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Stereoselective synthesis of (+)-cryptocarya diacetate by an iterative Prins cyclisation and reductive cleavage sequence

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Abstract—A highly stereoselective synthesis of (+)-cryptocarya diacetate is achieved through our recently developed strategy for the construction of 1,3-diols via Prins cyclisation. The route relies mainly on the reductive cleavage of allylic ethers, ozonolysis and Wittig olefination along with Prins cyclisation.

Cryptocarya diacetate **1**, cryptocarya triacetate **2**, cryptocaryolone **3** and cryptocaryolone diacetate **4** along with several other compounds were isolated by Horn et al. from the leaves and bark of the South African plant, *Cryptocarya latifolia*, which has long been noted for its medicinal properties.[1] These range from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases and various bacterial and fungal infections.[2] Inspired by the broad range of properties of structurally related 1,3-diol containing polyketides, we have been interested in the development of practical and concise stereoselective approaches to 1,3-diol functionalities.[3] As part of our efforts towards the total synthesis of such natural products, via Prins cyclisation,[3–5] we have achieved a stereoselective total synthesis of (+)-cryptocarya diacetate **1**[6] via a Prins cyclisation and reductive cleavage sequence (see Fig. 1).

In our retrosynthetic plan, we envisioned the construction of the 1,3,5-triol backbone of cryptocarya diacetate **1** from a suitably substituted tetrahydropyran **5**, which in turn was to be assembled from homoallylic alcohol

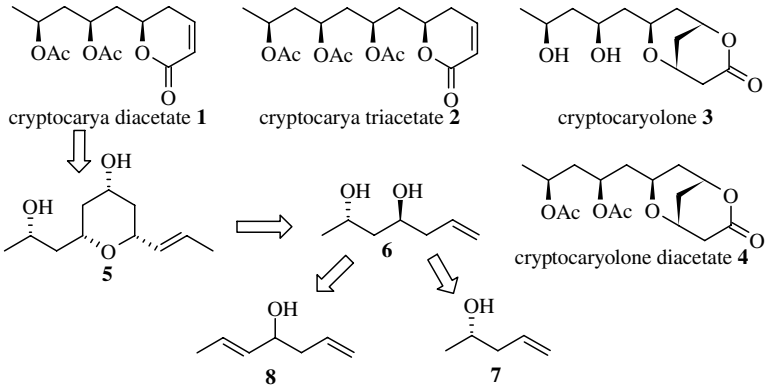

Figure 1.

Keywords: Prins cyclisation; Reductive cleavage; 1,3-Diol; Ozonolysis.
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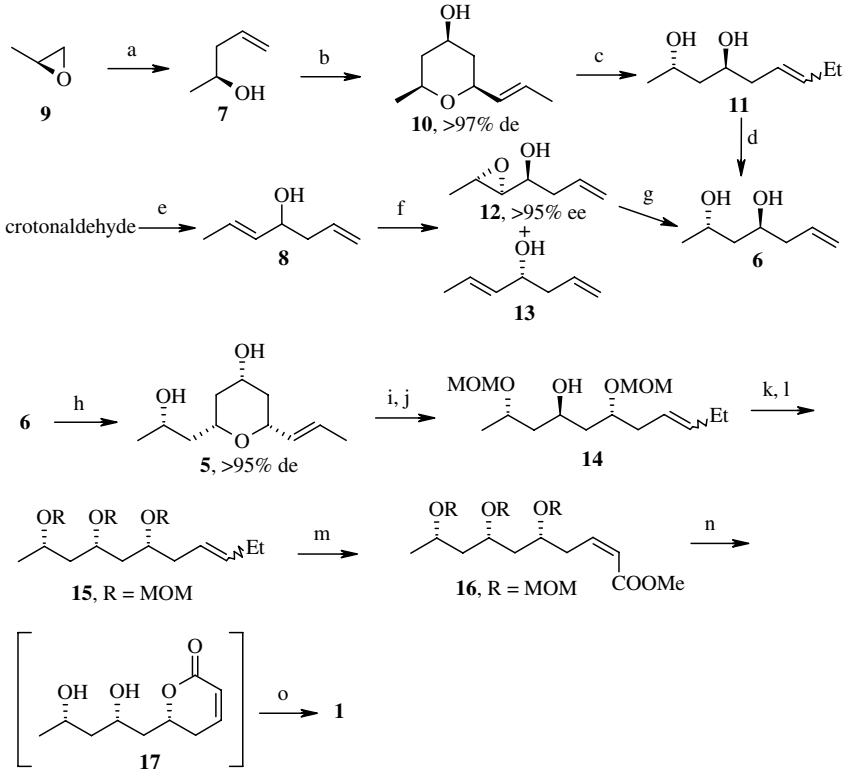
6 and crotonaldehyde. The synthesis of **6** was planned via two routes: either from a Prins cyclisation of homoallylic alcohol **7** followed by reductive cleavage or from the kinetic resolution of allylic alcohol **8** with Sharpless asymmetric epoxidation followed by regioselective reduction.

