Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3905–3907
Tetrahedron Letters

Stereoselective total synthesis of (+)-cryptocarya diacetate by an iterative Jacobsen's hydrolytic kinetic resolution protocol☆

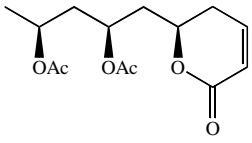
Palakodety Radha Krishna* and V. V. Ramana Reddy

D-206/B, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 28 January 2005; revised 14 March 2005; accepted 23 March 2005
Available online 14 April 2005

Abstract—A combination of iterative Jacobsen's hydrolytic kinetic resolution and reduction of a ketone for the construction of a 1,3-polyol moiety are key steps en route to a total synthesis of (+)-cryptocarya diacetate.

Cryptocarya diacetate **1**, the simplest 6-substituted 5,6-dihydropyran-2-one, was isolated along with other structurally similar compounds from the leaves and bark of the South African plant *Cryptocarya latifolia* that has long been noted for its legendary medicinal properties.[1] These properties range from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[2]



(+)-cryptocarya diacetate **1**

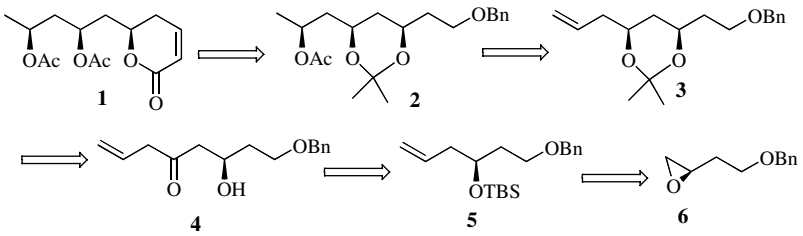
Earlier syntheses[3a–c] of **1** were based either on Sharpless asymmetric epoxidation[3a] and regioselective ring opening as the key steps, or involved an enantioselective synthesis from ethyl sorbate by a Sharpless asymmetric dihydroxylation-RCM strategy.[3b,c] Herein a stereoselective total synthesis of **1** is reported, using a combination of Jacobsen's hydrolytic kinetic resolution and diastereoselective ketone reduction to garner the required chiral centers.

The retrosynthetic analysis, as depicted in Scheme 1, envisions that **1** could be obtained from **2** by functional group transformations, elaboration, and lactonization while **2** in turn could be visualized from **3** by a Jacobsen's hydrolytic kinetic resolution (HKR) and reductive ring-opening reaction of a chiral epoxide. Compound **3** in turn could conveniently be derived from **4** by diastereoselective reduction to afford the *syn*-1,3-diol structural unit, while **4** was to be obtained from **5** by allylation of the aldehyde generated by ozonolysis followed by oxidation of the ensuing alcohol and desilylation. Similarly **5** could be obtained from the known epoxide **6** (obtained by Jacobsen's HKR of a homoallylic alcohol derivative) through a ring-opening reaction with vinylmagnesium bromide and subsequent hydroxyl group protection.

