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Stereoselective total synthesis of (–)-(6S,2′R)-cryptocaryalactone

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ABSTRACT

We described a novel stereoselective total synthesis of (–)-(6S,2′R)-cryptocaryalactone, a natural product containing syn/anti-6,8-diol/5,6-dihydro-2H-pyran-2-one unit. The approach, which characterised a highly diastereoselective chelation-controlled Mukaiyama aldol reaction of a benzyl-protected aldehyde and a Yamaguchi lactonisation of a δ-hydroxy-trans-α,β-unsaturated carboxylic acid, is an alternative synthetic strategy towards cryptocaryalactones.

1. Introduction

Natural products are an important source of lead compounds in medicine because of their variety and novel architecture. The syn/anti-6,8-diol/5,6-dihydro-2H-pyran-2-one moiety is a ubiquitous motif present in many natural products that has captured the interest of chemists because of their broad range of pharmacological properties (Larsen et al. 2003; Richetti et al. 2003; Koizumi et al. 2003; Yang et al. 2017). For example, they have been proven to inhibit HIV protease and to induce apoptosis, as well as to be antileukemic (Chrusciel & Strohbach 2004; Inayat-Hussain et al. 2002; Inayat-Hussain et al. 2003; Blatt & Glick 2001; Kikuchi et al. 2004). Their ω,β-unsaturated unit is assumed to play a key biological role as a Michael acceptor. Pertinent natural products having this moiety include cryptocaryalactones (1–4), goniothalamin (5) and (+)-cryptofolione (6) (Figure 1). Members of cryptocaryalactones have been isolated from Cryptocarya species by the groups of Govindachari and Spencer (Govindachari et al. 1972; Govindachari & Parthasarathy 1971; Spencer et al. 1984). They have been found to be natural germination inhibitors with no effect on corn (Drewes et al. 1998).

To our knowledge, four groups have described the total syntheses of (+)-(6S,2′R)-cryptocaryalactones (Meyer 1984; Mori & Furukawa 1994; Sabitha et al. 2008; Krishna et al. 2007).
one producing (–)-(6S,2′R)-cryptocaryalactone (Balasubramanyam et al. 2011) and three producing its diastereoisomer (–)-(6S,2′S)-cryptocaryalactone (Meyer 1984; Sabitha et al. 2008; Yadav et al. 2012). There has been no recent report on the total synthesis of cryptocaryalactones. Inspired by the potential medicinal value of biologically active, natural products with substituted α,β-unsaturated δ-lactones and in continuation of our studies on developing concise approaches towards such lactones (Huang, Liu et al. 2015), we focused on the total synthesis of (–)-(6S,2′R)-cryptocaryalactone (Huang et al. 2014a; Huang et al. 2014b; Huang, Tang et al. 2015). Herein, we report a novel, efficient and concise total synthetic route to synthesize (–)-(6S,2′R)-cryptocaryalactone.

In our earlier study on tarchonanthus lactone (Huang et al. 2015), we utilized a highly diastereoselective chelation-controlled Mukaiyama aldol reaction and Yamaguchi lactonisation of a δ-hydroxy-trans-α,β-unsaturated carboxylic acid to construct the core anti-6,8-diol/5,6-dihydro-2H-pyran-2-one unit. Considering the similarity between tarchonanthus lactone and (–)-(6S,2′R)-cryptocaryalactone, we decided to apply such strategy in the synthesis of (–)-(6S,2′R)-cryptocaryalactone. Our retrosynthetic analysis is depicted in Scheme 1. We
assumed that (-)-(6S,2′R)-cryptocaryalactone could be prepared from δ-hydroxy-trans-α,β-unsaturated carboxylic ester 7 according Akita’s protocol (Ono et al. 2007). Compound 7 could be prepared via chelation-controlled Mukaiyama aldol reaction (Perry et al. 1986) between aldehyde 9 and silyl enol ether 8. Intermediate 9 could be readily obtained from compound 10, which was derivatised by chiral hydroxyl through a Crimmins modified Evans aldol reaction between aldehyde 11 and aldehyde 12 (Yadav et al. 2012).

