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Stereoselective total synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone and (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone

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ABSTRACT

The total synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone and (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone is reported based on stereoselective reduction of δ-hydroxy β-keto ester to install 1,3-polyol system, cis Wittig olefination, and lactonization as the key steps. The synthesis of (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone is also reported using *syn*-benzylidene acetal formation and a preferential *Z*-Wittig olefination reaction and lactonization as the key steps.

1. Introduction

Substituted α,β-unsaturated δ-lactones (e.g., styryllactones) are an important class of natural products with a wide range of biological activity.[1] Over the past two decades an increasing number of α-pyrones have been isolated from a variety of sources. Recently identified lactone natural products include Tarchonanthus lactone **1**,[2] Strictifolione **2**,[3] Cryptocarya diacetate **3**,[4] and Cryptocarya triacetate **4**.[4] (+)-(6*R*,2′*R*)-Cryptocaryalactone **5**,[5] (+)-(6*R*,2′*S*)-cryptocaryalactone **7**,[6] and its enantiomer (−)-(6*S*,2′*R*)-cryptocaryalactone **8**[7] (1,3-polyol-derived α,β-unsaturated δ-lactones) are such examples isolated from *Cryptocarya wyliei*, *Cryptocarya bourdilloni*, and *Cryptocarya moschata*, respectively (Fig. 1). Meyer synthesized (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone **6**,[8] enantiomeric pair of (+)-(6*R*,2′*R*)-cryptocaryalactone **5**. *Cryptocarya* species have been used as traditional medicines in South Africa for their anti-inflammatory and other activities.[9,10] Some of the pyrones and styrylpyrones showed larvicidal and antifertility activities, in addition to inhibition of breast cancer cell lines growth.[11–14]

Therefore, the synthesis of various cryptolactones is of much importance. Till date, two reports on the synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone **7**[15,8] and a single report on the synthesis of (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone **6**[8] have appeared. As part of our studies directed toward the synthesis of biologically active lactones,[16] we herein report the synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone **7** and (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone **6**.

2. Results and discussion

The synthesis of these molecules started from δ-hydroxy β-keto ester **11** (Schemes 1 and 2) prepared from iodobenzene **9** and chiral acetylenic alcohol **10** using Cosford protocol as reported by us.[16d] *anti*-Selective reduction of **11** with $Me_4NBH(OAc)_3$[17] in acetonitrile/acetic acid (1:1) at 0 °C resulted in exclusive formation of the *anti*-3,5-dihydroxy ester **12** in 79% yield (*syn*/*anti* 1:9). The mixture was separated by flash column chromatography, and the *anti*-dihydroxy ester **12** was characterized as acetonide **13** (91%), prepared under conventional reaction conditions using 2,2′-dimethoxy propane in CH_2Cl_2 catalyzed by pyridinium *para*-toluenesulfonate. The stereochemical assignment of the newly created center was made based on Rychnovsky's analogy[18] wherein the ^{13}C NMR spectra of **13** exhibited acetonide methyl carbon peaks at δ 24.6 and 25.2 and quaternary carbon at δ 100.7, which were characteristic of the acetonide of an *anti*-1,3-diol moiety (Scheme 1).

The ester group in **13** was reduced by LAH in THF at 0 °C, the subsequent oxidation of which by *ortho*-iodoxybenzoic acid (IBX) in DCM/DMSO at 0 °C furnished the corresponding aldehyde in good yield, which was then chain-elongated on reaction with a Still–Gennari reagent[19] [$(F_3CCH_2O)_2POCH_2COOMe$, NaH, THF, −78 °C, 67% over three steps] to provide the corresponding α,β-unsaturated ester **14** predominantly as the (*Z*)-isomer, along with

