3, 62.9, 78.9, 123.6, 123.9, 125.2, 126.2, 126.4, 126.5, 127.1, 127.2, 139.7, 140.2, 143.9, 144.4, 170.5, 172.7. IR ($CHCl_3$) ν_{max}: 3072, 3023, 2925, 1765, 1717, 1462, 1270, 1094 cm^{-1}. EIMS (70 eV) *m*/*z* (relative intensity): 390 (M^+, 0.4), 178 (100), 59 (10.3). Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68. Found: C, 73.56; H, 5.45.

8′-Ethyl-3′,6′-dioxo-2′,7′-dioxabicyclo[3.3.0]octan-4′-spiro-11−9,10-dihydro-9,10-ethanoanthracene (16d). Diiodomethane (0.1 mL, 1.28 mmol) was added dropwise to a slurry of samarium powder (0.3 g, 2.13 mmol) and THF (60 mL) at 0 °C under argon. The mixture was stirred for 15 min at 0 °C and at rt for 2 h. *N*,*N*-Dimethyl-2-hydroxyethylamine (DMAE) (0.256 mL, 2.55 mmol) was added to a solution of **11d** (0.2 g, 0.51 mmol) in THF (10 mL). The solution was then added to the resulting deep blue-green solution of SmI_2 at 0 °C, and the reaction mixture was stirred at rt for 0.5 h. Basic workup with saturated aqueous sodium bicarbonate solution and the crude product was extracted into dichloromethane. The combined organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to dryness. The benzene solution of the obtained product, after flash chromatographic purification, was boiled with the presence of DBU (catalytic amount) for 2 h, after which the mixture was quenched with dilute hydrochloric acid and evaporated to dryness. Silica gel PLC purification using hexane:ethyl acetate:dichloromethane (11:1:8 as eluent) gave, after crystallization with a mixture of dichloromethane−hexane, the bislactone adduct **16d** (56.6 mg, 60%); mp 254−255 °C (colorless needles from dichloromethane−hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, J = 7.4 Hz), 1.82−2.01 (m, 2H), 1.97, 2.97, 4.45 (ABX, 3H, J = 2.5, 3.0, 13.3 Hz), 2.86 (d, 1H, J = 5.2 Hz), 4.16 (s, 1H), 4.35 (dt, 1H, J = 3.6, 7.3 Hz), 5.33 (dd, 1H, J = 3.6, 5.2 Hz), 7.11−7.39 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0, 22.4, 31.3, 44.0, 49.7, 52.1, 52.2, 76.9, 82.4, 123.6, 124.9, 125.5, 125.6, 126.5, 127.6, 128.0, 137.7, 139.2, 143.7, 144.2, 173.0, 175.7. IR ($CHCl_3$) ν_{max}: 3029, 3012, 2955, 1791, 1777, 1460, 1221, 1158 cm^{-1}. EIMS (70 eV) *m*/*z* (relative intensity): 360 (M^+, 3.3), 178 (100). ESITOF exact mass calcd for $C_{23}H_{20}O_4$ (M^+ + H): 361.1440. Found: 361.1442.

Xylobovide (1a). Flash vacuum pyrolysis of **16d**, according to the method already described,[11] provided **1a** in almost quantitative yield.[4]

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Supporting Information Available: Experimental and spectroscopic data of compounds **10a**,**b**; **11c**−**f**; **12a**,**b**; **13c**−**f**; **14d**−**f**; and **16d**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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