Our synthetic programme is described in Scheme 1. Cu-mediated opening[7] of the epoxide in (*S*)-propylene oxide **9**[8] with vinylmagnesium bromide yielded homoallylic alcohol **7**. Prins cyclisation of **7** with crotonaldehyde in the presence of TFA[4] followed by hydrolysis of the resulting trifluoroacetate yielded tetrahydropyran **10** (>97% de, as determined by ^{1}H NMR analysis) which, when treated with Na in liq NH_3, underwent clean allylic cleavage[3b] to furnish 1,3-diol **11** as a 1:1 diastereomeric mixture in a 90% yield. Ozonolytic cleavage of the double bond in **11** followed by the Wittig olefinination of the resulting aldehyde with excess of the one-carbon ylide produced diol **6**. An alternative strategy was also evaluated for the synthesis of diol **6**. Thus, allylation of crotonaldehyde using Zn and allyl bromide in DMF[9] yielded alcohol **8** which on kinetic resolution via Sharpless asymmetric epoxidation using L-(+)-DIPT resulted in epoxy alcohol **12** and unreacted **13**. Regioselective reduction of the epoxy group in **12** using Red-Al furnished the desired diol **6**.

Prins cyclisation of **6** with crotonaldehyde in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate yielded tetrahydropyran **5** (>95% de, as determined by ^{1}H NMR analysis). Protection of **5** using excess of MOMCl and DIPEA in DCM yielded the corresponding di-MOM ether which when treated with Na in liq NH_3 underwent a clean allylic cleavage to furnish alcohol **14** as a 1:1 diastereomeric mixture in an 86% yield. The inversion of hydroxy group in **14** in Mitsunobu conditions[10] neatly produced the desired 1,3,5-*syn* alcoholic backbone which on protection as its MOM ether resulted in **15**. Ozonolytic cleavage of the alkene bond in **15** gave the corresponding aldehyde which on subjection to a modified Wadsworth–Emmons reaction using methyl(bistrifluoroethyl)phosphonoacetate in the presence of NaH in THF produced the *Z*-unsaturated ester **16**, predominantly. The three MOM groups in **16** were deprotected using HCl in MeOH[11] to give the corresponding triol which on treatment with *p*TSA in benzene afforded lactone **17**. Diacetylation of **17** afforded the target compound **1**, which was identical in all respects with the natural product.[12]

In conclusion, we have proved that the iterative Prins cyclisation and reductive cleavage sequence can be used as an effective strategy for 1,3,5-polyol systems by synthesizing a representative natural product, (+)-cryptocarya diacetate.



Scheme 1. Reagents and conditions: (a) vinylmagnesium bromide, CuCN, THF, −78 to −40 °C, 4 h, 92%; (b) crotonaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, rt, 4 h, 70%; (c) Na, liq NH_3, THF, −33 °C, 45 min, 90%; (d) O_3, TPP, CH_2Cl_2, −78 °C, then $CH_3P(Ph_3)_3I$, KO^{t}Bu, THF, 0 °C, 2 h, 60%; (e) allyl bromide, Zn, DMF, rt, 30 min, 85%; (f) (+)-DIPT, Ti(O^{i}Pr)$_4$, CH_2Cl_2, TBHP (49 mol %), 4 Å MS, −20 °C, 20 h, 40% of **12**; (g) Red-Al, THF, rt, 12 h, 82 %; (h) crotonaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, rt, 4 h, 55%; (i) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C–rt, 4 h, 92%; (j) Na, liq NH_3, THF, −33 °C, 45 min, 86%; (k) DEAD, TPP, *p*-$C_6H_4(NO_2)COOH$, THF, 30 min, 0 °C–rt then K_2CO_3, MeOH, rt, 1 h, 78%; (l) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C–rt, 4 h, 90%; (m) O_3, TPP, CH_2Cl_2, −78 °C then $(F_3CCH_2O)_2POCH_2COOMe$, NaH, 0 °C, 2 h, 70%; (n) concd HCl, MeOH, rt, 6 h then *p*TSA, benzene, rt, 4 h; (o) Ac_2O, py, DMAP, CH_2Cl_2, rt, 3 h, 70% (three steps).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.068.