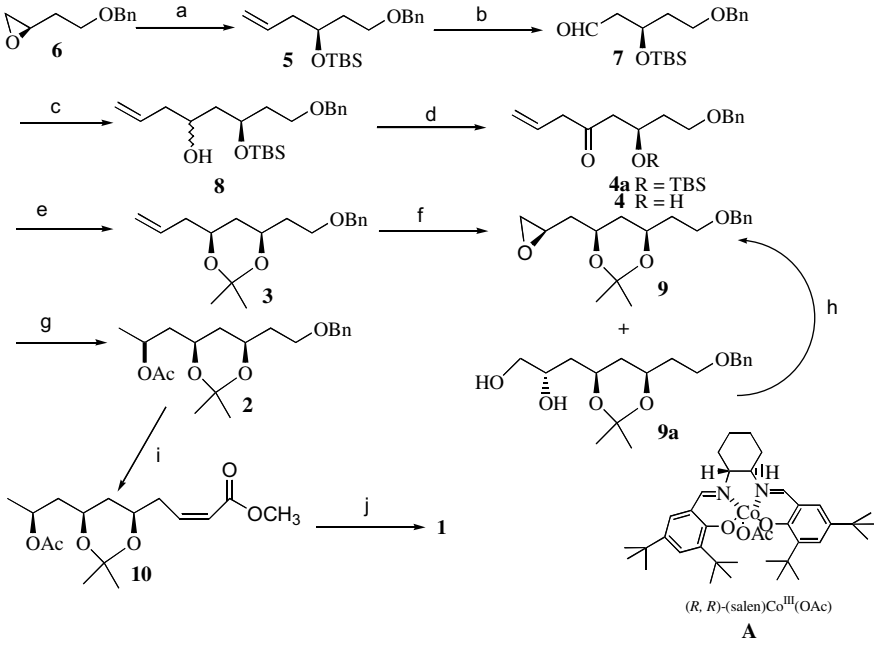
The known[4] epoxide **6** on exposure to vinylmagnesium bromide in THF afforded a homoallylic alcohol in good yield (74%) that was then protected as its TBS ether **5** (82%) with TBSCl in CH_2Cl_2 at room temperature (Scheme 2). Reductive ozonolysis of olefin **5** afforded an aldehyde **7**, which was immediately converted to homoallylic alcohol **8** (82%) with allyl bromide/Zn, subsequent PCC oxidation in the presence of NaOAc providing ketone **4a** (72%). Desilylation of **4a** with HF–pyridine gave β-hydroxy ketone **4** in 63% yield. Selective reduction of **4** with $NaBH_4$ in the presence of the chelating agent $B(Et)_2OMe$[5] in THF resulted in exclusive formation of the *syn*-1,3-diol (de > 98%), which was characterized as acetonide **3** (94%), prepared under conventional reaction conditions using 2,2′-DMP in DMSO catalyzed by PTSA. The stereochemical assignment of the newly created center was made based

Keywords: Jacobsen hydrolytic kinetic resolution; α,β-unsaturated δ-lactone; 1,3-*syn*-polyol.
☆ IICT Communication No. 050111.
* Corresponding author. Fax: +91 40 271 60387/+91 40 271 60757; e-mail: prkgenius@iict.res.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.202



Scheme 1.



Scheme 2. Reagents and conditions: (a) (i) vinylmagnesium bromide, THF, CuI, rt, 74%, (ii) TBSCl, imidazole, rt, 82%; (b) O_3, CH_2Cl_2, 78 °C, 0.5 h, then Me_2S, rt, 0.5 h; (c) allyl bromide, Zn NH_4Cl, THF, rt, 82%; (d) PCC, NaOAc, CH_2Cl_2, rt, 72%; (e) (i) HF–pyridine, THF, rt, 63%, (ii) $B(Et)_2OMe$, $NaBH_4$, THF, 75%, (iii) 2,2′-dimethoxypropane, PTSA, DMSO, 94%; (f) (i) oxone, acetone, $NaHCO_3$, EDTA (cat.) 73%, (ii) (*R*,*R*)-(salen)Co^{III}(OAc) **A**, 0.55 equiv H_2O, 43%; (g) (i) LAH, THF, rt, 89%, (ii) Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, rt, 94%; (h) (i) PhCOCl, Et_3N, CH_2Cl_2, rt, (ii) TsCl, Et_3N, CH_2Cl_2, rt, (iii) K_2CO_3, MeOH, rt; (i) (i) Pd/C, H_2, EtOAc, rt, 95%, (ii) IBX, DMSO, rt, (iii) $(F_3CCH_2O)_2POCH_2COOMe$, KH MDS, 18-crown-6, THF, 78 °C, 79% over two steps; (j) (i) 80% aq AcOH, (ii) PTSA, C_6H_6, (iii) Ac_2O, pyridine, CH_2Cl_2, DMAP (cat.), rt, 86% over three steps.

on Rychnovsky's analogy[6] wherein the ^{13}C NMR spectra of **3** exhibited acetonide methyl carbons at δ 19.8 and 30.2 characteristic of the acetonide of a *syn*-1,3-diol moiety.