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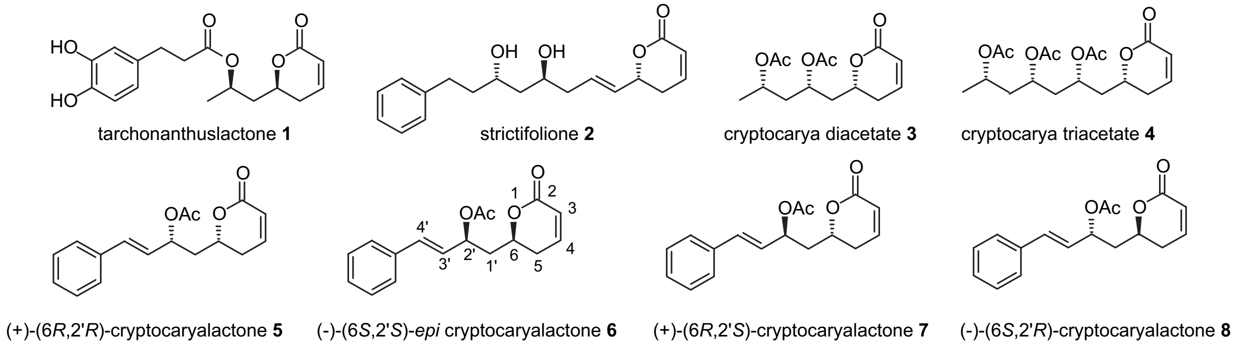
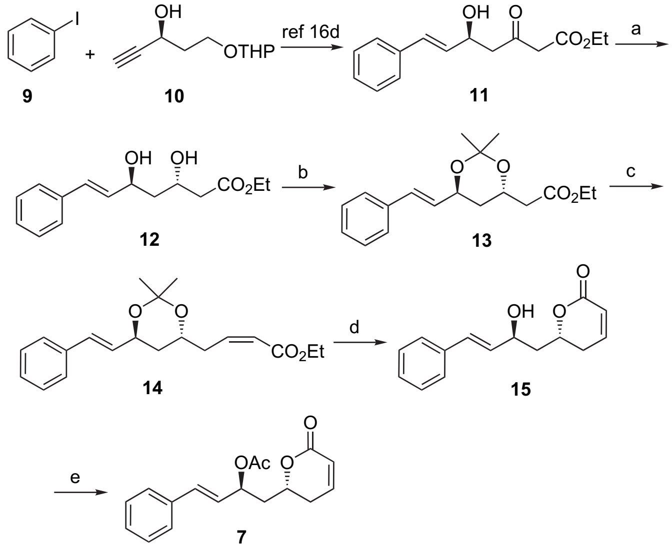


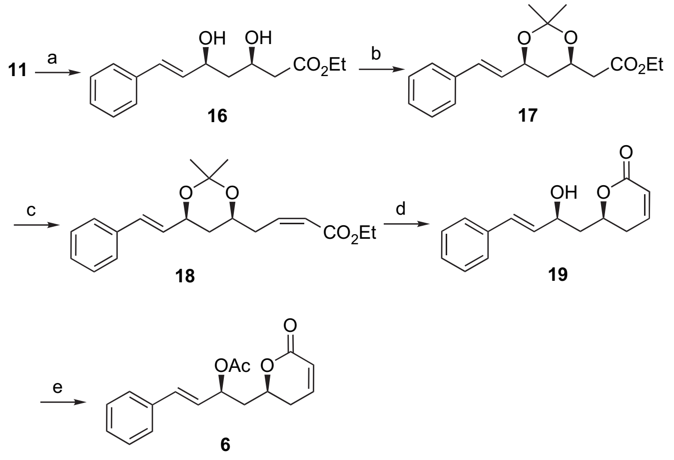
Figure 1.



Scheme 1. Reagents and conditions: (a) $Me_4NBH(OAc)_3$, acetonitrile/acetic acid (1:1), 0 °C, 3 h, 79%; (b) 2,2′-dimethoxy propane, CH_2Cl_2, PPTS, 2 h, rt, 91%; (c) (i) $LiAlH_4$, THF, 30 min, 0 °C to rt, 30 min; (ii) IBX, DCM/DMSO, 0 °C to rt, 4 h; (iii) $(F_3CCH_2O)_2POCH_2CO_2Me$, NaH, dry THF, −78 °C, 60 min, 67% (over three steps); (d) PPTS, methanol, rt, 4 h; (e) Ac_2O/pyridine, CH_2Cl_2, rt, 2 h, 56%.