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12. Selected physical data for compound **6**. Viscous liquid; $[\alpha]_D^{20}$ +22.1 (*c* 3.2, $CHCl_3$); $R_f = 0.5$ (EtOAc–hexanes, 6:4); IR (KBr): ν_{max} 3365, 2926, 2856, 1638, 1458, 970 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.93–5.66 (m, 1H), 5.17–5.00 (m, 2H), 4.23–4.04 (m, 1H), 3.96–3.84 (m, 1H), 2.80 (br s, 2H), 2.27–2.20 (m, 2H), 1.55 (t, 2H, $J = 5.8$ Hz), 1.22 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.6, 117.4, 67.9, 64.7, 43.6, 41.7, 23.2; LSIMS: 153.0 (M^++Na), 131.0 (M^++H). Compound **5**. Viscous liquid; $[\alpha]_D^{20}$ +23.4 (*c* 2.0, $CHCl_3$); $R_f = 0.2$ (EtOAc–hexanes, 6:4); IR (KBr): ν_{max} 3407, 2929, 2856, 1460, 1377, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.63 (dq, 1H, $J = 15.1$, 6.7 Hz), 5.43 (dd, 1H, $J = 15.1$, 7.5 Hz), 4.18–4.02 (m, 1H), 3.86–3.59 (m, 3H), 1.93 (ddd, 1H, $J = 12.8$, 4.5, 2.2 Hz), 1.83 (ddd, 1H, $J = 12.8$, 4.0, 2.1 Hz), 1.69 (d, 3H, $J = 6.7$ Hz), 1.67–1.58 (m, 2H), 1.46 (br s, 2H), 1.36–1.19 (m, 2H), 1.17 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.2, 127.0, 76.1, 73.0, 67.6, 64.7, 43.8, 40.9, 40.6, 23.4, 17.6; LSIMS: 223.0 (M^++Na), 201.0 (M^++H). Compound **16**. Colourless liquid; $[\alpha]_D^{20}$ −14.6 (*c* 1.5, $CHCl_3$); $R_f = 0.6$ (EtOAc–hexanes, 2:8); IR (KBr): ν_{max} 2985, 1716, 1651, 1382, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.30 (ddd, 1H, $J = 11.5$, 8.0, 7.0 Hz), 5.8 (dd, 1H, $J = 11.5$, 2.2 Hz), 4.68–4.52 (m, 6H), 3.85–3.63 (m, 3H), 3.69 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.99–2.90 (m, 1H), 2.80–2.65 (m, 1H), 1.72–1.49 (m, 4H), 1.20 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 149.9, 120.9, 95.4, 95.2, 94.8, 74.3, 73.7, 72.1, 70.4, 55.5, 55.1, 50.8, 42.1, 39.6, 20.3; LSIMS: 401.2 (M^++Na). Compound **1**. Colourless oil; $[\alpha]_D^{20}$ +54.2(*c* 0.5, $CHCl_3$); lit.[1] $[\alpha]_D^{20}$ +55.8 (*c* 0.5, $CHCl_3$); $R_f = 0.5$ (EtOAc–hexanes, 1:1); IR (neat): 2980, 1730, 1434, 1238, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (ddd, 1H, $J = 9.8$, 6.7, 3.0 Hz), 6.04 (ddd, 1H, $J = 9.8$, 3.0, 0.8 Hz), 5.10 (dddd, 1H, $J = 9.2$, 7.2, 6.0, 4.5 Hz), 5.02 (m, 1H), 4.50 (ddd, 1H, $J = 11.0$, 6.7, 3.8 Hz), 2.5 (ddd, 1H, $J = 18.0$, 5.0, 1.0 Hz), 2.31 (m, 1H), 2.16 (ddd, 1H, $J = 6.0$, 4.2, 1.0 Hz), 2.07 (s, 3H), 2.04 (s, 3H), 2.00 (ddd, 1H, $J = 14.1$, 8.0, 6.0 Hz), 1.96 (ddd, 1H, $J = 14.1$, 6.6, 4.0 Hz), 1.78 (ddd, 1H, $J = 14.1$, 8.0, 6.0 Hz), 1.26 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.5, 163.8, 144.6, 121.4, 74.9, 67.8, 67.7, 40.5, 39.2, 29.3, 21.1, 20.1; ESIMS: 307 (M^++Na), 285 (M+H).