Epoxidation of **3** with oxone furnished the epoxide and Jacobsen's hydrolytic kinetic resolution[4] with 0.55 equiv of water using (*R*,*R*)-(salen)Co^{III}(OAc) **A** as the catalyst provided enantiomerically pure **9** and diol **9a** in 43% yield each. The chiral homogeneity of both **9** (de ~ 94%) and **9a** was confirmed by HPLC analysis.[7] Diol **9a** was recycled to **9** by a three-step sequence. Thus, **9a** was mono benzoylated ($BzCl/Et_3N/CH_2Cl_2$/rt) followed by tosylation of the secondary hydroxyl (TsCl/Et_3N/CH_2Cl_2/DMAP/rt) to give the diprotected compound. Base induced deprotection of the benzoate generated an alkoxide, which prompted simultaneous elimination of tosylate and ring closure by an S_N2 mode to afford the desired epoxide **9**[7] $[\alpha]_D^{25}$ +16.3 (*c* 0.5, $CHCl_3$) in 58% yield over three steps (de 80%).

Next, reductive ring-opening of epoxide **9** with LAH gave the secondary alcohol (89%), which was acetylated (Ac_2O/pyridine/CH_2Cl_2/rt) to afford **2** (94%). Removal of the benzyl protecting group (Pd–C/H_2/EtOAc/rt) in **2** (95%) released the terminal hydroxyl group, the subsequent oxidation of which by IBX in DMSO at room temperature gave the aldehyde, which was then chain elongated on reaction with a Wittig ylide to provide the corresponding α,β-unsaturated ester **10** $(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, −78 °C, 79% over two steps) predominantly as the (*Z*)-isomer,[8] as characterized by ^1H and ^{13}C NMR spectroscopy. For example the coupling constant (J = 6.8 Hz) of the olefinic protons confirmed the (*Z*)-geometry of olefin. Finally, acid catalyzed deprotection of the acetonide group (80% aq AcOH), concomitant cyclization under PTSA conditions and acetylation (Ac_2O/pyridine/CH_2Cl_2/rt) afforded the target compound **1** (86% over three steps), $[\alpha]_D^{25}$ +55.4 (*c* 0.3, $CHCl_3$); lit.[1] $[\alpha]_D^{25}$ +55.8 (*c* 1.06, $CHCl_3$). The spectral data of synthetic **1**[9] were

in accordance with those of the natural product.[1] The synthesis of **1** also established the assigned stereochemistry of **9**.

In conclusion, the stereoselective synthesis of (+)-cryptocarya diacetate was accomplished by a combination of Jacobsen's hydrolytic kinetic resolution of a multichiral synthon and diastereoselective ketone reduction as the key steps for installing the chiral centers of the 1,3-polyol system and subsequent elaboraation to the α,β-unsaturated-δ-lactone moiety.

Acknowledgements

One of us (V.V.R.R.) thank the UGC, New Delhi, for financial support in the form of a research fellowship.