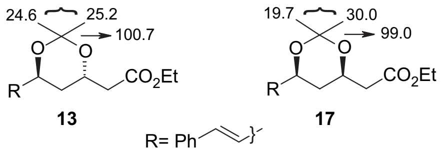
the traces of trans isomer that could be separated by flash column chromatography. Compound **14** was characterized by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum, the olefinic protons resonated at δ 5.84 as a doublet of triplet (J=11.7, 1.5 Hz) and at δ 6.35 as doublet of doublet (J=11.7, 4.7 Hz) confirming the (*Z*)-geometry of the double bond. Finally, acid catalyzed deprotection of the acetonide group, concomitant cyclization using pyridinium *para*-toluenesulfonate in methanol at room temperature for 4 h, and acetylation (Ac_2O/pyridine/CH_2Cl_2/rt) afforded the target compound **7** (56% over two steps), $[\alpha]_D^{25}$ +17.8 (*c* 0.25, $CHCl_3$); lit.[6] $[\alpha]_D^{25}$ +15.55 (*c* 2.52, $CHCl_3$). The spectral data of synthetic **7** were in accordance with those of the natural product.[6]

Similarly, the other stereoisomer **6**, $[\alpha]_D^{25}$ −75.4 (*c* 0.7, $CHCl_3$), lit.[8] $[\alpha]_D^{25}$ −75.1 (*c* 0.68, $CHCl_3$) (Scheme 2), was also obtained from **11** by stereoselective *syn* reduction using catecholborane[18b,20] and then by following a similar sequence of reactions as detailed in Scheme 1. The stereochemical assignment of the newly created center was made based on Rychnovsky's analogy[18] wherein the ^{13}C NMR spectra of **17** exhibited acetonide methyl carbon peaks at δ 19.7 and 30.0 and quaternary carbon at δ 99.0, which were characteristic of the acetonide of *syn*-1,3-diol moiety. The target molecule **6** was isolated as a white solid, mp 127–129 °C (reported as liquid in lit. 8).



Scheme 2. Reagents and conditions: (a) catecholborane, dry THF, −10 °C, 4 h, 92%; (b) 2,2′-dimethoxy propane, CH_2Cl_2, PPTS, 2 h, rt, 89%; (c) (i) DIBAL–H, DCM, −78 °C, 60 min; (ii) $(F_3CCH_2O)_2POCH_2CO_2Me$, NaH, dry THF, −78 °C, 30 min, 66% (over two steps); (d) PPTS, methanol, rt, 4 h, 63%; (e) Ac_2O/pyridine, CH_2Cl_2, 0 °C to rt, 1 h, 57%.

Diagnostic ^{13}C NMR shifts of the acetonides **13** and **17** derived from the diols **12** and **16** are shown in Scheme 3.



Scheme 3.

We also report an alternate and convenient synthesis of (−)-(6*S*,2′*S*)-*epi* cryptocaryalactone **6** based on benzylidene acetal and *Z*-Wittig olefination reactions as key steps (Scheme 4). The synthesis of **6** began from the known aldehyde **20**[16d] prepared from iodobenzene **9** and an acetylenic alcohol **10**. The aldehyde **20** was subjected to a Wittig reaction with the stable ylide, ethoxycarbonylmethylene triphenylphosphorane to furnish the α,β-unsaturated ester **21** in 91% yield. Next, the TBDPS group was removed using TBAF in THF to afford **22** in 82% yield. Benzylidene acetal (protected *syn*-1,3-diol) **23** was prepared in 60% yield by base catalyzed intramolecular conjugate addition using benzaldehyde and potassium *tert*-butoxide in dry THF at 0 °C for 2 h and pH 7 buffer phosphate solution.[21]

Next, the ester group in **23** was reduced with LAH in THF to furnish the alcohol **24** in 85% yield. The primary alcohol **24** was subjected to oxidation in the presence of *o*-iodoxybenzoic acid (IBX) in DCM/DMSO at 0 °C to furnish the corresponding aldehyde