### 2. Results and discussion

Thus, the synthesis of (-)-(6S,2′R)-cryptocaryalactone (Scheme 2) was commenced with commercially available (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl)-ethanone 11 and trans-cinnamaldehyde 12. Treatment of 11 with 12 readily produced alcohol 10 in about 81% yield in the presence of titanium(IV) chloride and diisopropylethylamine in CH2Cl2 at −78 °C. Retrosynthetically, we needed to protect the hydroxyl with an alkyl group. Considering that deprotection is simple, we initially attempted to protect the hydroxyl in 10 with p-methoxybenzyl (PMB) group using various methods but failed. Therefore, we attempted to convert 10 to a Weinreb amide and then protected it. Treatment of 10 with methoxylamine hydrochloride (MeONHMe·HCl) catalysed by imidazole at room temperature gave amide 13 in 94% yield (Fuwa et al. 2013). The hydroxyl group in 13 was protected in the form of PMB ether using p-methoxybenzyl bromide (PMBBr) and NaH to provide aldehyde 14. Using 14, we then performed a reduction with disobutyl aluminium hydride (DIBAL-H). Without purification, the resulting aldehyde was then used in a two-step Mukaiyama aldol reaction with silyl enol ether 8 in the presence of diisopropoxytitanium chloride (Ti(iOPr)2Cl2) to afford the desired trans-diol 15 as a single product (~65% yield). According to Prof. Akita’s known procedure, compound 15 was subjected to hydrolysis with treatment with LiOH. Without further purification, the resulting δ-hydroxy-trans-α,β-unsaturated carboxylic acid intermediate was readily converted to the desired δ-lactone 16 by treatment with...
2,4,6-trichlorobenzoyl chloride and pyridine. Unfortunately, deprotection of the PMB group was problematic. We obtained a very low yield of deprotected product with treatment with either acid or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Consequently, we diverted the PMB to a Bn group. Following the preparation of the corresponding compound 16, we prepared the Bn-protected compound 19 from Weinreb amide 13 via Bn protection using BnBr, DIBAL-H reduction and Ti(iOPr₂)Cl₂-catalysed chelation-controlled Mukaiyama aldol reaction with silyl enol ether 8 followed by hydrolysis and intramolecular δ-lactone formation, which was shown in Scheme 3. Finally, the δ-lactone 19 was converted into (−)-(6S,2′R)-cryptocaryalactone in 80% yield through a well-established procedure (Sabitha et al. 2010).

As described in Figure 2, we considered that the high diastereoselectivity arised from the β-chelation of complex A formed between Ti⁴⁺ and the aldehyde that was prepared from Weinreb amide 17 and the ether oxygen of the Bn group. The styryl group occupied a pseudoaxial position, and silyl enol ether 8 attacked from the less hindered side to give the anti-diol product 18, which was proposed by Munro (Perry et al. 1986).

As proposed in Akita’s report, we similarly propose the mechanism of δ-lactone formation from δ-hydroxy-trans-α,β-unsaturated carboxylic acid, as shown in Scheme 4. Upon activation of carboxylic acid using 2,4,6-trichlorobenzoyl chloride, pyridine promoted a trans-cis isomerisation via consecutive Michael addition and elimination, forming δ-hydroxy-cis-α,β-unsaturated intermediate III. The latter was smoothly converted to δ-lactone 19 via intramolecular lactonisation.

3. Experimental

3.1. General

All reactions were carried out under a N₂ atmosphere and with dry solvents unless otherwise noted. They were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254). Silica gel (200–300 mesh) used for flash column chromatography was supplied by Qingdao Marine chemical factory in China. Anhydrous toluene and tetrahydrofuran (THF) were distilled from sodium benzophenone. Dichloromethane (DCM) and N,
N-dimethyl formamide (DMF) was distilled from CaH$_2$. Yield refers to that obtained chromato-
graphically and spectroscopically ($^1$H, $^{13}$C NMR), unless otherwise stated. NMR spectra
were recorded on a 400 MHz spectrometer (400 MHz for $^1$H NMR, 100 MHz for $^{13}$C NMR).
High-resolution mass spectra were obtained using a MALDI-TOF Mass Spectrometer. IR spec-
tra were recorded on a Bruker Vertex-70 spectrometer. Optical rotations were measured on
a digital polarimeter in CHCl$_3$ at 25 °C.