References and notes

1. Drewes, S. E.; Sehlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, P. *Phytochemistry* **1995**, *38*, 1427–1430.
2. Sam, T. W.; Yeu, C. S.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199–205.
3. (a) Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855–8858; (b) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780; (c) Smith, G. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959–1962.
4. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938; (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.
5. Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926.
6. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.
7. Compound **9**: $[\alpha]_D^{25}$ +21.3 (*c* 0.5, $CHCl_3$); HPLC analysis: Column: Chiralcel OBH 250 × 4.6 mm, PDA detector at 254 nm, 10% EtOH, 10% ^{i}PrOH, 80% *n*-hexane, flow rate 1 mL/min, t_r(minor) = 4.56 min, t_r(major) = 4.97 min with a diastereomeric ratio of 0.3:9.7. Recycled compound **9**: $[\alpha]_D^{25}$ +16.3 (*c* 0.5, $CHCl_3$); HPLC analysis: Column: Chiralcel OBH 250 × 4.6 mm, PDA detector at 254 nm, 10% EtOH, 10% ^{i}PrOH, 80% *n*-hexane, flow rate 1 mL/min, t_r(minor) = 4.58 min, t_r(major) = 4.96 min with a diastereomeric ratio of 1.0:9.0.
8. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
9. Spectral data for selected compounds: Compound **3**: $[\alpha]_D^{25}$ +5.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33, 1.4 (2 × s, 6H, 2 × *CH*$_3$), 1.44 (t, *J* = 3.0 Hz, 1H, –*CH*$_2$), 1.48 (t, *J* = 3.0 Hz, 1H, –*CH*$_2$), 1.68 (m, 2H, –*CH*$_2$), 2.1 (m, 1H, –*CH*$_2$), 2.25 (m, 1H, –*CH*$_2$), 3.43–3.58 (m, 2H, –*CH*$_2$OBn), 3.82 (m, 1H, –*CH*), 3.97 (ddt, *J* = 2.3, 5.3, 7.5 Hz, 1H, –*CH*), 4.45 (d, *J* = 2.3 Hz, 2H, –OCH$_2$Ph), 5.0–5.07 (m, 2H, –CH=*CH*$_2$), 5.67–5.82 (m, 1H, –*CH*=CH$_2$), 7.27 (br s, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.8, 30.2, 36.5, 40.8, 66.1, 66.2, 68.6, 72.9, 116.9, 127.5, 127.6, 128.3, 134.2; IR (neat): 2942, 1645, 1378, 1268, 1198, 1102 cm^{-1}; EIMS: 290 (M^+). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02%. Found: C, 74.48; H, 9.03%. Compound **10**: $[\alpha]_D^{25}$ +27.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.20 (d, *J* = 6.0 Hz, 3H, –CH$_3$), 1.33–1.6 (m, 10H, 2 × CH$_2$ and 2 × CH$_3$), 2.0 (s, 3H, –O*Ac*), 2.7 (ddq, *J* = 2.2, 4.5, 6.8 Hz, 1H, *CH*$_2$), 2.90 (ddq, *J* = 2.3, 3.7, 6.9 Hz, 1H, CH$_2$), 3.69 (s, 3H, –COOCH$_3$), 3.78–3.94 (m, 2H, –*CH*), 5.05 (m, 1H, –*CH*OAc), 5.80 (dd, *J* = 2.2, 6.8 Hz, 1H, –*CH*=CH), 6.36 (ddd, *J* = 1.5, 2.5, 6.0 Hz, 1H, –CH=*CH*); ^{13}C NMR (75 MHz, $CDCl_3$): 19.5, 20.1, 20.7, 21.3, 30.1, 35.5, 36.7, 42.8, 50.0, 65.5, 67.6, 67.9, 68.4, 120.6, 145.9, 146.0; EIMS 314 (M^+); IR (neat): 2922, 2853, 1720, 1649, 1340 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34%. Found: C, 61.12; H, 8.36%. Compound **1**: $[\alpha]_D$ +55.4 (*c* 0.3, $CHCl_3$); lit.[1] $[\alpha]_D$ +55.8 (*c* 1.06, $CHCl_3$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.8 Hz, 3H, –CH$_3$), 1.79 (ddd, *J* = 6.0, 8.0, 14.3 Hz, 1H, –CH$_2$), 1.97 (ddd, *J* = 4.0, 6.6, 14.3 Hz, 1H, –CH$_2$), 2.00 (ddd, *J* = 6.0, 8.0, 14.3 Hz, 1H, –CH$_2$), 2.04 (s, 3H, –O*CH*$_3$), 2.07 (s, 3H,–OCH$_3$), 2.16 (ddd, *J* = 1.0, 4.0, 6.0 Hz, 1H, –CH$_2$), 2.31 (m, 1H, –CH$_2$), 2.5 (ddd, *J* = 1.0, 5.0, 18.0 Hz, 1H, –CH$_2$), 4.5 (ddd, *J* = 3.8, 6.7, 11.0 Hz, 1H, –CH), 5.0 (m, 1H, *CH*), 5.11 (dddd, *J* = 4.5, 6.0, 7.2, 9.0 Hz, 1H, –CH), 6.02 (ddd, *J* = 0.75, 3.0, 9.8 Hz, 1H, *CH*), 6.88 (ddd, *J* = 0.75, 3.0, 6.7 Hz, 1H, –CH); ^{13}C NMR: 20.1, 21.1, 29.3, 39.2, 40.5, 67.7, 67.8, 74.9, 121.4, 144.6, 163.8, 170.5, 170.6; FABMS (*m*/*z*): 307 (M^++23, 12), 285 (M^++1, 22), 225 (40), 154 (100), 137 (96), 107 (92); IR (neat): 2980, 1730, 1434, 1238, 1037 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.09%. Found: C, 59.18; H, 7.11%.