### 3.2. Procedures

#### 3.2.1. (2E,5S,7R,8E)-methyl 7-(benzyloxy)-5-hydroxy-9-phenylnona-2,8-dienoate (18)

To a stirred solution of 17 (0.73 g, 2.26 mmol) in dry CH$_2$Cl$_2$ (18 mL) was added a solution of
DIBAL-H (4.5 mL, 6.78 mmol, 1.5 M in toluene) at −78 °C. The reaction mixture was stirred at
−78 °C for 30 min and then it was quenched with methanol (9 mL). Afterwards, saturated
sodium potassium tartrate solution (9 mL) was added to the reaction mixture, which was
then stirred at room temperature for 1 h. The resulting mixture was extracted with CH$_2$Cl$_2$
(3 × 20 mL). The combined organic layers were sequentially washed with 1 N HCl solution
(2.3 mL) and brine (30 mL), dried over Na$_2$SO$_4$, filtered and evaporated to afford crude alde-
hyde, which was directly used in the next reaction without further purification.

To a solution of Ti(O-Pr)$_4$ (0.76 mL, 2.57 mmol) in toluene (3.3 mL) under a nitrogen atmos-
phere was added TiCl$_4$ (0.26 mL, 2.36 mmol) in dropwise fashion. The solution was stirred at
0 °C for 20 min, and then toluene (11 mL) was added. The mixture was cooled to −78 °C to
allow formation of a milky white slurry. This slurry was treated with a solution of the above crude aldehyde (2.26 mmol) in toluene (4.5 mL) via a cannula. The solution was stirred at −78 °C for another 10 min and then treated with a solution of (Z)-((1-methoxybuta-1,3-dien-1-yl)oxy)trimethylsilane \(8\) (1.2 g, 6.78 mmol) in toluene (2.7 mL). The resulting mixture was stirred at the same temperature for 1 h and then quenched with saturated \(\text{NaHCO}_3\) solution (4 mL). Afterwards, the mixture was filtered through a plug of Celite and extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous \(\text{Na}_2\text{SO}_4\), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hexane/EtOAc = 10:1) to provide a colourless oil \(18\) as a single product (522 mg, 63% yield). 

\[ \alpha_{D}^{25} = 55.625 \ (c = 1.44 \text{ in CHCl}_3) \]

\(1^H \text{ NMR (400 MHz, CDCl}_3\): } \delta 7.46–7.28 (m, 10H), 7.07–7.00 (m, 1H), 6.64 (d, \(J = 16.0 \text{ Hz, 1H}\), 6.23 (dd, \(J = 15.9, 7.8 \text{ Hz, 1H}\)), 5.92 (d, \(J = 15.7 \text{ Hz, 1H}\)), 4.70 (d, \(J = 11.7 \text{ Hz, 1H}\)), 4.44 (d, \(J = 11.8 \text{ Hz, 1H}\)), 4.34–4.29 (m, 1H), 4.18–4.12 (m, 1H), 3.75 (s, 3H), 3.0–2.99 (m, 1H), 2.41–2.38 (m, 2H), 1.91–1.79 (m, 2H);

\(1^C \text{ NMR (100 MHz, CDCl}_3\): } \delta 166.6, 145.4, 138.0, 136.2, 132.6, 129.0, 128.6, 128.4, 127.9, 127.8, 127.7, 126.5, 123.2, 77.2, 70.4, 67.2, 51.3, 42.1, 40.1; HRMS (ESI): m/z calcd. for \(\text{C}_{23}\text{H}_{26}\text{O}_{4}\text{Na}[\text{M + Na}]^+ 389.1723\), found 389.1724.

3.2.2. \(\text{(S)-6-}((\text{R,E)-2-}((\text{benzyloxy})-4-\text{phenylbut-3-en-1-yl)})-5,6\text{-dihydro-2H-pyran-2-one (19)}\)

To a solution of compound \(18\) (314 mg, 0.86 mmol) in the mixture solution of THF:MeOH:H\(2\text{O}\) \(2:1:1\) (24 mL) was added LiOH (412 mg, 17.2 mmol) in one portion. The solution was stirred at room temperature for 3 h. When the reaction was deemed complete by TLC monitoring, the reaction mixture was acidified with 1 N HCl solution to pH 6.0 and then extracted with AcOEt (3 × 25 mL). The combined organic layers were dried over \(\text{Na}_2\text{SO}_4\) and concentrated to afford the crude acid, which was used for the next reaction without further purification.

To the solution of the above crude acid in the mixture of pyridine (2 mL) and dichloromethane (0.2 mL) was added 2,4,6-trichlorobenzoyl chloride (0.2 mL, 1.29 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h and then quenched with aqueous saturated \(\text{NaHCO}_3\) solution (3 × 25 mL). The combined organic layers were washed with dichloromethane (3 × 5 mL). The resulting solution was extracted with dichloromethane (2 mL). The residue was purified via flash chromatography (Hexane/AcOEt = 10:1) to produce the desired compound \(19\) (164 mg, 57% yield) as a solid. 

\[ \alpha_{D}^{25} D = -1.702 \ (c = 0.94 \text{ in CHCl}_3) \]

\(1^H \text{ NMR (400 MHz, CDCl}_3\): } \delta 7.45–7.27 (m, 10H), 6.91–6.87 (m, 1H), 6.68 (d, \(J = 15.9 \text{ Hz, 1H}\)), 6.15 (dd, \(J = 15.9, 8.0 \text{ Hz, 1H}\)), 6.07–6.04 (m, 1H), 4.84–4.76 (m, 1H), 4.67 (d, \(J = 11.4 \text{ Hz, 1H}\)), 4.44 (d, \(J = 11.4 \text{ Hz, 1H}\)), 4.44–4.38 (m, 1H), 2.40–2.30 (m, 2H), 2.08–1.94 (m, 2H);

\(1^C \text{ NMR (100 MHz, CDCl}_3\): } \delta 164.1, 145.0, 138.3, 136.2, 132.7, 129.3, 128.6, 128.3, 127.9, 127.8, 127.6, 126.5, 121.4, 75.6, 74.4, 70.7, 41.7, 29.8; HRMS (ESI): m/z calcd. for \(\text{C}_{23}\text{H}_{22}\text{O}_3\text{Na}[\text{M + Na}]^+ 357.1461\), found 357.1462.

3.2.3. \(\text{(R,E)-1-}((\text{S)-6-oxo-3,6-dihydro-2H-pyran-2-yl})-4-\text{phenylbut-3-en-2-yl acetate (1)}\)

To a stirred solution of \(2\) (86 mg, 0.26 mmol) in anhydrous \(\text{CH}_2\text{Cl}_2\) (2.6 mL) under a nitrogen atmosphere, \(\text{TiCl}_4\) (0.029 g, 0.26 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 30 min. When the reaction was completed as indicated by TLC, it was quenched with saturated \(\text{NaHCO}_3\) solution (1 mL) and filtered through a plug of Celite. The filtrate was extracted with \(\text{CH}_2\text{Cl}_2\) (4 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over \(\text{Na}_2\text{SO}_4\) and evaporated under reduced pressure to remove the solvent. To the residue, \(\text{CH}_2\text{Cl}_2\) (1.3 mL), pyridine (0.025 mL, 0.31 mmol) and catalytic DMAP were
added, and then Ac₂O (0.03 mL, 0.31 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and then diluted with CH₂Cl₂ (2 mL), the organic layer was separated and washed with saturated NaHCO₃ solution (3 mL) and brine (3 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc = 2:1) to provide compound 1 (60 mg, 82% yield over two steps) as a white solid. ¹H NMR (400 MHz, CDCl₃): ⑤ 7.39–7.24 (m, 5H), 6.91–6.86 (m, 1H), 6.67 (d, J = 15.9 Hz, 1H), 6.13 (d, J = 15.9, 7.4 Hz, 1H), 6.04 (d, J = 9.8 Hz, 1H), 5.67–5.62 (m, 1H), 4.59–4.52 (m, 1H), 2.41–2.38 (m, 2H), 2.23–2.17 (m, 1H), 2.12–2.05 (m, 1H), 2.09 (s, 3H); HRMS (ESI): m/z calcd. for C₁₇H₁₈O₄Na [M + Na]+ 309.1097, found 309.1098.

4. Conclusions

In conclusion, we have accomplished the concise stereoselective total synthesis of (−)-(6S,2′R)-cryptocaryalactone. We constructed the chiral hydroxyl at C-2′ via a Crimmins modified Evans aldol reaction, which then induced the other chiral centres. The key structure of the target molecule was constructed by 1,3-inductive nucleophilic addition of silyl enol ether to β-alkoxy aldehyde and Yamaguchi lactonisation of a δ-hydroxy-trans-α,β-unsaturated carboxylic acid. This approach is an alternative synthetic strategy towards cryptocaryalactones, especially for the molecules containing syn/anti-6,8-diol/5,6-dihydro-2H-pyran-2-one moiety.

Disclosure statement

No potential conflict of interest was reported by the authors.

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